Effects on the blood. There have been reports of agranulocytosis associated with pentazocine.[1-3]

1. Marks A, Abramson N. Pentazocine and agranulocytosis. *Ann Intern Med* 1980; **92:** 433.
2. Haibach H, *et al*. Pentazocine-induced agranulocytosis. *Can Med Assoc J* 1984; **130:** 1165–6.
3. Sheehan M, *et al*. Pentazocine-induced agranulocytosis. *Can Med Assoc J* 1985; **132:** 1401.

Effects on the CNS. Oculogyric crisis has been associated with the use of pentazocine.[1]

1. Burstein AH, Fullerton T. Oculogyric crisis possibly related to pentazocine. *Ann Pharmacother* 1993; **27:** 874–6.

Effects on the skin. Toxic epidermal necrolysis in a 62-year-old man was attributed to pentazocine;[1] he had taken 50 to 75 mg every 4 hours for 8 days. His severe uraemia was attributed to fluid loss through the skin.

1. Hunter JAA, Davison AM. Toxic epidermal necrolysis associated with pentazocine therapy and severe reversible renal failure. *Br J Dermatol* 1973; **88:** 287–90.

Treatment of Adverse Effects

As for Opioid Analgesics in general, p.102.

As pentazocine has both opioid agonist and antagonist activity its effects may not be completely reversed by naloxone, but use of the latter is still recommended in pentazocine overdosage.

Precautions

As for Opioid Analgesics in general, p.103.

Pentazocine has weak opioid antagonist actions and may precipitate withdrawal symptoms if given to patients who are physically dependent on opioids. It should generally be avoided after myocardial infarction and in patients with heart failure or arterial or pulmonary hypertension.

When frequent injections are needed, pentazocine should be given intramuscularly rather than subcutaneously and the injection sites should be varied.

Abuse. See under Dependence and Withdrawal, above.

Porphyria. Pentazocine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

For interactions associated with opioid analgesics, see p.103.

Tobacco smoking. Smokers metabolised about 40% more pentazocine than non-smokers, although there was large inter-subject variation;[1] tobacco smoking might induce liver enzymes responsible for drug oxidation.

1. Vaughan DP, *et al*. The influence of smoking on the inter-subject variation in pentazocine elimination. *Br J Clin Pharmacol* 1976; **3:** 279–83.

Pharmacokinetics

Pentazocine is well absorbed from the gastrointestinal tract; after an oral dose, peak plasma concentrations occur in 1 to 3 hours and the half-life is reported to be about 2 to 3 hours. After intramuscular injection, peak plasma concentrations are reached in 15 minutes to 1 hour and the half-life is about 2 to 5 hours. About 50 to 75% has been reported to be bound to plasma proteins. Pentazocine undergoes extensive first-pass metabolism in the liver; oral bioavailability is low with only about half of a dose reaching the systemic circulation. Metabolites and a small amount of unchanged drug are excreted in the urine. It crosses the placenta and is distributed into breast milk.

Hepatic impairment. Clearance of pentazocine was significantly reduced and terminal half-life and oral bioavailability increased in cirrhotic patients when compared with healthy subjects.[1]

1. Neal EA, *et al.* Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. *Gastroenterology* 1979; **77:** 96–102.

Uses and Administration

Pentazocine, a benzomorphan derivative, is an opioid analgesic (p.104) that has mixed opioid agonist and antagonist actions. Agonist activity is thought to be mainly at κ opioid receptors (with possibly some σ receptor activity); it acts as a weak antagonist or partial agonist at μ receptors. Pentazocine is used for the relief of moderate to severe pain including the pain of labour. Combined preparations with paracetamol or aspirin may also be used in the treatment of moderate pain. It may also be used for pre-operative sedation and as an adjunct to anaesthesia. Its analgesic effect declines more rapidly than that of morphine.

Pentazocine is given orally as the hydrochloride; doses may be expressed as either the base or the salt. Pentazocine is also given parenterally and rectally as the lactate; doses are expressed in terms of the base. Pentazocine 100 mg is equivalent to about 112.8 mg of pentazocine hydrochloride or 131.6 mg of pentazocine lactate.

A usual oral dose is the equivalent of 50 to 100 mg of pentazocine or pentazocine hydrochloride every 3 to 4 hours after food, to a maximum of 600 mg daily.

The usual initial dose by subcutaneous, intramuscular, or intravenous injection is the equivalent of pentazocine 30 mg as a single dose. Thereafter, the dose may be adjusted according to response; in some patients 45 to 60 mg by subcutaneous or intramuscular injection may be required. In the USA single intravenous doses of not more than 30 mg are advised. Doses may be repeated every 3 to 4 hours; it should not be necessary to exceed 360 mg daily. Also if frequent injections are needed, the intramuscular route should be used rather than the subcutaneous route, and the injection sites should be varied. In obstetric analgesia 30 mg may be given as a single dose by intramuscular injection during labour; alternatively, 20 mg may be given by intravenous injection as soon as contractions occur at regular intervals and repeated 2 or 3 times at intervals of 2 to 3 hours if necessary.

For details of doses in children, see below.

Pentazocine is given rectally in suppositories usually in a dose equivalent to pentazocine 50 mg up to 4 times daily.

As a deterrent to abuse a combined oral preparation of pentazocine hydrochloride and naloxone hydrochloride is available in some countries.

Administration in children. In the UK, pentazocine is licensed for the relief of moderate to severe pain in children and doses may be repeated every 3 to 4 hours if necessary. Those aged 6 to 12 years may be given a usual oral dose of 25 mg. Children aged 1 to 12 years may be given doses of up to 1 mg/kg by subcutaneous or intramuscular injection or up to 500 micrograms/kg by intravenous injection.

Preparations

BP 2008: Pentazocine Capsules; Pentazocine Injection; Pentazocine Suppositories; Pentazocine Tablets;
USP 31: Pentazocine and Aspirin Tablets; Pentazocine and Naloxone Tablets; Pentazocine Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Fortral†; ***Austria:*** Fortral; ***Belg.:*** Fortal; ***Canad.:*** Talwin; ***Cz.:*** Fortral; ***Denm.:*** Fortral†; ***Fr.:*** Fortal†; ***Ger.:*** Fortral; ***Gr.:*** Fortal; ***India:*** Fortwin; Pentawin; ***Israel:*** Rafazocine†; Talwin NX†; Talwin†; ***Ital.:*** Talwin; ***Jpn:*** Peltazon†; Pentagin†; Sosegon†; ***Neth.:*** Fortral; ***Norw.:*** Fortralin†; ***NZ:*** Fortral†; ***Port.:*** Sosegon†; ***S.Afr.:*** Ospronim; Sosenol; ***Spain:*** Sosegon; ***Switz.:*** Fortalgesic†; ***Thai.:*** Fortwin†; Pangon; Sosegon†; ***UK:*** Fortral; ***USA:*** Talwin; Talwin NX.

Multi-ingredient: ***India:*** Expergesic; Foracet; ***Irl.:*** Fortagesic†; ***USA:*** Emergent-Ez; Talacen; Talwin Compound†.

Pethidine Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de petidina; Meperidine Hydrochloride; Péthidine, chlorhydrate de; Pethidin-hydrochlorid; Pethidini hydrochloridum; Petidiinihydrokloridi; Petidin Hidroklorür; Petidin-hidroklorid; Petidinhydroklorid; Petidino hidrochloridas; Petydyny chlorowodorek. Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.

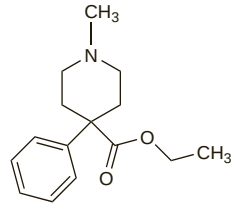
Петидина Гидрохлорид

$C_{15}H_{21}NO_2$,HCl = 283.8.

CAS — 57-42-1 (pethidine); 50-13-5 (pethidine hydrochloride).

ATC — N02AB02.

ATC Vet — QN02AB02.



(pethidine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of pethidine:
Bam; Peth.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet*.

Ph. Eur. 6.2 (Pethidine Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers. Protect from light.

USP 31 (Meperidine Hydrochloride). A fine white odourless crystalline powder. Very soluble in water; soluble in alcohol; sparingly soluble in ether. pH of a 5% solution in water is about 5. Protect from light.

Incompatibility. Solutions of pethidine hydrochloride are acidic. They are incompatible with barbiturate salts and loss of clarity was also seen in an early additive study[1] with other drugs including aminophylline, heparin sodium, meticillin sodium, morphine sulfate, nitrofurantoin sodium, phenytoin sodium, sodium iodide, sulfadiazine sodium, and sulfafurazole diolamine. Colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with pethidine hydrochloride in 5% glucose injection.[2] In the same study an immediate precipitate occurred on admixture with cefoperazone sodium or mezlocillin sodium; with nafcillin sodium an immediate cloudy appearance cleared on agitation. Incompatibility has also been seen between pethidine hydrochloride and aciclovir sodium, imipenem, furosemide,[3] liposomal doxorubicin hydrochloride,[4] and idarubicin.[5] Solutions of cefazolin sodium[6] and pethidine hydrochloride mixed in 5% glucose injection turned light yellow after storage for 5 days at 25°; the admixture was stable for at least 20 days at 4°.

1. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23:** 409–11.
2. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
3. Pugh CB, *et al.* Visual compatibility of morphine sulfate and meperidine hydrochloride with other injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 123–5.
4. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.
5. Turowski RC, Durthaler JM. Visual compatibility of idarubicin hydrochloride with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 2181–4.
6. Lee DKT, *et al.* Stability of cefazolin sodium and meperidine hydrochloride. *Am J Health-Syst Pharm* 1996; **53:** 1608–10.

Stability. Pethidine hydrochloride injection 100 mg/mL was stable[1] for at least 24 hours at room temperature when diluted to a concentration of 300 mg/litre in glucose 5% and 4% and in sodium chloride injection (0.9%) and sodium chloride injection (0.9%) diluted 1 in 5.

Accelerated stability studies using elevated temperatures and humidities to simulate tropical conditions classified pethidine hydrochloride as a 'less stable drug substance'.[2] It was suggested that during quality assurance of preparations containing pethidine hydrochloride particular attention should be paid to their stability.

1. Rudd L, Simpson P. Pethidine stability in intravenous solutions. *Med J Aust* 1978; **2:** 34.
2. WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. *WHO Tech Rep Ser 790* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_790.pdf (accessed 26/06/08)

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Doses of pethidine as large as 3 or 4 g daily have been taken by addicts. As tolerance to the CNS stimulant and antimuscarinic effects is not complete with these very large doses, muscle twitching, tremor, mental confusion, dilated pupils, and sometimes convulsions may be present.

Withdrawal symptoms appear more rapidly than with morphine and are of shorter duration.

For the abuse of pethidine analogues, see under Precautions, below.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

The effects on smooth muscle may be relatively less intense than with morphine and constipation occurs less frequently. Local reactions often follow injection of pethidine; general hypersensitivity reactions occur rarely. Pethidine given intravenously may increase the heart rate. After overdosage, symptoms are generally similar to those of morphine poisoning. However, stimulation of the CNS and convulsions may also occur, especially in tolerant individuals or after toxic oral doses; these have been attributed mainly to the metabolite norpethidine.

Incidence of adverse effects. The incidence of adverse effects in hospitalised patients receiving pethidine was monitored by the Boston Collaborative Drug Surveillance Program.[1] Adverse reactions to oral pethidine were reported in 16 of 366 patients and mainly involved the gastrointestinal tract. After pethidine by injection 102 of 3268 patients had adverse effects, the CNS being involved in 38.

More recently, 20 adverse reactions were identified in a chart review of 141 patients given pethidine and considered to be at high risk of developing toxicity;[2] high-risk patients were defined as those with renal impairment (creatinine clearance 50 mL/minute or less), those receiving patient-controlled analgesia (PCA) with pethidine, and those given intravenous pethidine in doses of over 200 mg daily for several days. The most common adverse reactions were confusion and anxiety; other reported adverse effects included nervousness, seizures, and hallucinations. Patients who developed adverse reactions were significantly older, more likely to be taking a benzodiazepine, and had longer hospital stays than those without adverse effects. Out of the 20 reports, 16 adverse effects were noted in the 123 patients who received pethidine via

a PCA pump; cumulative doses for patients using PCA were found to be a significant risk factor in the development of adverse effects.

1. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. *J Clin Pharmacol* 1978; **18:** 180–9.
2. Seifert CF, Kennedy S. Meperidine is alive and well in the new millennium: evaluation of meperidine usage patterns and frequency of adverse drug reactions. *Pharmacotherapy* 2004; **24:** 776–83.

Effects on the cardiovascular system. Histamine release was more frequent after pethidine than after morphine, fentanyl, or sufentanil given intravenously for the induction of anaesthesia.[1] Increased plasma-histamine concentrations occurred in 5 of 16 patients given pethidine in a mean dose of 4.3 mg/kg and were generally accompanied by hypotension, tachycardia, erythema, and increased plasma-adrenaline concentrations. Only 1 of 10 given morphine and none of those receiving fentanyl or sufentanil showed evidence of histamine release. All of the histamine releasers were young women.

1. Flacke JW, *et al.* Histamine release by four narcotics: a double-blind study in humans. *Anesth Analg* 1987; **66:** 723–30.

Effects on the nervous system. CNS excitatory effects of pethidine such as tremors, muscle twitches, and convulsions have been associated with toxic doses and have been attributed to the metabolite norpethidine. Accumulation of norpethidine may occur if large doses of pethidine are repeated at short intervals (including for patient-controlled analgesia) and is especially likely when renal function is impaired.[1-13]

1. Kaiko RF, *et al.* Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 1983; **13:** 180–5.
2. Lieberman AN, Goldstein M. Reversible parkinsonism related to meperidine. *N Engl J Med* 1985; **312:** 509.
3. Mauro VF, *et al.* Meperidine-induced seizure in a patient without renal dysfunction or sickle cell anemia. *Clin Pharm* 1986; **5:** 837–9.
4. Morisy L, Platt D. Hazards of high-dose meperidine. *JAMA* 1986; **255:** 467–8.
5. Armstrong PJ, Bersten A. Normeperidine toxicity. *Anesth Analg* 1986; **65:** 536–8.
6. Eisendrath SJ, *et al.* Meperidine-induced delirium. *Am J Psychiatry* 1987; **144:** 1062–5.
7. Kyff JV, Rice TL. Meperidine-associated seizures in a child. *Clin Pharm* 1990; **9:** 337–8.
8. Pryle BJ, *et al.* Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; **304:** 1478–9.
9. Hagmeyer KO, *et al.* Meperidine-related seizures associated with patient-controlled analgesia pumps. *Ann Pharmacother* 1993; **27:** 29–32.
10. Stone PA, *et al.* Norpethidine toxicity and patient controlled analgesia. *Br J Anaesth* 1993; **71:** 738–40.
11. Marinella MA. Meperidine-induced generalized seizures with normal renal function. *South Med J* 1997; **90:** 556–8.
12. McHugh GJ. Norpethidine accumulation and generalized seizure during pethidine patient-controlled analgesia. *Anaesth Intensive Care* 1999; **27:** 289–91.
13. Hubbard GP, Wolfe KR. Meperidine misuse in a patient with sphincter of Oddi dysfunction. *Ann Pharmacother* 2003; **37:** 534–7.

Precautions

As for Opioid Analgesics in general, p.103.

Pethidine should also be given cautiously to patients with a history of convulsive disorders or supraventricular tachycardias.

Abuse. A synthetic analogue of pethidine, MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), manufactured illicitly for recreational use, achieved notoriety when it was accidentally contaminated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) leading to an epidemic of parkinsonism among intravenous drug abusers.[1] WHO has also identified another analogue, PEPAP (1-phenylethyl-4-phenyl-4-acetoxypiperidine) as being liable to abuse.[2]

1. Buchanan JF, Brown CR. 'Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; **3:** 1–17.
2. WHO. WHO expert committee on drug dependence: twenty-fourth report. *WHO Tech Rep Ser 761* 1988. Also available at: http://libdoc.who.int/trs/WHO_TRS_761.pdf (accessed 26/06/08)

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were given pethidine, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

The elderly. Pethidine had a slower elimination rate in elderly compared with young patients and a reduction in total daily dose might be necessary in elderly patients receiving repeated doses of pethidine.[1] Another study concluded that age-related changes in disposition were not sufficient to warrant modification of pethidine dosage regimens.[2]

1. Holmberg L, *et al.* Comparative disposition of pethidine and norpethidine in old and young patients. *Eur J Clin Pharmacol* 1982; **22:** 175–9.
2. Herman RJ, *et al.* Effects of age on meperidine disposition. *Clin Pharmacol Ther* 1985; **37:** 19–24.

Phaeochromocytoma. Pethidine provoked episodes of hypertension in a patient with phaeochromocytoma; the effect was suppressed by labetalol.[1] Like other histamine-releasing opioids, pethidine should be used with caution in such patients.

1. Lawrence CA. Pethidine-induced hypertension in phaeochromocytoma. *BMJ* 1978; **1:** 149–50.

Pregnancy and the neonate. Pethidine has been widely used for analgesia during labour. It rapidly crosses the placenta and like other opioid analgesics may cause respiratory depression in the neonate, although perhaps less so than morphine. Respiratory depression varies according to the timing and size of the maternal dose.

Fetal depression was not apparent when delivery occurred within 1 hour of giving pethidine, but was present in 6 of 24 infants delivered 1 to 3 hours after injection and in all of 5 infants delivered 3 to 6 hours after injection.[1] However, higher blood concentrations of pethidine were seen in infants delivered within 1 hour of an intramuscular dose of pethidine compared with those delivered 1 to 4 hours after injection. The role of pethidine metabolites was uncertain. It has also been reported[2] that depressed neonatal responses persisted for the first 2 days of life; depression was dose-related being greatest with the highest dose of pethidine (75 to 150 mg within 4 hours of delivery). Neonates appear able to metabolise pethidine, although probably more slowly than adults.[3] The amounts of pethidine and norpethidine excreted by the neonate increased significantly with the maternal dose-delivery interval for intervals of up to 5 hours and most of the placentally transferred pethidine should be excreted by the third day. Elimination of pethidine took up to 6 days in the neonates in another study.[4]

Further references on the transplacental transfer of pethidine can be found in Pregnancy under Pharmacokinetics, below.

Neither psychological nor physical effects were found in 5-year-olds born to mothers who had received pethidine during labour.[5] Neonatal behaviour does not appear to have been affected significantly by pethidine, although it has been acknowledged that the relationship between maternal analgesia in labour and subsequent infant behaviour is by no means simple.[6] The results of early studies that suggested an excess of cases of cancer in children whose mothers received pethidine during labour have been refuted by a later and larger study.[7]

1. Morrison JC, *et al.* Metabolites of meperidine related to fetal depression. *Am J Obstet Gynecol* 1973; **115:** 1132–7.
2. Hodgkinson R, *et al.* Double-blind comparison of the neurobehaviour of neonates following the administration of different doses of meperidine to the mother. *Can Anaesth Soc J* 1978; **25:** 405–11.
3. Hogg MIJ, *et al.* Urinary excretion and metabolism of pethidine and norpethidine in the newborn. *Br J Anaesth* 1977; **49:** 891–9.
4. Cooper LV, *et al.* Elimination of pethidine and bupivacaine in the newborn. *Arch Dis Child* 1977; **52:** 638–41.
5. Buck C. Drugs in pregnancy. *Can Med Assoc J* 1975; **112:** 1285.
6. Anonymous. To measure life. *Lancet* 1981; **ii:** 291–2.
7. Golding J, *et al.* Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992; **305:** 341–6.

Renal impairment. Caution is necessary when pethidine is given to patients with renal impairment; UK licensed product information recommends that it should be avoided in those with severe impairment, whereas US product information suggests to use reduced doses. Evidence of CNS excitation, including seizures and twitches, in 2 patients with renal insufficiency given multiple doses of pethidine was attributed to accumulation of the metabolite norpethidine; both patients had high norpethidine : pethidine plasma concentration ratios.[1]

See also under Pharmacokinetics, below.

1. Szeto HH, *et al.* Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure or cancer. *Ann Intern Med* 1977; **86:** 738–41.

Interactions

For interactions associated with opioid analgesics, see p.103.

Very severe reactions, including coma, severe respiratory depression, cyanosis, and hypotension have occurred in patients receiving MAOIs (including moclobemide and selegiline) and given pethidine. There are also reports of hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Pethidine should not be given to patients receiving MAOIs or within 14 days of their discontinuation. Use of pethidine with phenothiazines has produced severe hypotensive episodes and may prolong the respiratory depression due to pethidine.

Plasma concentrations of norpethidine are increased by ritonavir, with a resultant risk of toxicity; use together should be avoided (see also p.103).

Antibacterials. See MAOIs below for interactions between pethidine and *isoniazid* and *linezolid*.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of pethidine and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p.397. See also MAOIs, below.

Barbiturates. Opioid analgesics and barbiturates can be expected to have additive CNS depressant effects. Prolonged sedation with pethidine in the presence of *phenobarbital* has also been attributed to induction of *N*-demethylation of pethidine, resulting in the enhanced formation of the potentially neurotoxic metabolite norpethidine.[1,2]

1. Stambaugh JE, *et al.* A potentially toxic drug interaction between pethidine (meperidine) and phenobarbitone. *Lancet* 1977; **i:** 398–9.
2. Stambaugh JE, *et al.* The effect of phenobarbital on the metabolism of meperidine in normal volunteers. *J Clin Pharmacol* 1978; **18:** 482–90.

Histamine H_2-antagonists. See under Opioid Analgesics, p.103.

MAOIs. Some of the most serious interactions involving pethidine have been with non-selective MAOIs and have been manifest as enhanced depressant effects or hyperexcitability (see Interactions, above). However, a life-threatening interaction has also been reported between pethidine and *selegiline*, a selective monoamine oxidase type B inhibitor.[1] Also, symptoms suggestive of a mild serotonin syndrome developed in a 73-year-old woman taking *moclobemide* (a reversible inhibitor of monoamine oxidase type A), nortriptyline, and lithium after she was given pethidine intravenously.[2]

Use of the antibacterial *isoniazid* with pethidine led to a drop in blood pressure and lethargy in a 54-year-old man.[3] Serotonin syndrome developed in a 27-year-old man after the use of pethidine with *linezolid*;[4] symptoms resolved when pethidine was stopped. The authors of both studies attributed the interaction to the inhibitory action of isoniazid and linezolid on monoamine oxidase.

1. Zornberg GL, *et al.* Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; **337:** 246. Correction. *ibid.*; 440.
2. Gillman PK. Possible serotonin syndrome with moclobemide and pethidine. *Med J Aust* 1995; **162:** 554.
3. Gannon R, *et al.* Isoniazid, meperidine, and hypotension. *Ann Intern Med* 1983; **99:** 415. Correction. *ibid.*; 740.
4. Das PK, *et al.* Serotonin syndrome after concomitant treatment with linezolid and meperidine. *Clin Infect Dis* 2008; **46:** 264–5.

Phenothiazines. *Prochlorperazine* prolonged the respiratory depressant effect of pethidine in healthy subjects.[1] Enhanced CNS depression and hypotension were reported when healthy subjects were given *chlorpromazine* in addition to pethidine; there was evidence of increased *N*-demethylation of pethidine.[2]

1. Steen SN, Yates M. Effects of benzquinamide and prochlorperazine, separately and combined with meperidine, on the human respiratory center. *Clin Pharmacol Ther* 1972; **13:** 153.
2. Stambaugh JE, Wainer IW. Drug interaction: meperidine and chlorpromazine, a toxic combination. *J Clin Pharmacol* 1981; **21:** 140–6.

Phenytoin. The hepatic metabolism of pethidine appears to be enhanced by phenytoin; use together resulted in reduced half-life and bioavailability in healthy subjects; blood concentrations of norpethidine were increased.[1]

1. Pond SM, Kretschzmar KM. Effect of phenytoin on meperidine clearance and normeperidine formation. *Clin Pharmacol Ther* 1981; **30:** 680–6.

Pharmacokinetics

Pethidine hydrochloride is absorbed from the gastrointestinal tract, but only about 50% of the drug reaches the systemic circulation because of first-pass metabolism. Absorption after intramuscular injection is variable. Peak plasma concentrations have been reported 1 to 2 hours after oral doses. It is about 60 to 80% bound to plasma proteins.

Pethidine is metabolised in the liver by hydrolysis to pethidinic acid (meperidinic acid) or demethylation to norpethidine (normeperidine) and hydrolysis to norpethidinic acid (normeperidinic acid), followed by partial conjugation with glucuronic acid. Norpethidine is pharmacologically active and its accumulation may result in toxicity. Pethidine is reported to have a plasma elimination half-life of about 3 to 6 hours in healthy subjects; the metabolite norpethidine is eliminated more slowly, with a half-life reported to be up to about 20 hours. Both pethidine and norpethidine appear in the CSF. At the usual values of urinary pH or if the urine is alkaline, only a small amount of pethidine is excreted unchanged; urinary excretion of pethidine and norpethidine is enhanced by acidification of the urine. Pethidine crosses the placenta and is distributed into breast milk.

◊ Reviews.

1. Edwards DJ, *et al.* Clinical pharmacokinetics of pethidine: 1982. *Clin Pharmacokinet* 1982; **7:** 421–33.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.

Administration. The elimination half-life of pethidine was prolonged and plasma clearance decreased when given perioperatively compared with postoperatively.[1]

During labour the pharmacokinetics of pethidine may depend on how it is given. In a comparison of intramuscular injection at different sites, absorption of pethidine from the gluteus muscle was impaired and the deltoid muscle was preferred.[2]

No statistically significant differences were found in pharmacokinetic parameters for deltoid and gluteal intramuscular injections in elderly postoperative patients.[3] However, substantial interpatient variability was noted for both sites, and the authors suggested that more rapid and predictable routes such as intravenous injection may be more appropriate for postoperative use in the elderly.

1. Tamsen A, *et al.* Patient-controlled analgesic therapy, part 1: pharmacokinetics of pethidine in the per- and postoperative periods. *Clin Pharmacokinet* 1982; **7:** 149–63.
2. Lazebnik N, *et al.* Intravenous, deltoid, or gluteus administration of meperidine during labor? *Am J Obstet Gynecol* 1989; **160:** 1184–9.
3. Erstad BL, *et al.* Site-specific pharmacokinetics and pharmacodynamics of intramuscular meperidine in elderly postoperative patients. *Ann Pharmacother* 1997; **31:** 23–8.

Hepatic impairment. The terminal half-life of pethidine was prolonged to about 7 hours in cirrhotic patients compared with 3 hours in healthy subjects, which was attributed to impairment of the drug-metabolising activity of the liver.[1] Another study concluded that although impaired hepatic metabolism might confer relative protection from norpethidine toxicity in patients with cirrhosis, there might be an increased risk of cumulative toxicity because of slow elimination of the metabolite.[2]

1. Klotz U, *et al.* The effect of cirrhosis on the disposition and elimination of meperidine in man. *Clin Pharmacol Ther* 1974; **16:** 667–75.
2. Pond SM, *et al.* Presystemic metabolism of meperidine to normeperidine in normal and cirrhotic subjects. *Clin Pharmacol Ther* 1981; **30:** 183–8.

Pregnancy. Some references to the pharmacokinetics of pethidine during labour are given below.

1. Tomson G, *et al.* Maternal kinetics and transplacental passage of pethidine during labour. *Br J Clin Pharmacol* 1982; **13:** 653–9.
2. Kuhnert BR, *et al.* Disposition of meperidine and normeperidine following multiple doses during labor: I mother. *Am J Obstet Gynecol* 1985; **151:** 406–9.
3. Kuhnert BR, *et al.* Disposition of meperidine and normeperidine following multiple doses during labor: II fetus and neonate. *Am J Obstet Gynecol* 1985; **151:** 410–15.

Renal impairment. Plasma protein binding of pethidine was reported to be decreased in renal disease and ranged from 58.2% in healthy subjects to 31.8% in anuric patients.[1] The same workers also reported prolonged elimination of pethidine in patients with renal dysfunction.[2]

See also under Precautions, above.

1. Chan K, *et al.* Plasma protein binding of pethidine in patients with renal disease. *J Pharm Pharmacol* 1983; **35:** 94P.
2. Chan K, *et al.* Pharmacokinetics of low-dose intravenous pethidine in patients with renal dysfunction. *J Clin Pharmacol* 1987; **27:** 516–22.

Uses and Administration

Pethidine, a phenylpiperidine derivative, is a synthetic opioid analgesic (p.104) that acts mainly as a μ opioid agonist. Pethidine is used for the relief of most types of moderate to severe acute pain including the pain of labour. It is more lipid soluble than morphine and has a less potent and shorter lasting analgesic effect; analgesia usually lasts for 2 to 4 hours. Its short duration of action and accumulation of its potentially neurotoxic metabolite norpethidine on repeated dosage make it unsuitable for the management of chronic pain. Pethidine has a weaker action on smooth muscle than morphine and its lower potential to increase biliary pressure may make it a more suitable opioid analgesic for pain associated with biliary colic and pancreatitis (but see Biliary-tract Disorders, p.103). It is also used for premedication and as an adjunct to anaesthesia. It has been given with phenothiazines such as promethazine to achieve basal narcosis. Pethidine has little effect on cough or on diarrhoea.

For the relief of **pain**, pethidine hydrochloride is given in oral doses of 50 to 150 mg every 4 hours if necessary. It may also be given by intramuscular or subcutaneous injection in doses of 25 to 100 mg and by slow intravenous injection in doses of 25 to 50 mg repeated after 4 hours. For *postoperative* pain, the *BNF* suggests that the subcutaneous or intramuscular doses may be given every 2 to 3 hours if necessary.

In *obstetric analgesia* 50 to 100 mg may be given by intramuscular or subcutaneous injection as soon as contractions occur at regular intervals. This dose may be repeated after 1 to 3 hours if necessary up to a maximum of 400 mg in 24 hours.

For **premedication** 25 to 100 mg may be given intramuscularly about 1 hour before surgery. It may also be given subcutaneously in similar doses. As an **adjunct to anaesthesia** 10 to 25 mg may be given by slow intravenous injection.

For details of doses in children, see below.

Administration. In addition to the conventional routes pethidine has been given epidurally,[1-4] intraperitoneally,[5,6] and intrathecally.[7-9] It has also been given by various routes as a patient-controlled system.[10-13] However, some consider that the use of pethidine should be avoided for patient-controlled analgesia because of the increased risk of norpethidine-induced seizures[14] (see also Incidence of Adverse Effects and Effects on the Nervous System, above).

1. Perriss BW. Epidural pethidine in labour: a study of dose requirements. *Anaesthesia* 1980; **35:** 380–2.
2. Husemeyer RP, *et al.* A study of pethidine kinetics and analgesia in women in labour following intravenous, intramuscular and epidural administration. *Br J Clin Pharmacol* 1982; **13:** 171–6.
3. Perriss BW, *et al.* Analgesia following extradural and im pethidine in post-caesarean section patients. *Br J Anaesth* 1990; **64:** 355–7.
4. Blythe JG, *et al.* Continuous postoperative epidural analgesia for gynecologic oncology patients. *Gynecol Oncol* 1990; **37:** 307–10.
5. Colbert ST, *et al.* An assessment of the value of intraperitoneal meperidine for analgesia postlaparoscopic tubal ligation. *Anesth Analg* 2000; **91:** 667–70.
6. O'Hanlon DM, *et al.* Intraperitoneal pethidine versus intramuscular pethidine for the relief of pain after laparoscopic cholecystectomy: randomized trial. *World J Surg* 2002; **26:** 1432–6.
7. Acalovschi I, *et al.* Saddle block with pethidine for perineal operations. *Br J Anaesth* 1986; **58:** 1012–16.
8. Yu SC, *et al.* Addition of meperidine to bupivacaine for spinal anaesthesia for caesarean section. *Br J Anaesth* 2002; **88:** 379–83.
9. Vranken JH, *et al.* Plasma concentrations of meperidine and normeperidine following continuous intrathecal meperidine in patients with neuropathic cancer pain. *Acta Anaesthesiol Scand* 2005; **49:** 665–70.
10. Striebel HW, *et al.* Patient-controlled intranasal analgesia (PCINA) for the management of postoperative pain: a pilot study. *J Clin Anesth* 1996; **8:** 4–8.
11. Kee N, *et al.* Comparison of patient-controlled epidural analgesia with patient-controlled intravenous analgesia using pethidine or fentanyl. *Anaesth Intensive Care* 1997; **25:** 126–32.
12. Sharma SK, *et al.* Cesarean delivery: a randomized trial of epidural versus patient-controlled meperidine analgesia during labor. *Anesthesiology* 1997; **87:** 487–94.
13. Chen PP, *et al.* Patient-controlled pethidine after major upper abdominal surgery: comparison of the epidural and intravenous routes. *Anaesthesia* 2001; **56:** 1106–12.
14. Hagmeyer KO, *et al.* Meperidine-related seizures associated with patient-controlled analgesia pumps. *Ann Pharmacother* 1993; **27:** 29–32.

Administration in children. Pethidine is used for the relief of moderate to severe acute pain and for premedication in children.

For the relief of **pain**, the *BNFC* suggests that children aged 2 months to 12 years may be given pethidine hydrochloride 0.5 to 2 mg/kg orally or by subcutaneous or intramuscular injection every 4 to 6 hours if necessary; older children up to 18 years of age may be given 50 to 100 mg orally, or 25 to 100 mg intramuscularly or subcutaneously, every 4 to 6 hours if necessary. Injection solutions may be given orally if needed, to achieve a suitable dose. Pethidine may also be given by intravenous injection in doses of 0.5 to 1 mg/kg to neonates and children up to 12 years of age, repeated every 10 to 12 hours if necessary in those up to 2 months of age and every 4 to 6 hours if necessary in older children; those aged 12 to 18 years may be given the usual adult intravenous dose (see above) repeated every 4 to 6 hours if necessary. An intravenous injection of 1 mg/kg as a loading dose followed by continuous intravenous infusion of 100 to 400 micrograms/kg per hour adjusted according to response may also be given to those aged 1 month and over.

For **premedication**, UK licensed product information recommends that 1 to 2 mg/kg is given intramuscularly about 1 hour before surgery.

See also Lytic Cocktails, below.

Eclampsia and pre-eclampsia. See Lytic Cocktails under Sedation, below.

Pain. Pethidine produces prompt but short-lasting analgesia, and may be preferred to morphine when rapid control of acute pain is required. It has been widely used in obstetrics to control the pain of labour (although the *BNF* notes that morphine or other opioids are often preferred for obstetric pain), and for postoperative pain relief after caesarean section or other surgical procedures.

In a study of patients with intractable pain the minimum effective analgesic blood concentration ranged from 100 to 820 nanograms/mL (median 250 nanograms/mL) in 15 of 16; the remaining patient failed to obtain analgesia with pethidine. Additional measures were considered necessary[1] if the minimum effective concentration exceeded 400 nanograms/mL.

Pethidine has traditionally been given by intermittent intramuscular injection in the treatment of acute pain, but inconsistent pain relief can be expected because of fluctuating blood-pethidine concentrations;[2] continuous intravenous infusion might be more effective for acute pain. For reference to use by other routes see Administration, above.

1. Mather LE, Glynn CJ. The minimum effective analgesic blood concentration of pethidine in patients with intractable pain. *Br J Clin Pharmacol* 1982; **14:** 385–90.
2. Edwards DJ, *et al.* Clinical pharmacokinetics of pethidine: 1982. *Clin Pharmacokinet* 1982; **7:** 421–33.

SICKLE-CELL CRISIS. Concern has been expressed over the continued use of pethidine for analgesia in painful crises in sickle-cell disease. Control of pain may be inadequate and doses commonly used to manage crises may lead to accumulation of the neuroexcitatory metabolite of pethidine and precipitate seizures.[1,2] See also Effects on the Nervous System, above.

1. Pryle BJ, *et al.* Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; **304:** 1478–9.
2. Harrison JFM, *et al.* Pethidine in sickle cell crisis. *BMJ* 1992; **305:** 182.

Sedation. Some references to the use of pethidine for endoscopy are given below.

1. Bahal-O'Mara N, *et al.* Sedation with meperidine and midazolam in pediatric patients undergoing endoscopy. *Eur J Clin Pharmacol* 1994; **47:** 319–23.
2. Diab FH, *et al.* Efficacy and safety of combined meperidine and midazolam for EGD sedation compared with midazolam alone. *Am J Gastroenterol* 1996; **91:** 1120–5.
3. Laluna L, *et al.* The comparison of midazolam and topical lidocaine spray versus the combination of midazolam, meperidine, and topical lidocaine spray to sedate patients for upper endoscopy. *Gastrointest Endosc* 2001; **53:** 289–93.

LYTIC COCKTAILS. Lytic cocktails consisting of chlorpromazine, pethidine, and/or promethazine have been given intravenously in some countries for the management of pre-eclampsia and imminent eclampsia. However, the use of phenothiazines is generally not recommended late in pregnancy, and other treatments are preferred for hypertension (see Hypertension in Pregnancy, under Hypertension, p.1171); the management of eclampsia, which is the convulsive phase, is discussed on p.470.

Lytic cocktails have also been used for sedation and analgesia in children, by intramuscular or occasionally intravenous injection. However, there is a high rate of therapeutic failure as well as serious adverse effects with such combinations, and the American Academy of Pediatrics[1] had recommended that alternative sedatives and analgesics should be considered. Lytic cocktails are not the most appropriate means of sedation for short procedures since patients must be monitored for about 1 hour before the procedure while the drugs take effect, and for even longer during the recovery period.[2]

1. American Academy of Pediatrics Committee on Drugs. Reappraisal of Lytic cocktail/Demerol, Phenergan, and Thorazine (DPT) for the sedation of children. *Pediatrics* 1995; **95:** 598–602.
2. Barst SM, *et al.* A comparison of propofol and Demerol-Phenergan-Thorazine for brief, minor, painful procedures in a pediatric hematology-oncology clinic. *Int J Pediatr Hematol/Oncol* 1995; **1:** 587–91.

Shivering. For reference to the use of pethidine in the management of shivering associated with anaesthesia, see under Adverse Effects of General Anaesthetics, p.1779. Pethidine has also been used to treat amphotericin B-induced shaking chills.[1]

1. Burks LC, *et al.* Meperidine for the treatment of shaking chills and fever. *Arch Intern Med* 1980; **140:** 483–4.

Preparations

BP 2008: Pethidine Injection; Pethidine Tablets;
USP 31: Meperidine Hydrochloride Injection; Meperidine Hydrochloride Syrup; Meperidine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cluyer; Meperol; ***Austria:*** Alodan; ***Belg.:*** Dolantine; ***Braz.:*** Dolantina; Dolosal; Dornot; ***Canad.:*** Demerol; ***Chile:*** Demerol†; ***Cz.:*** Dolsin; ***Ger.:*** Dolantin; ***Hung.:*** Dolargan; ***Israel:*** Dolestine; ***Philipp.:*** Demerol; ***Pol.:*** Dolargan; Dolcontral; ***Spain:*** Dolantina; ***Turk.:*** Aldolan; ***USA:*** Demerol; ***Venez.:*** Demerol†; Dispadol†.

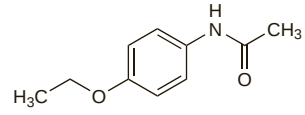
Multi-ingredient: ***Austral.:*** Marcain with Pethidine†; ***UK:*** Pamergan P100.

Phenacetin *(rINN)*

Aceto-*p*-phenetidide; Acetophenetidin; Acetylphenetidin; Fenacetin; Fenacetina; Fenasetiini; Paracetophenetidin; Phénacétine; Phenacetinum. *p*-Acetophenetidide; 4′-Ethoxyacetanilide; *N*-(4-Ethoxyphenyl)acetamide.

Фенацетин

$C_{10}H_{13}NO_2$ = 179.2.
CAS — 62-44-2.
ATC — N02BE03.
ATC Vet — QN02BE03.



Adverse Effects and Precautions

Phenacetin may cause methaemoglobinaemia, sulfhaemoglobinaemia, and haemolytic anaemia.