parecoxib after coronary artery bypass graft surgery has been associated with an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, and stroke.[1] When compared with patients in the placebo group, the risk of such effects was almost 4 times greater in those given intravenous parecoxib for 3 days followed by oral valdecoxib for the next 7 days.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p.34.

1. Nussmeier NA, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; **352:** 1081–91.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as parecoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information reports that upper gastrointestinal perforation, ulceration, and bleeds have occurred with parecoxib treatment and therefore it should be used with caution in patients with a history of such events.

Effects on the kidneys. Increasing evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as parecoxib suggests that such NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p.98).

Up to June 2004, the Australian Adverse Drug Reactions Advisory Committee had received 20 reports of adverse reactions associated with parecoxib.[1] Of these, 13 mentioned renal impairment with raised creatinine levels and/or oliguria; acute renal failure was reported in 4 of the 13 cases and multiple doses of parecoxib had been given in 6 cases. (In Australia, parecoxib was approved for single-dose use only because of safety concerns about multiple doses.)

1. Adverse Drug Reactions Advisory Committee (ADRAC). Parecoxib—one shot only. *Aust Adverse Drug React Bull* 2004; **23:** 10–11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0406.pdf (accessed 08/11/07)

Interactions

For interactions associated with NSAIDs, see p.99.

Parecoxib is rapidly hydrolysed to its active metabolite, valdecoxib; the metabolism of valdecoxib is mainly mediated by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. Consequently, caution is recommended when using parecoxib with inhibitors of such isoenzymes. Licensed product information advises that the dose of parecoxib should be reduced if given with fluconazole, a CYP2C9 inhibitor; however, dose adjustment of parecoxib is not generally necessary when giving with ketoconazole, a CYP3A4 inhibitor, despite increased plasma concentrations of valdecoxib. The effects of enzyme inducers such as carbamazepine, dexamethasone, phenytoin, and rifampicin have not been studied; theoretically, the metabolism of valdecoxib may be increased by these drugs.

Valdecoxib has been noted to increase the plasma levels of dextromethorphan, a CYP2D6 substrate, and therefore caution is recommended when giving parecoxib with drugs that are metabolised via CYP2D6 and that have a narrow therapeutic index. Such drugs include flecainide, metoprolol, and propafenone. Valdecoxib may also affect the plasma levels of drugs that are metabolised via CYP2C19: an increase in the plasma levels of omeprazole was seen in patients using valdecoxib.

Pharmacokinetics

On intravenous or intramuscular injection, parecoxib is rapidly hydrolysed in the liver to its active metabolite, valdecoxib, and propionic acid; the plasma half-life of parecoxib is about 22 minutes. Plasma protein binding is about 98%. Valdecoxib is also extensively metabolised in the liver; pathways involved include those via the cytochrome P450 isoenzymes CYP3A4 and CYP2C9, and glucuronidation. Another active metabolite has been identified but it is not considered to contribute a significant clinical effect. Excretion is mainly via the urine with about 70% of a dose appearing as inactive metabolites. Less than 5% of a dose appears as unchanged valdecoxib in the urine. No unchanged parecoxib is found in the urine with only trace amounts in the faeces. The elimination half-life of valdecoxib is about 8 hours.

◊ References.

1. Karim A, *et al.* A pharmacokinetic study of intramuscular (IM) parecoxib sodium in normal subjects. *J Clin Pharmacol* 2001; **41:** 1111–19.

Uses and Administration

Parecoxib is an NSAID (p.99) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is a prodrug of valdecoxib (p.132) and is used for the short-term treatment of postoperative pain in patients aged 18 years and over. Parecoxib is given as the sodium salt although doses are expressed as the base; 42.4 mg of parecoxib sodium is equivalent to about 40 mg of parecoxib. The recommended dose is 40 mg given by intravenous or slow intramuscular injection; this may be followed by 20 or 40 mg every 6 to 12 hours as required. The maximum daily dose is 80 mg. Elderly patients weighing less than 50 kg should begin treatment with half the usual dose, repeated to a maximum of 40 mg daily. Doses may need to be reduced in hepatic impairment, see below.

Parecoxib should be reconstituted with either sodium chloride 0.9%, glucose 5%, or sodium chloride 0.45% with glucose 5%; no other solvents are recommended in licensed product information. In addition the reconstituted solution may only be injected into intravenous lines delivering sodium chloride 0.9%, glucose 5%, sodium chloride 0.45% with glucose 5%, or lactated Ringer's solution. (See above for details on incompatibilities.)

◊ References.

1. Cheer SM, Goa KL. Parecoxib (parecoxib sodium). *Drugs* 2001; **61:** 1133–41.
2. Amabile CM, Spencer AP. Parecoxib for parenteral analgesia in postsurgical patients. *Ann Pharmacother* 2004; **38:** 882–6.
3. Mehlisch DR, *et al.* The analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. *J Am Dent Assoc* 2004; **135:** 1578–90.
4. Malan TP, *et al.* The cyclooxygenase-2-specific inhibitor parecoxib sodium is as effective as 12 mg of morphine administered intramuscularly for treating pain after gynecologic laparotomy surgery. *Anesth Analg* 2005; **100:** 454–60.
5. Beaussier M, *et al.* A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients. *Anesth Analg* 2005; **100:** 1309–15.
6. Sindhvananda W, *et al.* Parecoxib versus tramadol for post-appendectomy pain. *J Med Assoc Thai* 2005; **88:** 1557–62.
7. Gajraj NM. COX-2 inhibitors celecoxib and parecoxib: valuable options for postoperative pain management. *Curr Top Med Chem* 2007; **7:** 235–49.

Administration in hepatic impairment. Licensed product information in the UK states that no dosage adjustment is generally necessary for parecoxib in patients with *mild* hepatic impairment (Child-Pugh score 5 or 6). For those with *moderate* impairment (Child-Pugh score 7 to 9) parecoxib should be given at half the usual dose (see above), repeated to a maximum dose of 40 mg daily. Use in patients with *severe* impairment (Child-Pugh score 10 and over) is not recommended as there is no clinical experience in such patients.

Preparations

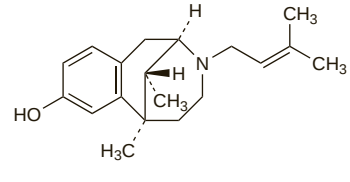
Proprietary Preparations (details are given in Part 3)
Austral.: Dynastat; ***Austria:*** Dynastat; ***Belg.:*** Dynastat; ***Chile:*** Pro-Bextra; ***Cz.:*** Dynastat; ***Denm.:*** Dynastat; ***Fin.:*** Dynastat; ***Fr.:*** Dynastat; ***Ger.:*** Dynastat; ***Gr.:*** Dynastat; ***Hong Kong:*** Dynastat; ***Hung.:*** Dynastat; ***India:*** Bioval-P†; Valcox; Valdix; Valdone-P; Valus-P†; Vorth-P; ***Indon.:*** Dynastat; ***Irl.:*** Dynastat; ***Ital.:*** Dynastat; ***Mex.:*** Dynastat; ***Neth.:*** Dynastat; ***Norw.:*** Dynastat; ***NZ:*** Dynastat; ***Port.:*** Dynastat; ***Rus.:*** Dynastat (Династат); ***S.Afr.:*** Rayzon; ***Spain:*** Dynastat; ***Swed.:*** Dynastat; ***Switz.:*** Bextra†; ***Thai.:*** Dynastat; ***UK:*** Dynastat; ***Venez.:*** Dynastat†.

Pentazocine *(BAN, USAN, rINN)* ⊗

NIH-7958; NSC-107430; Pentatsosiini; Pentazocin; Pentazocina; Pentazocinas; Pentazocinum; Win-20228. (2*R**,6*R**,11*R**)-1,2,-3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methylbut-2-enyl)-2,6-methano-3-benzazocin-8-ol.

Пентазоцин

$C_{19}H_{27}NO$ = 285.4.
CAS — 359-83-1.
ATC — N02AD01.
ATC Vet — QN02AD01.



Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Pentazocine). A white or almost white powder. It shows polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. Protect from light.
USP 31 (Pentazocine). A white or very pale, tan-coloured powder. Practically insoluble in water; soluble 1 in 11 of alcohol, 1 in 2 of chloroform, and 1 in 42 of ether; soluble in acetone; sparingly soluble in ethyl acetate and in benzene. Store in airtight containers. Protect from light.

Pentazocine Hydrochloride *(BANM, USAN, rINNM)* ⊗

Hidrocloruro de pentazocina; Pentatsosiinihydrokloridi; Pentazocine, chlorhydrate de; Pentazocin-hidroklorid; Pentazocin-hydrochlorid; Pentazocinhydroklorid; Pentazocini hydrochloridum; Pentazocino hidrochloridas.

Пентазоцина Гидрохлорид

$C_{19}H_{27}NO,HCl$ = 321.9.
CAS — 2276-52-0; 64024-15-3.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Pentazocine Hydrochloride). A white or almost white powder. It shows polymorphism. Sparingly soluble in water and in dichloromethane; soluble in alcohol. A 1% solution in water has a pH of 4.0 to 6.0. Protect from light.
USP 31 (Pentazocine Hydrochloride). A white crystalline powder. It exhibits polymorphism, one form melting at about 254° and the other at about 218°. Soluble 1 in 30 of water, 1 in 20 of alcohol, and 1 in 4 of chloroform; very slightly soluble in acetone and in ether; practically insoluble in benzene. Store in airtight containers. Protect from light.

Pentazocine Lactate *(BANM, USAN, rINNM)* ⊗

Lactato de pentazocina; Pentatsosiinilaktaatti; Pentazocine, lactate de; Pentazocini lactas; Pentazocinlaktat; Pentazocin-laktát; Pentazocino laktatas.

Пентазоцина Лактат

$C_{19}H_{27}NO,C_3H_6O_3$ = 375.5.
CAS — 17146-95-1.

Pharmacopoeias. In *Eur.* (see p.vii). *US* includes only Pentazocine Lactate Injection.
Ph. Eur. 6.2 (Pentazocine Lactate). A white or almost white powder. Sparingly soluble in water; slightly soluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.5 to 6.5. Protect from light.
BP 2008 (Pentazocine Lactate). A white to pale cream powder. Sparingly soluble in water, in alcohol, and in chloroform; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.5 to 6.5.

Incompatibility. Commercial injections of pentazocine lactate are reported to be incompatible with soluble barbiturates and other alkaline substances including sodium bicarbonate. Diazepam and chlordiazepoxide have also been reported to be incompatible, as have glycopyrronium bromide[1] and nafcillin sodium.[2]

1. Ingallinera TS, *et al.* Compatibility of glycopyrrolate injection with commonly used infusion solutions and additives. *Am J Hosp Pharm* 1979; **36:** 508–10.
2. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462, 464.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Pentazocine is subject to abuse.

◊ Pentazocine does produce physical dependence, but withdrawal symptoms are substantially less severe than with morphine. It does not typically produce drug-seeking behaviour of the same degree or intensity as morphine or other prototypic μ agonists, nor does it substitute for morphine in dependent subjects.[1] Pentazocine injection has been abused,[2] but street abuse, especially in the USA, has more often involved the intravenous use of crushed tablets of pentazocine and tripelennamine ('T's and Blues').[3-5] A decreased incidence of pentazocine abuse in the USA appeared to coincide with the introduction of oral tablets incorporating naloxone,[1] the rationale being that naloxone antagonises the effect of pentazocine if illicitly injected, but has no effect when taken orally. Some continued to abuse the new pentazocine/naloxone formulation;[6] intravenous abuse in one woman, who was unaware of the reformulation, resulted in opioid withdrawal symptoms and severe hypertension.[7] A 1989 report from the WHO committee[1] rated the likelihood of abuse of pentazocine as moderate, based on its pharmacological profile, dependence potential, and actual abuse. The committee considered that it should continue to be scheduled as a psychotropic substance rather than a narcotic drug.

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 27/06/08)
2. Hunter R, Ingram IM. Intravenous pentazocine abuse by a nurse. *Lancet* 1983; **ii:** 227.
3. Poklis A, Whyatt PL. Current trends in the abuse of pentazocine and tripelennamine: the metropolitan St. Louis experience. *J Forensic Sci* 1980; **25:** 72–8.
4. Senay EC. Clinical experience with T's and B's. *Drug Alcohol Depend* 1985; **14:** 305–11.
5. Jackson C, *et al.* Fatal intracranial hemorrhage associated with phenylpropanolamine, pentazocine, and tripelennamine overdose. *J Emerg Med* 1985; **3:** 127–32.
6. Reed DA, Schnoll SH. Abuse of pentazocine-naloxone combination. *JAMA* 1986; **256:** 2562–4.
7. Reinhart S, Barrett SM. An acute hypertensive response after intravenous use of a new pentazocine formulation. *Ann Emerg Med* 1985; **14:** 591–3.

Adverse Effects

As for Opioid Analgesics in general, p.102.

Pentazocine may cause hallucinations and other psychotomimetic effects such as nightmares and thought disturbances. High doses may result in hypertension and tachycardia; increased aortic and pulmonary artery pressure with an increase in cardiac work has followed intravenous use in patients with myocardial infarction. Like morphine it causes respiratory depression, but pentazocine is said to have a 'ceiling' effect and the depth of respiratory depression does not increase proportionately with higher doses.

Rare adverse effects with pentazocine have included agranulocytosis and serious skin reactions such as erythema multiforme and toxic epidermal necrolysis.

Pentazocine injections may be painful. Local tissue damage may occur at injection sites particularly after subcutaneous injection or multiple doses; there have been reports of muscle fibrosis associated with intramuscular injections.

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.

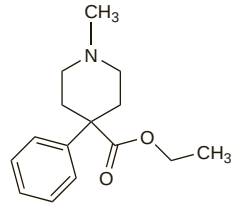
Петидина Гидрохлорид

$C_{15}H_{21}NO_2$,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