

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

- Cheer SM, Goa KL. Parecoxib (parecoxib sodium). *Drugs* 2001; **61**: 1133–41.
- Amabile CM, Spencer AP. Parecoxib for parenteral analgesia in postoperative patients. *Ann Pharmacother* 2004; **38**: 882–6.
- Mehlich DR, et al. The analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. *J Am Dent Assoc* 2004; **135**: 1578–90.
- 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.
- Beaussier M, et al. A randomized, double-blind comparison between parecoxib sodium and propacetamol for parental post-operative analgesia after inguinal hernia repair in adult patients. *Anesth Analg* 2005; **100**: 1309–15.
- Sindhvananda W, et al. Parecoxib versus tramadol for post-appendectomy pain. *J Med Assoc Thai* 2005; **88**: 1557–62.
- 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-Bexdra; **Cz.:** Dynastat; **Denm.:** Dynastat; **Fin.:** Dynastat; **Fr.:** Dynastat; **Ger.:** Dynastat; **Gr.:** Dynastat; **Hong Kong:** Dynastat; **Hung.:** Dynastat; **India:** Bio-val-P†; Valco; Validox; Valdione-F; Valus-P†; **North-P.:** Dynastat; **Irl.:** Dynastat; **Ital.:** Dynastat; **Mex.:** Dynastat; **Neth.:** Dynastat; **Norw.:** Dynastat; **NZ:** Dynastat; **Port.:** Dynastat; **Rus.:** Dynastat (Династат); **S.Afr.:** Rayzori; **Spain:** Dynastat; **Swed.:** Dynastat; **Switz.:** Bextra†; **Thai:** Dynastat; **UK:** Dynastat; **Venez.:** Dynastat†.

Pentazocine (BAN, USAN, rINN) ⓧ

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

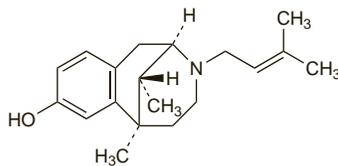
Пентазоцин

C₁₉H₂₇NO = 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, rINN) ⓧ

Hidrocloruro de pentazocina; Pentatosiinihidrokloridi; Pentazocine, chlorhydrate de; Pentazocin-hidrokloridi; Pentazocin-hydrochlorid; Pentazocinhydrochlorid; Pentazocini hydrochloridum; Pentazocino hydrochloridas.

Пентазоцина Гидрохлорид

C₁₉H₂₇NO.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, rINN) ⓧ

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

Пентазоцина Лактат

C₁₉H₂₇NO.C₃H₅O₃ = 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 chloridazepoxide have also been reported to be incompatible, as have glycopyrronium bromide¹ and nafcillin sodium.²

- Ingallinera TS, et al. Compatibility of glycopyrrolate injection with commonly used infusion solutions and additives. *Am J Hosp Pharm* 1979; **36**: 508–10.
- 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 tripeleminamine ('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 committee¹ 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.

- 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)
- Hunter R, Ingram IM. Intravenous pentazocine abuse by a nurse. *Lancet* 1983; **ii**: 227.
- Poklis A, Whyatt PL. Current trends in the abuse of pentazocine and tripeleminamine: the metropolitan St. Louis experience. *J Forensic Sci* 1980; **25**: 72–8.
- Senay EC. Clinical experience with T's and B's. *Drug Alcohol Depend* 1985; **14**: 305–11.
- Jackson C, et al. Fatal intracranial hemorrhage associated with phenylpropanolamine, pentazocine, and tripeleminamine overdose. *J Emerg Med* 1985; **3**: 127–32.
- Reed DA, Schnoll SH. Abuse of pentazocine-naloxone combination. *JAMA* 1986; **256**: 2562–4.
- 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.