Pharmacokinetics. References.

1. Debord P, *et al.* Influence of renal function on the pharmacokinetics of diacerein after a single oral dose. *Eur J Drug Metab Pharmacokinet* 1994; **19:** 13–19.
2. Nicolas P, *et al.* Clinical pharmacokinetics of diacerein. *Clin Pharmacokinet* 1998; **35:** 347–59.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Artrodar; Artroglobina†; ***Austria:*** Artrolyt; Verboril; ***Braz.:*** Artrodar; ***Chile:*** Artrizona; ***Cz.:*** Artrodar; ***Fr.:*** Art; Zondar; ***Gr.:*** Arthrofar; Arthrorein; Deserein; Diacer; Diaceril; Idealite; Inflabion; Myobloc; Ostirein; Pentacrin; Reumanisal; Verboril; ***Indon.:*** Artrodar; ***Israel:*** Art; Diatrim; ***Ital.:*** Fisiodar; ***Malaysia:*** Artrodar; ***Port.:*** Artrolyt; Cartivix; ***Spain:*** Galaxdar; Glizolan; ***Thai.:*** Artrodar; ***Venez.:*** Artrodar.

Multi-ingredient: *Mex.:* Dolocartigen.

Diamorphine Hydrochloride

(BANM) ⊗

Diacetilmorfina, hidrocloruro de; Diacetylmorphine Hydrochloride; Heroin Hydrochloride; Hidrocloruro de diamorfina; Hidrocloruro de heroína. 4,5-Epoxy-17-methylmorphinan-3,6-diyl diacetate hydrochloride monohydrate.

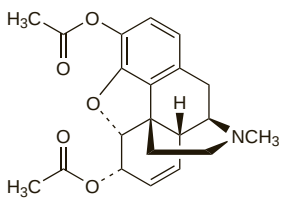
Героина Гидрохлорид; Диаморфина Гидрохлорид

$C_{21}H_{23}NO_5,HCl,H_2O$ = 423.9.

CAS — 561-27-3 (diamorphine); 1502-95-0 (diamorphine hydrochloride).

ATC — N02AA09.

ATC Vet — QN02AA09.



(diamorphine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of diamorphine:
57 Chevy; A Sidani; AIP; Al Capone; Amelia; Antifreeze; Aries; Aunt Hazel; Auntie Hazel; Aunty Hazel; Bacalhau; Bad bundle; Bad seed; Ball; Ballot; Bart Simpson; Batman; Beast; Big Bad Boy; Big bag; Big doodig; Big H; Big Harry; Bin laden; Bindle; Birdie powder; Black; Black Dragon; Black eagle; Black Girl; Black pearl; Black stuff; Black tar; Black tootsie roll; Blanche; Blanco; Blast; Bleue; Block busters; Blow; Blows; Blue bag; Blue hero; Blue star; Bobby Brown; Bomb; Bomba; Bombe; Bombido; Bombita; Bombitas; Bombs away; Bone; Bonita; Boy; Bozo; Brad; Brain damage; Brea; Brick gum; Broja; Brother; Brown; Brown crystal; Brown rhine; Brown sugar; Brown tape; Bugger; Bull dog; Bundle; Burra; Butu; Caballo; Caca; Calbo; Capital H; Caps; Captain Jack; Carga; Carne; Cavalo; Chang; Chapopote; Charley; Chatarra; Cheese; Cheva; Cheval; Chi; Chiba; Chick; Chicken; Chicle; Chieva; China cat; China white; Chinche; Chinese H; Chinese red; Chinese Rocks; Chinoise; Chip; Chiva; Chocofan; Choco-fan; Chueva; Chunks; Climax; Cocofan; Coffee; Cotics; Cotton Candy; Courage pills; Crank; Crap; Crop; Crown crap; Cura; Dead on arrival; Dead president; Deuce; Diesel; Diggidy; Dirt; DOA; Dog food; Dogee; Dogie; Doogie; Doojee; Dookey Rocks; Dooley; Doosey; Dope; Downtown; Dr. Feelgood; Dragon; Dreck; DT; Dugee; Dugie; Duji; Dujra; Dujre; Dust; Dyno; Dyno-pure; Eggs; Eight; Eighth; Elephant; Estuffa; Fachiva; Ferry dust; Fix; Flea powder; Foil; Foo foo stuff; Foolish powder; Furra; Galloping horse; Gallup; Gamot; Garbage; Gato; Gear; George; George smack; Ghost; Girl; Glacines; Glass; Goat; Gold; Golden Brown; Golden girl; Golpe; Goma; Good; Good H; Good Horse; Good and plenty; Goods; Goop; Grape Jolly Rancher; Gravy; Grey shields; H; H22; H-bomb; H Caps; Hache; Hair; Hairpiece; Hairy; Hammer; Hard candy; Hard stuff; Harriet Tubman; Harry; Harry Jones; Hayron; Hazel; Heaven; Heaven dust; Heavy stuff; Helen; Hell dust; Henry; Hera; Hero; Hero of the underworld; Heroa; Heroina; Heron; Herone; Hessle; Him; Holy terror; Hombre; Homebake; Homicide; Hong-yen; Hood; Hop; Horning; Horse; Horsebite; Hot dope; Hot heroin; HRN; Isda; Jack; Jee gee; Jerry Springer; Jesus; Jive; Jive doo jee; Joharito; Jojee; Jones; Joy; Joy dust; Joy flakes; Joy powder; Judas; Junco; Junk; Kabayo; Kaka Water; Karachi; Kermit the Frog; La Buena; La Chiva; Lady H; Layne; LBJ; Lemonade; Life saver; Little bomb; Man; Manteca; Matsakow; Mayo; Mexican Black Tar; Mexican brown; Mexican Dirt; Mexican horse; Mexican mud; Mister Brownstone; Mojo; Money talks; Monkey; Montego; Morse Code Features; Morotgara; Mortal combat; Mother pearl; Mr. Brownstone; Mud; Murotugora; Muzzle; Nanoo; Nice and easy; Nickel bag; Nickel deck; Nixon; Noddy Brown; Noise; Nose; Nose drops; Number 3; Number 4; Number 8; Nurse; Oddy Noddy; Of course my horse; Ogoy; Oil; Old garbage; Old navy; Old Steve; One way; Orange line; Outfit; Pack; Pakistanaise; Pako; Pangonadalot; Parachute; P-dope; Peg; Pepper; Perfect high; P-funk; Pluto; Po; Poeira; Poison; Polvo; Poppy; Poudre; Powder; Predator; Primo; Produto; Pulborn; Pure; Quill; Race horse Charlie; Racehorse Charlie; Ragweed; Rain; Rambo; Rane; Raw; Raw fusion; Raw hide; Raw Opportunities; Ready rock; Red chicken; Red devil; Red eagle; Red rock; Red rum; Reindeer dust; Rhine; Ring of Turd; Rob Flaherty; Rock; Rocks; Rush hour; Sack; Salt; Scag; Scat; Scate; Schmack; Schmeck; Schmeek; Scott; Scramble; Second to none; Shit; Shmeck; Shmeek; Shmek; Shoot; Silk; Skag; Skid; Skunk; Slack-dad-eat-your-heart-out; Slam; Sleeper; Sleepers; Slime; Slow; Sludge; Smack; Snotty; Snow; Spider; Spider blue; Stuff; Stunna; Sugar; Suicide; Sweet dreams; Sweet Jesus; Sweet stuff; Synthe; Tang; Tar; Taste; Tecata; Tecate; Thailandaise; Thanie; The beast; The fake throwdown; The Jack Bauer; The Loud-House Permadillo; The Nax; The witch; Thing; Thunder; Tiger; Tigre; Tigre Blanco; Tigre del Norte; Tits; TNT; T.N.T.; Tongs; Tootsie roll; Top drool; Train; Trash; Twin towers; Twists; Vidrio; Whack; Whicked; White; White Bitch; White boy; White dragon; White dynamite; White girl; White horse; White junk; White lady; White nurse; "White Pony"; White stuff; White Tiger; Wicked; Wings; Witch; Witch hazel; WTC; Zoquete.

Pharmacopoeias. In *Br.* and *Swiss*. *Swiss* also includes the anhydrous form.

BP 2008 (Diamorphine Hydrochloride). A white or almost white crystalline powder, odourless when freshly prepared but develops an odour characteristic of acetic acid on storage. Freely soluble in water and in chloroform; soluble in alcohol; practically insoluble in ether. Protect from light.

Incompatibility. Diamorphine hydrochloride is incompatible with mineral acids and alkalis and with chlorocresol.[1]

The *BNF* notes that cyclizine may precipitate from mixtures with diamorphine hydrochloride at concentrations of cyclizine greater than 10 mg/mL, or in the presence of sodium chloride 0.9%, or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also liable to precipitate after 24 hours.

It also considers that mixtures of diamorphine and haloperidol are liable to precipitate after 24 hours if the haloperidol concentration is above 2 mg/mL. Under some conditions mixtures of metoclopramide and diamorphine may become discoloured and should be discarded.

1. McEwan JS, Macmorran GH. The compatibility of some bactericides. *Pharm J* 1947; **158:** 260–2.

Stability. Diamorphine is relatively unstable in aqueous solution and is hydrolysed to 6-*O*-monoacetylmorphine and then morphine to a significant extent at room temperature; 3-*O*-monoacetylmorphine is only occasionally detected. The rate of decomposition is at a minimum at about pH 4.[1,2]

In a study of the stability of aqueous solutions of diamorphine in chloroform water it was concluded that such solutions should be used within 3 weeks of preparation when stored at room temperature.[3] Another study[4] noted that the degradation products of diamorphine were not devoid of analgesic activity. Using a more sensitive analytical method it was reported that although the pH range of maximum stability of diamorphine in aqueous solution was 3.8 to 4.4, the addition of buffers reduced stability.[5] Simple unbuffered chloroform water gave maximum stability, the shelf-life of such a solution being 4 weeks at room temperature.

The BP 2008 recommends that solutions for injection be prepared immediately before use by dissolving Diamorphine Hydrochloride for Injection in Water for Injections. This may pose a problem with solutions for subcutaneous infusion when concentrated solutions may remain in infusion pump reservoirs for some time.[6] Investigation of 9 concentrations of diamorphine stored at 4 different temperatures for 8 weeks[7] revealed instability under conditions of concentration, time, and temperature prevalent during subcutaneous infusion. Degradation of diamorphine occurred at all concentrations (0.98 to 250 mg/mL) at temperatures of 4° and above; the effect of temperature was significant at 21° and 37°. The percentage fall in diamorphine concentration was directly related to initial concentration and was accompanied by a corresponding increase in 6-*O*-monoacetylmorphine and, to a lesser extent, morphine; other possible breakdown products such as 3-*O*-monoacetylmorphine were not present in detectable quantities. Diamorphine degradation was associated with a fall in pH and the development of a strong acetic acid-like odour. Precipitation and a white turbidity was seen in solutions of 15.6 mg/mL and above after incubation for 2 weeks at 21° and 37°. It has been noted that solutions for infusion are generally freshly prepared and used within 24 hours, but that signs of precipitation should be watched for, especially when using longer-term infusions and high concentrations of diamorphine.[7]

In another stability study[8] diamorphine hydrochloride in concentrations of both 1 and 20 mg/mL in sodium chloride 0.9% was stable for a minimum of 15 days at room temperature (23° to 25°) and 4° when stored in a PVC container. In one type of disposable infusion device (Infusor) similar solutions were stable for 15 days even at 31°. In another infusion device (Intermate 200) diamorphine was stable for a minimum of 15 days at both concentrations and all temperatures except for the 1 mg/mL solution kept at 31° when stability was only maintained for a minimum of 2 days. When stored in glass syringes both strengths of diamorphine hydrochloride were stable for 15 days at 4° and at room temperature the 1 mg/mL solution was stable for a minimum of 7 days and the 20 mg/mL solution was stable for a minimum of 12 days. There were no substantial changes in physical appearance or pH.

1. Davey EA, Murray JB. Hydrolysis of diamorphine in aqueous solutions. *Pharm J* 1969; **203:** 737.
2. Davey EA, Murray JB. Determination of diamorphine in the presence of its degradation products using gas liquid chromatography. *Pharm J* 1971; **207:** 167.
3. Cooper H, *et al.* Stability of diamorphine in chloroform water mixture. *Pharm J* 1981; **226:** 682–3.
4. Twycross RG. Stability of diamorphine in chloroform water. *Pharm J* 1981; **227:** 218.
5. Beaumont IM. Stability of diamorphine in chloroform water. *Pharm J* 1981; **227:** 41.
6. Jones VA, *et al.* Diamorphine stability in aqueous solution for subcutaneous infusion. *Br J Clin Pharmacol* 1987; **23:** 651P.
7. Omar OA, *et al.* Diamorphine stability in aqueous solution for subcutaneous infusion. *J Pharm Pharmacol* 1989; **41:** 275–7.
8. Kleinberg ML, *et al.* Stability of heroin hydrochloride in infusion devices and containers for intravenous administration. *Am J Hosp Pharm* 1990; **47:** 377–81.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Diamorphine is subject to abuse (see under Adverse Effects, Treatment, and Precautions, below).

Diamorphine is used for substitution therapy in the management of opioid dependence (see under Uses and Administration, below).

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

Pulmonary oedema after overdosage is a common cause of fatalities among diamorphine addicts. Nausea and hypotension are claimed to be less common than with morphine.

There are many reports of adverse effects associated with the abuse of diamorphine, usually obtained illicitly in an adulterated form.

Abuse. Most of the reports of adverse effects with diamorphine involve its abuse. In addition to the central effects, there are effects caused by the administration methods and by the adulterants.[1,2] Thus in many instances it is difficult to identify the factor causing the toxicity. Most body systems are involved including the immune system,[3] kidneys,[4,5] liver,[6] respiratory system,[7-10] and the nervous system.[11-16]

Other aspects of the illicit use of diamorphine include fatal overdose[17] and smuggling by swallowing packages of drug[18,19] or other methods of internal bodily concealment.

1. Hendrickse RG, *et al.* Aflatoxins and heroin. *BMJ* 1989; **299:** 492–3.
2. CDC. Atypical reactions associated with heroin use: five states, January–April 2005. *MMWR* 2005; **54:** 793–6. Correction. *ibid.*; 852.
3. Husby G, *et al.* Smooth muscle antibody in heroin addicts. *Ann Intern Med* 1975; **83:** 801–5.
4. Cunningham EE, *et al.* Heroin-associated nephropathy. *JAMA* 1983; **250:** 2935–6.
5. do Sameiro Faria M, *et al.* Nephropathy associated with heroin abuse in Caucasian patients. *Nephrol Dial Transplant* 2003; **18:** 2308–13.
6. Weller IVD, *et al.* Clinical, biochemical, serological, histological and ultrastructural features of liver disease in drug abusers. *Gut* 1984; **25:** 417–23.
7. Anderson K. Bronchospasm and intravenous street heroin. *Lancet* 1986; **i:** 1208.
8. Cygan J, *et al.* Inhaled heroin-induced status asthmaticus: five cases and a review of the literature. *Chest* 2000; **117:** 272–5.
9. Boto de los Bueis A, *et al.* Bronchial hyperreactivity in patients who inhale heroin mixed with cocaine vaporized on aluminium foil. *Chest* 2002; **121:** 1223–30.
10. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema: a case series. *Chest* 2001; **120:** 1628–32.
11. Sempere AP, *et al.* Spongiform leucoencephalopathy after inhaling heroin. *Lancet* 1991; **338:** 320.
12. Roulet Perez E, *et al.* Toxic leucoencephalopathy after heroin ingestion in a 2½-year-old child. *Lancet* 1992; **340:** 729.
13. Zuckerman GB. Neurologic complications following intranasal administration of heroin in an adolescent. *Ann Pharmacother* 1996; **30:** 778–81.
14. Kriegstein AR, *et al.* Heroin inhalation and progressive spongiform leukoencephalopathy. *N Engl J Med* 1997; **336:** 589–90.
15. Long H, *et al.* A fatal case of spongiform leukoencephalopathy linked to "chasing the dragon". *J Toxicol Clin Toxicol* 2003; **41:** 887–91.
16. Dabby R, *et al.* Acute heroin-related neuropathy. *J Peripher Nerv Syst* 2006; **11:** 304–9.
17. Kintz P, *et al.* Toxicological data after heroin overdose. *Hum Toxicol* 1989; **8:** 487–9.
18. Stewart A, *et al.* Body packing—a case report and review of the literature. *Postgrad Med J* 1990; **66:** 659–61.
19. Traub SJ, *et al.* Pediatric "body packing". *Arch Pediatr Adolesc Med* 2003; **157:** 174–7.

Administration. Although generally free from complications, sterile abscess formation was reported in 2 patients with advanced cancer receiving diamorphine by continuous *subcutaneous* infusions.[1] Acute dysphoric reactions have been reported after the use of *epidural* diamorphine.[2]

1. Hoskin PJ, *et al.* Sterile abscess formation by continuous subcutaneous infusion of diamorphine. *BMJ* 1988; **296:** 1605.
2. Holder KJ, Morgan BM. Dysphoria after extradural diamorphine. *Br J Anaesth* 1994; **72:** 728.

Breast feeding. The American Academy of Pediatrics has stated[1] that, when used as a drug of abuse by breast-feeding mothers, diamorphine has caused adverse effects in the infant, notably tremors, restlessness, vomiting, and poor feeding. However, the *BNF* considers that diamorphine when given in therapeutic doses to a breast-feeding mother is unlikely to affect the breast-fed infant.

See also Opioid Dependence under Uses and Administration, below.

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)

Hypersensitivity. Anaphylaxis occurred in a patient given *intrathecal* diamorphine and bupivacaine for surgical anaesthesia;[1] the authors noted that the patient received patient-controlled analgesia with morphine shortly after the reaction without problem. Subsequent skin prick tests identified diamorphine as the likely causative agent.

1. Gooch I, Gwinnutt C. Anaphylaxis to intrathecal diamorphine. *Resuscitation* 2006; **70:** 470–3.

Phaeochromocytoma. Diamorphine can liberate endogenous histamine which may in turn stimulate release of catecholamines. Its use provoked hypertension and tachycardia in a patient with phaeochromocytoma.[1]

1. Chaturvedi NC, *et al.* Diamorphine-induced attack of paroxysmal hypertension in phaeochromocytoma. *BMJ* 1974; **2:** 538.

Pregnancy and the neonate. Some references to diamorphine dependence in pregnant women and the effects on the fetus and neonate.

1. Fricker HS, Segal S. Narcotic addiction, pregnancy, and the newborn. *Am J Dis Child* 1978; **132:** 360–6.
2. Ostrea EM, Chavez CJ. Perinatal problems (excluding neonatal withdrawal) in maternal drug addiction: a study of 830 cases. *J Pediatr* 1979; **94:** 292–5.
3. Lifschitz MH, *et al.* Fetal and postnatal growth of children born to narcotic-dependent women. *J Pediatr* 1983; **102:** 686–91.
4. Klenka HM. Babies born in a district general hospital to mothers taking heroin. *BMJ* 1986; **293:** 745–6.
5. Gregg JEM, *et al.* Inhaling heroin during pregnancy: effects on the baby. *BMJ* 1988; **296:** 754.
6. Little BB, *et al.* Maternal and fetal effects of heroin addiction during pregnancy. *J Reprod Med* 1990; **35:** 159–62.
7. Mur Sierra A, *et al.* Asociación entre el consumo de heroína durante la gestación y anomalías estructurales de los cilios respiratorios en el período neonatal. *An Esp Pediatr* 2001; **55:** 335–8.

Interactions

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

Pharmacokinetics

Diamorphine hydrochloride is well absorbed from the gastrointestinal tract, although this may be erratic, and after subcutaneous or intramuscular injection. On injection it is rapidly hydrolysed to the active metabolite 6-*O*-monoacetylmorphine (6-acetylmorphine) in the blood and then to morphine (p.88). Oral doses are subject to extensive first-pass metabolism to morphine; neither diamorphine nor 6-acetylmorphine have been detected in the blood after giving diamorphine by this route. Both diamorphine and 6-acetylmorphine readily cross the blood-brain barrier. Morphine glucuronides are the main excretion products in the urine. A small amount is excreted in the faeces.

◊ References.

1. Boerner U, *et al.* The metabolism of morphine and heroin in man. *Drug Metab Rev* 1975; **4:** 39–73.
2. Inturrisi CE, *et al.* The pharmacokinetics of heroin in patients with chronic pain. *N Engl J Med* 1984; **310:** 1213–17.
3. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
4. Barrett DA, *et al.* Morphine kinetics after diamorphine infusion in premature neonates. *Br J Clin Pharmacol* 1991; **32:** 31–7.
5. Girardin F, *et al.* Pharmacokinetics of high doses of intramuscular and oral heroin in narcotic addicts. *Clin Pharmacol Ther* 2003; **74:** 341–52.

Administration. *INHALATIONAL ROUTE.* A literature review[1] found that intranasal diamorphine had a similar pharmacokinetic profile to that of intramuscular diamorphine. It is rapidly absorbed, as a dry powder, via the nasal mucosa although this is not as complete as by intramuscular injection; intranasal absorption appeared to be dose dependent.

The pharmacokinetics of inhaled diamorphine fumes ("chasing the dragon") has been studied[2] in diamorphine addicts receiving substitution therapy with diamorphine and methadone. Absorption through the lungs occurred very rapidly and was virtually complete immediately after inhalation; bioavailability was estimated to be about 53%.

1. Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* 2003; **42:** 501–13.
2. Rook EJ, *et al.* Population pharmacokinetics of heroin and its major metabolites. *Clin Pharmacokinet* 2006; **45:** 401–17.

INTRASPINAL ROUTE. Diamorphine is much more lipid-soluble and has a more rapid onset and shorter duration of action than morphine. Although deacetylation to morphine occurs rapidly in the blood it occurs only slowly in the CSF after intraspinal injection of diamorphine.[1] After intrathecal injection diamorphine was removed from the CSF much more rapidly than morphine.[2] Peak plasma concentrations of morphine after epidural diamorphine injection were significantly higher and were achieved significantly faster than after epidural injection of morphine.[3]

1. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
2. Moore A, *et al.* Spinal fluid kinetics of morphine and heroin. *Clin Pharmacol Ther* 1984; **35:** 40–5.
3. Watson J, *et al.* Plasma morphine concentrations and analgesic effects of lumbar extradural morphine and heroin. *Anesth Analg* 1984; **63:** 629–34.

Children. Loading doses of either 50 micrograms/kg or 200 micrograms/kg of diamorphine were given as an infusion over 30 minutes to 19 ventilated neonates followed by a continuous infusion of 15 micrograms/kg per hour, and the pharmacokinetics of the products of diamorphine metabolism (morphine, morphine-6-glucuronide, and morphine-3-glucuronide) studied.[1] Although the overall elimination of morphine was reduced compared with adults, the relative contributions of the various metabolic routes of morphine remained similar between neonates and adults. Data from this study did not indicate any advantage for the higher loading dose (see also under Uses and Administration, below).

1. Barrett DA, *et al.* Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. *Br J Clin Pharmacol* 1996; **41:** 531–7.

Uses and Administration

Diamorphine hydrochloride is an acetylated morphine derivative and is a more potent opioid analgesic (p.104) than morphine (p.89). Diamorphine is used for the relief of severe pain especially in palliative care. It is also used similarly to morphine for the relief of dyspnoea due to pulmonary oedema resulting from left ventricular failure. Diamorphine has a powerful cough suppressant effect and has been given as Diamorphine Linctus (BPC 1973) to control cough associated with terminal lung cancer although morphine is now preferred.

In the treatment of **acute pain** usual doses of diamorphine hydrochloride by subcutaneous or intramuscular injection are 5 to 10 mg every 4 hours. Doses equivalent to one-quarter to one-half of the corresponding intramuscular dose may be given by slow intravenous injection.

For the pain of myocardial infarction doses of 5 mg are given by slow intravenous injection at a rate of 1 mg/minute with a further dose of 2.5 to 5 mg if required; doses may be reduced by one-half for elderly or frail patients. Doses of 2.5 to 5 mg may be given intravenously at the same rate for acute **pulmonary oedema**.

For **chronic pain** 5 to 10 mg may be given by subcutaneous or intramuscular injection every 4 hours; the dose may be increased according to needs. Similar doses may be given orally, although it is converted to morphine by first-pass metabolism (see Pharmacokinetics, above). Diamorphine hydrochloride may also be given by continuous subcutaneous or intravenous infusion or intraspinally.

For details of doses in children, see below.

Action. Because of its abuse potential, supply of diamorphine is carefully controlled and in many countries it is not available for clinical use; morphine can provide equivalent analgesia by dose adjustment. There has been much debate regarding the relative merits of analgesia with diamorphine or morphine. Many now regard oral morphine to be the opioid analgesic of choice although diamorphine hydrochloride may be preferred for injection because it is more soluble in water thus allowing the use of smaller dose volumes. Diamorphine hydrochloride may also be preferred to morphine salts for intraspinal use because it is more lipid-soluble.

As a guide to relative potency diamorphine hydrochloride 5 mg given intramuscularly is equivalent to about 10 mg given orally, which in turn is equivalent to about 15 mg of oral morphine sulfate. When given by subcutaneous infusion, diamorphine hydrochloride 10 mg every 24 hours is equivalent to about 15 mg every 24 hours of morphine sulfate.

Administration in children. In the treatment of acute or chronic pain in children, the *BNFC* suggests the following doses according to age:

by continuous intravenous infusion

- neonates with spontaneous respiration may be given 2.5 to 7 micrograms/kg per hour
- ventilated neonates may be given 50 micrograms/kg initially by intravenous injection over 30 minutes followed by 15 micrograms/kg per hour by continuous intravenous infusion
- 1 month to 12 years, 12.5 to 25 micrograms/kg per hour

by intravenous injection

- 1 to 3 months, 20 micrograms/kg every 6 hours if necessary
- 3 to 6 months, 25 to 50 micrograms/kg every 6 hours if necessary
- 6 to 12 months, 75 micrograms/kg every 4 hours if necessary
- 1 to 12 years, 75 to 100 micrograms/kg every 4 hours if necessary

by mouth

- 1 month to 12 years, 100 to 200 micrograms/kg (maximum of 10 mg) every 4 hours if necessary

In a study[1] of the effects of diamorphine in 34 premature infants (gestational age 26 to 40 weeks), a loading dose of 50 micrograms/kg given as an *intravenous* infusion over 30 minutes followed by a continuous infusion at a rate of 15 micrograms/kg per hour was considered to be safe and resulted in plasma concentrations of morphine comparable with those that usually produce adequate analgesia in children and adults; the duration of the infusion ranged from 14 to 149 hours. Small but significant reductions in heart rate and mean blood pressure were noted but these were not associated with any clinical deterioration. The fall in respiration rate reflected the desired intention to encourage synchronisation of the infants' breathing with the ventilator. The authors concluded that intravenous diamorphine could be given safely to neonates and would provide adequate analgesia. A later study[2] indicated that the use of a 200 micrograms/kg loading dose conferred no benefit over a 50 micrograms/kg dose and might produce undesirable physiological effects. In a comparative study[3] with morphine (200 micrograms/kg loading dose over 2 hours, followed by maintenance infusion of 25 micrograms/kg per hour) in ventilated preterm neonates requiring sedation, diamorphine (120 micrograms/kg over 2 hours and then 15 micrograms/kg per hour) was as effective as morphine in producing sedation and also had a faster onset of action. The small but significant drop in blood pressure noted during morphine infusions was not seen with diamorphine infusions.

The *subcutaneous* route appeared to be as effective and safe as the intravenous route for infusions in children for postoperative pain relief after elective abdominal surgery.[4] The dose of diamorphine used in both groups of children was 1 mg/kg given at a rate of 20 micrograms/kg per hour.

Intranasal diamorphine has been investigated in adults and children, and appears to be effective and well tolerated; because it does not require a needle it may offer particular advantages in children.[5] Guidelines[6] for analgesia in children in Accident and Emergency departments in the UK recommend the use of intranasal diamorphine for severe pain such as that associated with large burns, long bone dislocation, appendicitis, or sickle-cell crisis. A suggested dose to be instilled into one nostril is 100 micrograms/kg given in 0.2 mL of sterile water.

1. Elias-Jones AC, *et al.* Diamorphine infusion in the preterm neonate. *Arch Dis Child* 1991; **66:** 1155–7.
2. Barker DP, *et al.* Randomised, double blind trial of two loading dose regimens of diamorphine in ventilated newborn infants. *Arch Dis Child* 1995; **73:** F22–F26.
3. Wood CM, *et al.* Randomised double blind trial of morphine versus diamorphine for sedation of preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 1998; **79:** F34–F39.
4. Semple D, *et al.* Comparison of iv and sc diamorphine infusions for the treatment of acute pain in children. *Br J Anaesth* 1996; **76:** 310–12.
5. Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* 2003; **42:** 501–13.
6. British Association for Emergency Medicine. Clinical Effectiveness Committee guideline for the management of pain in children (2004). Available at: http://www.emergencymed.org.uk/BAEM/CEC/assets/cec_pain_in_children.pdf (accessed 26/06/08)

Opioid dependence. The treatment of opioid dependence is discussed on p.101. Many opiate misusers have expressed a preference for withdrawal using diamorphine rather than methadone. In a comparative study stabilisation was achieved using either diamorphine or methadone 1 mg/mL oral solutions;[1] patients could not identify which they had been given. Whenever signs of physical withdrawal were seen 10 mL of either solution was given and the total amount over the first 24 hours taken as the pa-

tient's daily requirement. The mean dose of diamorphine required for stabilisation was 55 mg compared with 36 mg for methadone. Some centres have given diamorphine in the form of reefers. Diamorphine has also been prescribed with methadone in the management of addicts.[2] A systematic review[3] that included this study failed to produce conclusive results about the effectiveness of diamorphine (alone or with methadone) in maintenance treatment; however, since the studies were not directly comparable, continued evaluation in clinical studies is required. Oral tablets[4] and intravenous injection[5] of diamorphine have also been tried in severely dependent, treatment-resistant patients.

Breast feeding has been used to treat diamorphine dependence in the offspring of dependent mothers but this is no longer considered to be the best method and some authorities recommend that breast feeding should be stopped.

1. Ghodse AH, *et al.* Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300:** 719–20.
2. van den Brink W, *et al.* Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. Abridged version: *BMJ* 2003; **327:** 310–12. Correction. *ibid.*; 724. Full version: http://www.bmj.com/cgi/reprint/327/7410/310 (accessed 26/06/08)
3. Ferri M, *et al.* Heroin maintenance for chronic heroin dependents. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 26/06/08).
4. Frick U, *et al.* A prospective cohort study on orally administered heroin substitution for severely addicted opioid users. *Addiction* 2006; **101:** 1631–9.
5. March JC, *et al.* Controlled trial of prescribed heroin in the treatment of opioid addiction. *J Subst Abuse Treat* 2006; **31:** 203–11.

Pain. ***ACUTE PAIN.*** Rapid pain relief may be obtained with the intravenous injection of diamorphine. Other routes include the intraspinal route for which diamorphine is well suited because of its lipid solubility and pharmacokinetics. Epidural doses of diamorphine have ranged from 0.5 to 10 mg.[1] Analgesia was significantly more prolonged and more intense after epidural rather than intramuscular injection of diamorphine 5 mg in women who had had caesarean section;[2] itching was reported by 50% of patients undergoing epidural analgesia. Epidural diamorphine alone[3] or with bupivacaine[4] has been used for analgesia during labour; addition of adrenaline appeared to improve the quality and duration of analgesia with diamorphine.[3] In another study addition of diamorphine to bupivacaine produced a high incidence of pruritus and drowsiness.[5] A study[6] of patient-controlled analgesia for postoperative pain found that although epidural diamorphine, used alone or with bupivacaine, reduced the analgesic dose requirement, there was little clinical advantage over the subcutaneous route.

Continuous epidural infusion of diamorphine 500 micrograms/hour in 0.125% bupivacaine provided postoperative analgesia superior to that with either drug alone in patients undergoing major abdominal gynaecological surgery.[7] A similar infusion produced analgesia superior to that with either epidural bolus injection or patient-controlled intravenous diamorphine in patients undergoing total abdominal hysterectomy.[8] However, more patients receiving the continuous epidural infusion were hypoxaemic than in the other 2 groups.

Diamorphine has also been given intrathecally for postoperative analgesia and should be effective at lower doses than with the epidural route because of greater CSF concentrations. Diamorphine 250 or 500 micrograms given intrathecally with bupivacaine spinal anaesthesia both provided greater postoperative analgesia than bupivacaine alone,[9] but the incidence of adverse effects, especially nausea, vomiting, and urinary retention, was still high with either dose and routine use of this technique was not recommended. Intrathecal diamorphine with bupivacaine has also been used for analgesia during labour[10,11] and caesarean section.[12-16] In a study[12] in patients undergoing caesarean section, intrathecal diamorphine 250 micrograms showed comparable postoperative analgesia with a 5-mg epidural dose and was associated with less postoperative nausea and vomiting. Other studies[13,14] found that intrathecal diamorphine reduced supplemental analgesic requirements during and after caesarean section when compared with intrathecal fentanyl. Intrathecal diamorphine 400 micrograms was considered by some[15] to be the lowest dose required to reduce intraoperative analgesic supplementation to below 5%; however, lower doses of 300 micrograms have been used in practice.[16]

Diamorphine has been extensively used by cardiologists in the UK for the management of pain in acute left ventricular failure, unstable angina, and myocardial infarction. It has been theorised that diamorphine may offer benefits over morphine because its stimulatory effects at opioid δ receptors on the myocardium may reduce the extent of myocardial damage.[17] Evidence to support this theory is, however, lacking.

1. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
2. Macrae DJ, *et al.* Double-blind comparison of the efficacy of extradural diamorphine, extradural phenoperidine and im diamorphine following caesarean section. *Br J Anaesth* 1987; **59:** 354–9.
3. Keenan GMA, *et al.* Extradural diamorphine with adrenaline in labour: comparison with diamorphine and bupivacaine. *Br J Anaesth* 1991; **66:** 242–6.
4. McGrady EM, *et al.* Epidural diamorphine and bupivacaine in labour. *Anaesthesia* 1989; **44:** 400–3.
5. Bailey CR, *et al.* Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72:** 58–61.
6. Gopinathan C, *et al.* A comparative study of patient-controlled epidural diamorphine, subcutaneous diamorphine and an epidural diamorphine/bupivacaine combination for postoperative pain. *Eur J Anaesthesiol* 2000; **17:** 189–96.
7. Lee A, *et al.* Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. *Br J Anaesth* 1988; **60:** 845–50.
8. Madej TH, *et al.* Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia. *Br J Anaesth* 1992; **69:** 554–7.
9. Reay BA, *et al.* Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery. *Br J Anaesth* 1989; **62:** 248–52.
10. Kestin IG, *et al.* Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68:** 244–7.
11. Vaughan DJA, *et al.* Choice of opioid for initiation of combined spinal epidural analgesia in labour—fentanyl or diamorphine. *Br J Anaesth* 2001; **86:** 567–9.
12. Hallworth SP, *et al.* Comparison of intrathecal and epidural diamorphine for elective Caesarean section using a combined spinal-epidural technique. *Br J Anaesth* 1999; **82:** 228–32.
13. Cowan CM, *et al.* Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia. *Br J Anaesth* 2002; **89:** 452–8.
14. Lane S, *et al.* A comparison of intrathecal fentanyl and diamorphine as adjuncts in spinal anaesthesia for Caesarean section. *Anaesthesia* 2005; **60:** 453–7.
15. Saravanan S, *et al.* Minimum dose of intrathecal diamorphine required to prevent intraoperative supplementation of spinal anaesthesia for Caesarean section. *Br J Anaesth* 2003; **91:** 368–72.
16. Wrench IJ, *et al.* Dose response to intrathecal diamorphine for elective caesarean section and compliance with a national audit standard. *Int J Obstet Anesth* 2007; **16:** 17–21.
17. Poullis M. Diamorphine and British cardiology: so we are right! *Heart* 1999; **82:** 645–6.

CHRONIC PAIN. Patients with chronic opioid-sensitive pain are often treated with diamorphine given by continuous subcutaneous infusion using a small battery-operated syringe driver. The following technique has been described.[1] Diamorphine hydrochloride 1 g could be dissolved in 1.6 mL of water to give a solution with a volume of 2.4 mL (415 mg/mL), but the maximum suggested concentration was 250 mg/mL. If the analgesic requirement was not known the following protocol was recommended:

- Start injections every 4 hours of 2.5 or 5 mg diamorphine, or, if the patient has already been taking opioids, a dose that is equivalent to the last dose
- If this is unsatisfactory increase this dose in 50% increments until the patient reports even a little pain relief
- Calculate the 24-hour requirement by multiplying by six, and start the infusion at this level
- Increase the 24-hour dosage in the pump by 50% increments until the pain is controlled. Note that requirements may vary from less than 20 mg to more than 5 g per 24 hours

When starting an infusion it is important not to allow any breakthrough pain. This may be achieved either by starting the infusion more than 2 hours before the previous oral dose wears off or by giving a loading dose injection of the 4-hourly requirement.

Although generally free from complications, sterile abscess formation was reported in 2 patients with advanced cancer receiving diamorphine by continuous subcutaneous infusions.[2]

The intraspinal[3] and intraventricular[4] routes have also been used successfully in patients with intractable pain. Topical application of diamorphine has also been tried[5,6] for the control of pressure ulcer pain in a small number of palliative care patients.

1. Dover SB. Syringe driver in terminal care. *BMJ* 1987; **294:** 553–5.
2. Hoskin PJ, *et al.* Sterile abscess formation by continuous subcutaneous infusion of diamorphine. *BMJ* 1988; **296:** 1605.
3. Baker L, *et al.* Evolving spinal analgesia practice in palliative care. *Palliat Med* 2004; **18:** 507–15.
4. Reeve WG, Todd JG. Intraventricular diamorphine via an Ommaya shunt for intractable cancer pain. *Br J Anaesth* 1990; **65:** 544–7.
5. Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *J Pain Symptom Manage* 2003; **25:** 547–54.
6. Abbas SQ. Diamorphine-Intrasite dressings for painful pressure ulcers. *J Pain Symptom Manage* 2004; **28:** 532–4.

Preparations

BP 2008: Diamorphine Injection;
BPC 1973: Diamorphine Linctus.

Proprietary Preparations (details are given in Part 3)
Switz.: Diaphin.

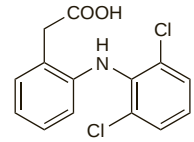
Diclofenac *(BAN, rINN)*

Diclofénac; Diclofenaco; Diclofenacum; Diklofenaakki; Diklofenak. [2-(2,6-Dichloroanilino)phenyl]acetic acid.

Диклофенак

$C_{14}H_{11}Cl_2NO_2 = 296.1$.

CAS — 15307-86-5.
ATC — D11AX18; M01AB05; M02AA15; S01BC03.
ATC Vet — QD11AX18; QM01AB05; QM02AA15; QS01BC03.



Diclofenac Diethylamine *(BANM)*

Diclofenac Diethylammonium; Diclofenaco dietilamina; Diklofenak Dietilamonyum.

Диклофенак Диэтиламин

$C_{18}H_{22}Cl_2N_2O_2 = 369.3$.

CAS — 78213-16-8.
ATC — D11AX18.
ATC Vet — QD11AX18.

Pharmacopoeias. In *Br.*

BP 2008 (Diclofenac Diethylamine). A white to light beige, crystalline powder. Sparingly soluble in water and in acetone; freely soluble in alcohol and in methyl alcohol; practically insoluble in 1M sodium hydroxide. The pH of a 1% solution in alcohol (10%) is between 6.4 and 8.4. Store in airtight containers. Protect from light.

Diclofenac Epolamine

DHEP; Diclofenac Hydroxyethylpyrrolidine.

Диклофенак Эполамин

$C_{14}H_{11}Cl_2NO_2$, $C_6H_{13}NO = 411.3$.

CAS — 119623-66-4.
ATC — D11AX18.
ATC Vet — QD11AX18.

Diclofenac Potassium *(BANM, USAN, rINNM)*

CGP-45840B; Diclofénac potassique; Diclofenaco potásico; Diclofenacum kalicum; Diklofenaakkikalium; Diklofenak draselná sůl; Diklofenak Potasyum; Diklofenakkalium; Diklofenák-kálium; Diklofenako kalio druska; Kalii Diclofenacum. Potassium [*o*-(2,6-dichloroanilino)phenyl]acetate.

Калия Диклофенак

$C_{14}H_{10}Cl_2KNO_2 = 334.2$.

CAS — 15307-81-0.
ATC — D11AX18.
ATC Vet — QD11AX18.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Diclofenac Potassium). A white or slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Diclofenac Potassium). pH of a 1% solution in water is between 7.0 and 8.5. Store at a temperature of 20° to 25°. Protect from light.

Diclofenac Sodium *(BANM, USAN, rINNM)*

Diclofénac sodique; Diclofenaco sódico; Diclofenacum natricum; Diclophenac Sodium; Diklofenaakkinatrium; Diklofenak sodná sůl; Diklofenak Sodyum; Diklofenaknatrium; Diklofenák-nátrium; Diklofenako natrio druska; GP-45840; Natrii Diclofenacum. Sodium [2-(2,6-dichloroanilino)phenyl]acetate.

Натрий Диклофенак

$C_{14}H_{10}Cl_2NNaO_2 = 318.1$.

CAS — 15307-79-6.
ATC — D11AX18.
ATC Vet — QD11AX18.

NOTE. DICL is a code approved by the BP 2008 for use on single unit doses of eye drops containing diclofenac sodium where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 6.2 (Diclofenac Sodium). A white to slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Diclofenac Sodium). A white to off-white, hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in methyl alcohol. pH of a 1% solution in water is between 7.0 and 8.5. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

There may be pain and, occasionally, tissue damage at the site of injection when diclofenac is given intramuscularly. Diclofenac suppositories can cause local irritation. Transient burning and stinging may occur with diclofenac ophthalmic solution; more serious corneal