dration. It darkens on prolonged exposure to light. Soluble 1 in 16 of water and 1 in 1 of water at 80°; soluble 1 in 570 of alcohol and 1 in 240 of alcohol at 60°; insoluble in chloroform and in ether. Store in airtight containers at a temperature up to 40° as permitted by the manufacturer. Protect from light.

Incompatibility. Incompatibility data for morphine has been extensively studied[1,2] and may depend on many factors such as the formulation used, and order and ratio of mixing; however, most studies are usually only short term and contain few details on mixing the same drugs in a variety of different situations.

Morphine salts are sensitive to changes in pH and morphine is liable to be precipitated out of solution in an alkaline environment. Compounds incompatible with morphine salts include aminophylline and sodium salts of barbiturates and phenytoin. Other incompatibilities, sometimes attributed to particular formulations, have included:

- Aciclovir sodium—precipitate noted 2 hours after admixture with morphine sulfate solution[3]
- Chlorpromazine hydrochloride injection—precipitation was considered to be due to chlorocresol present in the morphine sulfate injection[4]
- Doxorubicin—addition of morphine sulfate 1 mg/mL to doxorubicin hydrochloride liposomal injection 400 micrograms/mL in dextrose 5% resulted in turbidity changes[5]
- Fluorouracil—immediate precipitate formed after admixture of fluorouracil 1 or 16 mg/mL with morphine sulfate 1 mg/mL in dextrose 5% or sodium chloride 0.9%[6]
- Furosemide—precipitate noted 1 hour after admixture with morphine sulfate solution[3]
- Haloperidol—immediate precipitation seen after admixture of haloperidol and morphine sulfate solution[7]
- Heparin sodium—incompatibility has been reported from straightforward additive studies.[1] Another study[8] indicated that morphine sulfate and heparin sodium were only incompatible at morphine sulfate concentrations greater than 5 mg/mL and that this incompatibility could be prevented by using 0.9% sodium chloride solution as the admixture diluent rather than water
- Pethidine hydrochloride—incompatibility has been noted after admixture with morphine sulfate[1,9]
- Prochlorperazine edisilate—immediate precipitation was attributed to phenol in the morphine sulfate injection formulation[10,11]
- Promethazine hydrochloride—cloudiness was reported to develop when 12.5 mg of promethazine hydrochloride was drawn into a syringe containing morphine sulfate 8 mg.[12] Others[9] have noted no incompatibility
- Ranitidine hydrochloride—crystal needles and/or sticky spots observed in admixtures of morphine hydrochloride and ranitidine hydrochloride in various ratios stored at different temperatures[13]
- Tetracyclines—colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with morphine sulfate in 5% glucose injection[14]

1. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23:** 409–11.
2. Vermeire A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999; **187:** 17–51.
3. Pugh CB, *et al.* Visual compatibility of morphine sulphate and meperidine hydrochloride with other injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 123–5.
4. Crapper JB. Mixing chlorpromazine and morphine. *BMJ* 1975; **i:** 33.
5. 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.
6. Xu QA, *et al.* Stability and compatibility of fluorouracil with morphine sulfate and hydromorphone hydrochloride. *Ann Pharmacother* 1996; **30:** 756–61.
7. LeBelle MJ, *et al.* Compatibility of morphine and midazolam or haloperidol in parenteral admixtures. *Can J Hosp Pharm* 1995; **48:** 155–60.
8. Baker DE, *et al.* Compatibility of heparin sodium and morphine sulfate. *Am J Hosp Pharm* 1985; **42:** 1352–5.
9. Parker WA. Physical compatibilities of preanesthetic medications. *Can J Hosp Pharm* 1976; **29:** 91–2.
10. Stevenson JG, Patriarca C. Incompatibility of morphine sulfate and prochlorperazine edisylate in syringes. *Am J Hosp Pharm* 1985; **42:** 2651.
11. Zuber DEL. Compatibility of morphine sulfate injection and prochlorperazine edisylate injection. *Am J Hosp Pharm* 1987; **44:** 67.
12. Fleischer NM. Promethazine hydrochloride—morphine sulfate incompatibility. *Am J Hosp Pharm* 1973; **30:** 665.
13. Vermeire A, *et al.* A new method to obtain and present complete information on the compatibility: study of its validity for eight binary mixtures of morphine with drugs frequently used in palliative care. *Palliat Med* 2002; **16:** 417–24.
14. 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.

Stability. ***INTRAVENOUS PREPARATIONS.*** Solutions of morphine sulfate for intravenous infusion appear to be relatively stable. In a study[1] solutions containing 40 micrograms/mL and 400 micrograms/mL retained more than 90% of their initial concentration of morphine sulfate when stored at 4° or 23° for 7 days, whether or not they were protected from light. Solutions prepared from commercially available injection or from powder, in 0.9% sodium chloride or 5% glucose, and stored in PVC bags or glass bottles did not differ in stability from one another. In a further study[2] 10 mg/mL or 5 mg/mL solutions of morphine sulfate in glucose or sodium chloride and stored in portable infusion pump cassettes retained more than 95% of their initial concentration when kept at 23° for 30 days. A 0.9% solution of sodium chloride containing morphine sulfate 2 mg/mL was stable for 6 weeks when stored in polypropylene syringes at ambient temperatures in the light or dark but a similar solution which also contained 0.1% sodium metabisulfite lost 15% of its potency during the same period.[3] Stability of such a solution with or without sodium metabisulfite was considered to be unacceptable when stored in glass syringes in the dark.[4]

A more recent review[5] (which included some of the above studies) has concluded that the degradation of morphine solutions is not affected by oxygen, light, diluent type, salt form, or morphine concentration when stored under normal conditions; it was considered that morphine solutions could be stored for at least 3 months without stability problems.

1. Vecchio M, *et al.* The stability of morphine intravenous infusion solutions. *Can J Hosp Pharm* 1988; **41:** 5–9, 43.
2. Walker SE, *et al.* Hydromorphone and morphine stability in portable infusion pump cassettes and minibags. *Can J Hosp Pharm* 1988; **41:** 177–82.
3. Grassby PF. The stability of morphine sulphate in 0.9 per cent sodium chloride stored in plastic syringes. *Pharm J* 1991; **248:** HS24–HS25.
4. Grassby PF, Hutchings L. Factors affecting the physical and chemical stability of morphine sulphate solutions stored in syringes. *Int J Pharm Pract* 1993; **2:** 39–43.
5. Vermeire A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999; **187:** 17–51.

ORAL PREPARATIONS. Studies[1,2] have shown that for optimum stability of morphine content, Kaolin and Morphine Mixture (BP) needed to be stored in well-filled glass containers.

1. Helliwell K, Game P. Stability of morphine in kaolin and morphine mixture BP. *Pharm J* 1981; **227:** 128–9.
2. Helliwell K, Jennings P. Kaolin and morphine mixture BP: effects of containers on the stability of morphine. *Pharm J* 1984; **232:** 682.

TOPICAL PREPARATIONS. When mixed with about 8 g of *Intrasite* gel (*Smith & Nephew Healthcare, UK*) morphine sulfate, in a concentration of 1.25 mg/mL, remained chemically stable over a 28-day period stored at 4° or at room temperature, irrespective of light exposure.[1] However, unless prepared under sterile conditions, the mixture should be used within 7 days because of the risk of microbial contamination once the gel has been opened.

1. Zeppetella G, *et al.* Stability of morphine sulphate and diamorphine hydrochloride in Intrasite gel . *Palliat Med* 2005; **19:** 131–6.

Morphine Tartrate *(BANM)* ⊗

Morfina, tartrato de.

Морфина Тартрат

$(C_{17}H_{19}NO_3)_2,C_4H_6O_6,3H_2O$ = 774.8.

CAS — 302-31-8 (anhydrous morphine tartrate); 6032-59-3 (morphine tartrate trihydrate).

Incompatibility. See under Morphine Sulfate, above.

Dependence and Withdrawal

As for Opioid Analgesics in general, p.101.

Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than that associated with κ-receptor agonists. With morphine, withdrawal symptoms usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside.

Morphine is used for substitution therapy in the management of neonatal abstinence syndrome (see Administration in Children, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

◊ References.

1. Cherny N, *et al.* Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001; **19:** 2542–54.

Effects on the cardiovascular system. For a reference to the effects of morphine on histamine release compared with some other opioids, see under Pethidine, p.114.

Effects on the muscles. Severe rectovaginal spasms that occurred in a patient given intrathecal morphine[1] were successfully controlled with midazolam.

1. Littrell RA, *et al.* Muscle spasms associated with intrathecal morphine therapy: treatment with midazolam. *Clin Pharm* 1992; **11:** 57–9.

Effects on the nervous system. Myoclonus, often associated with hyperalgesia, has been reported in patients with advanced malignant disease treated with morphine.[1-5] It appears to be uncommon with typical oral doses of morphine and is more often associated with high intravenous and spinal doses. Neuroexcitatory metabolites of morphine are often implicated in the development of myoclonus;[2,4,5] however, other possible mechanisms such as drug interactions cannot be ruled out.[4-6]

It has been reported that myoclonus induced by morphine can be successfully controlled using a benzodiazepine such as midazolam.[7] Indeed, some researchers[8] consider benzodiazepines to be the drugs of choice: clonazepam, diazepam, and lorazepam were most frequently used. Dantrolene[5,8] and gabapentin[9] have also been tried.

1. Potter JM, *et al.* Myoclonus associated with treatment with high doses of morphine: the role of supplemental drugs. *BMJ* 1989; **299:** 150–3.
2. Glare PA, *et al.* Normorphine, a neurotoxic metabolite? *Lancet* 1990; **335:** 725–6.
3. De Conno F, *et al.* Hyperalgesia and myoclonus with intrathecal infusion of high-dose morphine. *Pain* 1992; **47:** 337–9.
4. Sjøgren P, *et al.* Hyperalgesia and myoclonus in terminal cancer patients treated with continuous intravenous morphine. *Pain* 1993; **55:** 93–7.
5. Mercadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. *Pain* 1998; **74:** 5–9.
6. Quinn N. Myoclonus associated with high doses of morphine. *BMJ* 1989; **299:** 683–4.
7. Holdsworth MT, *et al.* Continuous midazolam infusion for the management of morphine-induced myoclonus. *Ann Pharmacother* 1995; **29:** 25–9.
8. Ferris DJ. Controlling myoclonus after high-dosage morphine infusions. *Am J Health-Syst Pharm* 1999; **56:** 1009–10.
9. Mercadante S, *et al.* Gabapentin for opioid-related myoclonus in cancer patients. *Support Care Cancer* 2001; **9:** 205–6.

Precautions

As for Opioid Analgesics in general, p.103.

Biliary-tract disorders. See under Precautions of Opioid Analgesics, p.103.

Breast feeding. Measurable blood concentrations of morphine have been detected in 2 breast-fed infants whose mothers received oral or intrathecal morphine during and after their pregnancies; however, no adverse effects were reported in either of these infants.[1,2] In a group of 7 women given patient-controlled analgesia with intravenous morphine after caesarean delivery, the concentrations of morphine and its metabolite morphine-6 glucuronide in the colostrum were found to be very small.[3] Although no infants were breast fed during the study, it was considered that the effects of maternal morphine on breast-fed infants would be negligible.[3] The American Academy of Pediatrics[4] also states that the use of morphine is usually compatible with breast feeding.

1. Robieux I, *et al.* Morphine excretion in breast milk and resultant exposure of a nursing infant. *J Toxicol Clin Toxicol* 1990; **28:** 365–70.
2. Oberlander TF, *et al.* Prenatal and breast milk morphine exposure following maternal intrathecal morphine treatment. *J Hum Lact* 2000; **16:** 137–42.
3. Baka N-E, *et al.* Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. *Anesth Analg* 2002; **94:** 184–7.
4. 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)

Hepatic impairment. In view of its hepatic metabolism, caution is generally advised when giving morphine to patients with hepatic impairment (but see under Pharmacokinetics, below). The *BNF* advises that use should be avoided or the dose reduced because of the risk of precipitating a coma, although it is also noted that many patients with hepatic impairment tolerate morphine well. Others have considered that severe hepatic impairment may affect morphine metabolism but less severe impairment does not.[1]

The mean elimination half-life of morphine in 12 patients with cirrhosis was almost twice that in 10 healthy subjects after administration of a modified-release oral morphine preparation (*MST-Continus; Napp, UK*) and peak serum concentrations were almost three times as high.[2] Patients with cirrhosis had a greater degree of sedation but none developed encephalopathy. It was recommended that the dose for modified-release preparations should be reduced and that it be given less often when patients have cirrhosis.

In a later study[3] 15 patients with liver cancer were given the same oral morphine preparation and compared with 10 healthy subjects from the previous study; the area under the serum concentration-time curve of morphine was increased three- to fourfold in those with cancer. The elimination half-life of morphine was also prolonged in patients with primary cancer when compared with healthy subjects and those with secondary metastatic disease. Adverse effects were more frequent in the primary cancer group and included 2 cases of respiratory depression; the authors commented that altered blood-brain transportation may have been partly responsible for such effects.

1. Twycross R, Wilcock A. *Palliative Care Formulary.* 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 274.

2. Kotb HIM, *et al.* Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis. *Br J Anaesth* 1997; **79:** 804–6.
3. Kotb HIM, *et al.* Pharmacokinetics of controlled release morphine (MST) in patients with liver carcinoma. *Br J Anaesth* 2005; **94:** 95–9.

Phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release making them unsuitable for use in patients with phaeochromocytoma. For further details, see p.103.

Renal impairment. Severe and prolonged respiratory depression has occurred in patients with renal impairment given morphine. Toxicity in 3 such patients was attributed to the accumulation of the active metabolite morphine-6-glucuronide.[1] Plasma concentrations of this metabolite were found[2] to be ten times higher than normal in a 7-year-old girl with haemolytic uraemic syndrome given morphine intravenously although the half-life of morphine was also prolonged. Plasma concentrations of morphine-6-glucuronide were also reported[3] to be persistently increased 19 days after stopping morphine by intravenous infusion in a 17-year-old girl with normal renal function. The authors of the report suggested that alterations in bowel flora after antibacterial therapy or inhibition of morphine-3-glucuronide glucuronidation by lorazepam might be responsible. It has also been reported[4] that accumulation of morphine can occur in renal failure, although to a lesser extent than accumulation of metabolites (see also under Pharmacokinetics, below).

1. Osborne RJ, *et al.* Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *BMJ* 1986; **292:** 1548–9.
2. Hasselström J, *et al.* Long lasting respiratory depression induced by morphine-6-glucuronide? *Br J Clin Pharmacol* 1989; **27:** 515–18.
3. Calleja MA, *et al.* Persistently increased morphine-6-glucuronide concentrations. *Br J Anaesth* 1990; **64:** 649.
4. Osborne R, *et al.* The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993; **54:** 158–67.

Interactions

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

US licensed product information for some once-daily modified-release preparations of morphine sulfate states that patients must not ingest alcohol, including alcohol-containing medicines, at the same time due to the risk of rapid release and absorption of a potentially fatal dose of morphine; *in-vitro* studies showed that alcohol accelerated the release of morphine.

◊ For references to myoclonus associated with morphine and the concurrent use of other drugs, see Effects on the Nervous System under Adverse Effects, above.

Antibacterials. There is some evidence[1] that the potent enzyme inducer *rifampicin* can reduce the serum concentration of morphine and decrease its analgesic effect; induction of the enzymes responsible for conversion of morphine to the active glucuronide metabolite did not seem to occur.

1. Fromm MF, *et al.* Loss of analgesic effect of morphine due to coadministration of rifampin. *Pain* 1997; **72:** 261–7.

Benzodiazepines. An additive sedative effect is to be expected between opioid analgesics and benzodiazepines and has been reported with morphine and *midazolam*.[1]

For reference to a suggestion that *lorazepam* may inhibit morphine-3-glucuronide glucuronidation, see Renal Impairment under Precautions, above.

1. Tverskoy M, *et al.* Midazolam-morphine sedative interaction in patients. *Anesth Analg* 1989; **68:** 282–5.

Cisapride. Plasma concentrations of morphine have been increased by oral cisapride.[1]

1. Rowbotham DJ, *et al.* Effect of cisapride on morphine absorption after oral administration of sustained-release morphine. *Br J Anaesth* 1991; **67:** 421–5.

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

Local anaesthetics. Prior use of epidural *chloroprocaine*, when compared with lidocaine, has been reported to reduce the duration[1] and efficacy[2] of epidural morphine analgesia. However, a later study[3] found no such effects; the authors suggested that findings from the previous 2 studies were due to breakthrough pain caused by the early resolution of chloroprocaine anaesthesia occurring before the maximum onset of morphine analgesia.

1. Eisenach JC, *et al.* Effect of prior anesthetic solution on epidural morphine analgesia. *Anesth Analg* 1991; **73:** 119–23.
2. Karambelkar DJ, Ramanathan S. 2-Chloroprocaine antagonism of epidural morphine analgesia. *Acta Anaesthesiol Scand* 1997; **41:** 774–8.
3. Hess PE, *et al.* Chloroprocaine may not affect epidural morphine for postcesarean delivery analgesia. *J Clin Anesth* 2006; **18:** 29–33.

Metoclopramide. Reports on the effects of metoclopramide on morphine have included an increased rate of onset and degree of sedation when oral metoclopramide was given with modified-release morphine[1] and antagonism of the effects of morphine on gastric emptying by intravenous metoclopramide.[2]

1. Manara AR, *et al.* The effect of metoclopramide on the absorption of oral controlled release morphine. *Br J Clin Pharmacol* 1988; **25:** 518–21.
2. McNeill MJ, *et al.* Effect of iv metoclopramide on gastric emptying after opioid premedication. *Br J Anaesth* 1990; **64:** 450–2.

Tricyclic antidepressants. Both *clomipramine* and *amitriptyline* significantly increased the plasma availability of morphine when given to cancer patients taking oral morphine solution.[1] It was noted however that the potentiation of the analgesic effects of morphine by these drugs might not be confined to increased bioavailability of morphine; the dose of tricyclic to use with morphine in the treatment of cancer pain should be decided by clinical evaluation rather than by pharmacokinetic data.

1. Ventafridda V, *et al.* Antidepressants increase bioavailability of morphine in cancer patients. *Lancet* 1987; **i:** 1204.

Pharmacokinetics

Morphine salts are well absorbed from the gastrointestinal tract but have poor oral bioavailability since they undergo extensive first-pass metabolism in the liver and gut. After subcutaneous or intramuscular injection morphine is readily absorbed into the blood. The majority of a dose of morphine is conjugated with glucuronic acid in the liver and gut to produce morphine-3-glucuronide and morphine-6-glucuronide. The latter is considered to contribute to the analgesic effect of morphine, especially with repeated oral doses. Morphine-3-glucuronide on the other hand can antagonise the analgesic action and might be responsible for the paradoxical pain seen in some patients given morphine. Other active metabolites include normorphine, codeine, and morphine ethereal sulfate. Enterohepatic circulation probably occurs. Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs, and spleen, with lower concentrations in the brain and muscles. Morphine crosses the blood-brain barrier less readily than more lipid-soluble opioids such as diamorphine, but it has been detected in the CSF as have its highly polar metabolites morphine-3-glucuronide and morphine-6-glucuronide. Morphine diffuses across the placenta and traces also appear in breast milk and sweat. About 35% is protein bound. Mean plasma elimination half-lives of about 2 hours for morphine and 2.4 to 6.7 hours for morphine-3-glucuronide have been reported.

Up to 10% of a dose of morphine may eventually be excreted, as conjugates, through the bile into the faeces. The remainder is excreted in the urine, mainly as conjugates. About 90% of total morphine is excreted in 24 hours with traces in urine for 48 hours or more.

◊ Much has been published on the metabolism and disposition of morphine and its relevance to the clinical use of morphine, in particular the analgesic effect of repeated oral doses and the relative potency of oral to parenteral doses. There has been uncertainty as to the contributions in man of first-pass metabolism in the liver and gut,[1-4] the possible role of renal metabolism,[2,3,5,6] the analgesic activity and clinical importance of the metabolite morphine-6-glucuronide,[2,7-21] and enterohepatic circulation.[2,9] There has also been interest in the effects of the metabolite morphine-3-glucuronide.[21-24]

1. Hanks GW, Aherne GW. Morphine metabolism: does the renal hypothesis hold water? *Lancet* 1985; **i:** 221–2.
2. Hanks GW, *et al.* Explanation for potency of repeated oral doses of morphine? *Lancet* 1987; **ii:** 723–5.
3. Bodenham A, *et al.* Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* 1989; **63:** 380–4.
4. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
5. McQuay H, Moore A. Metabolism of narcotics. *BMJ* 1984; **288:** 237.
6. Moore A, *et al.* Morphine kinetics during and after renal transplantation. *Clin Pharmacol Ther* 1984; **35:** 641–5.
7. McQuay HJ, *et al.* Potency of oral morphine. *Lancet* 1987; **ii:** 1458–9.
8. Hanks GW, *et al.* Enterohepatic circulation of morphine. *Lancet* 1988; **i:** 469.
9. Osborne R, *et al.* Analgesic activity of morphine-6-glucuronide. *Lancet* 1988; **i:** 828.
10. Hanks GW, Wand PJ. Enterohepatic circulation of opioid drugs: is it clinically relevant in the treatment of cancer patients? *Clin Pharmacokinet* 1989; **17:** 65–8.
11. Paul D, *et al.* Pharmacological characterization of morphine-6β-glucuronide, a very potent morphine metabolite. *J Pharmacol Exp Ther* 1989; **251:** 477–83.
12. Hanna MH, *et al.* Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine. *Br J Anaesth* 1990; **64:** 547–50.
13. Osborne R, *et al.* Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990; **47:** 12–19.
14. McQuay HJ, *et al.* Oral morphine in cancer pain: influences on morphine and metabolite concentration. *Clin Pharmacol Ther* 1990; **48:** 236–44.
15. Hanna MH, *et al.* Disposition of morphine-6-glucuronide and morphine in healthy volunteers. *Br J Anaesth* 1991; **66:** 103–7.
16. Portenoy RK, *et al.* The metabolite morphine-6-glucuronide contributes to the analgesia produced by morphine infusion in patients with pain and normal renal function. *Clin Pharmacol Ther* 1992; **51:** 422–31.
17. Thompson PI, *et al.* Respiratory depression following morphine and morphine-6-glucuronide in normal subjects. *Br J Clin Pharmacol* 1995; **40:** 145–52.
18. Lötsch J, Geisslinger G. Morphine-6-glucuronide: an analgesic of the future? *Clin Pharmacokinet* 2001; **40:** 485–99.
19. Wittwer E, Kern SE. Role of morphine's metabolites in analgesia: concepts and controversies. *AAPS J* 2006; **8:** E348–E352.
20. van Dorp ELA, *et al.* Morphine-3-glucuronide—a potent antagonist of morphine analgesia. *Life Sci* 1990; **47:** 579–85.
21. Morley JS, *et al.* Paradoxical pain. *Lancet* 1992; **340:** 1045.
24. Morley JS, *et al.* Methadone in pain uncontrolled by morphine. *Lancet* 1993; **342:** 1243.

Administration. There have been many studies on the pharmacokinetics of morphine given by various routes and methods. These include the buccal route (see below), modified-release oral preparations,[1,2] the rectal route,[3,4] the topical route,[5] the pulmonary route,[6,7] continuous subcutaneous compared with intravenous infusion,[8] and the intraspinal route.[9-13]

Slow dural transfer of morphine and its prolonged presence in the CSF appear to correlate with its slow onset and long duration of action by epidural and intrathecal injection.[14] More lipid-soluble opioids, such as diamorphine and pethidine, enter and leave the CSF more rapidly than morphine.

The pharmacokinetics of morphine given by 5 different routes—intravenous bolus injection and oral, sublingual, buccal, and modified-release buccal tablets—were studied[15] with particular reference to morphine-6-glucuronide, the active metabolite. This metabolite occurred in large quantities after intravenous doses and plasma concentrations rapidly exceeded those of morphine. After oral doses morphine-6-glucuronide and morphine-3-glucuronide were present in quantities similar to those seen after intravenous morphine; morphine concentrations in plasma were very low and the mean morphine-6-glucuronide to morphine area under the curve ratio was 9.7 to 1. There was delayed absorption with attenuation and delay of peak morphine and metabolite plasma concentrations after sublingual or buccal dosage.

Compared with oral doses, concentrations of morphine were higher and those of its glucuronides lower when morphine was given rectally,[16] suggesting avoidance of first-pass metabolism.

Morphine was not absorbed systemically when applied topically to ulcers although some absorption may occur when a large surface area is involved.[5]

1. Pinnock CA, *et al.* Absorption of controlled release morphine sulphate in the immediate postoperative period. *Br J Anaesth* 1986; **58:** 868–71.
2. Savarese JJ, *et al.* Steady-state pharmacokinetics of controlled release oral morphine sulphate in healthy subjects. *Clin Pharmacokinet* 1986; **11:** 505–10.
3. Moolenaar F, *et al.* Drastic improvement in the rectal absorption profile of morphine in man. *Eur J Clin Pharmacol* 1985; **29:** 119–21.
4. Cole L, *et al.* Further development of a morphine hydrogel suppository. *Br J Clin Pharmacol* 1990; **30:** 781–6.
5. Ribeiro MDC, *et al.* The bioavailability of morphine applied topically to cutaneous ulcers. *J Pain Symptom Manage* 2004; **27:** 434–9.
6. Ward ME, *et al.* Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. *Clin Pharmacol Ther* 1997; **62:** 596–609.
7. Masood AR, Thomas SHL. Systemic absorption of nebulized morphine compared with oral morphine in healthy subjects. *Br J Clin Pharmacol* 1996; **41:** 250–2.
8. Waldmann CS, *et al.* Serum morphine levels: a comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients. *Anaesthesia* 1984; **39:** 768–71.
9. Gustafsson LL, *et al.* Disposition of morphine in cerebrospinal fluid after epidural administration. *Lancet* 1982; **i:** 796.
10. Moore A, *et al.* Spinal fluid kinetics of morphine and heroin. *Clin Pharmacol Ther* 1984; **35:** 40–5.
11. Max MB, *et al.* Epidural and intrathecal opiates: cerebrospinal fluid and plasma profiles in patients with chronic cancer pain. *Clin Pharmacol Ther* 1985; **38:** 631–41.
12. Nordberg G, *et al.* Extradural morphine: influence of adrenaline admixture. *Br J Anaesth* 1986; **58:** 598–604.
13. Ionescu TI, *et al.* The pharmacokinetics of intradural morphine in major abdominal surgery. *Clin Pharmacokinet* 1988; **14:** 178–86.
14. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
15. Osborne R, *et al.* Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990; **47:** 12–19.
16. Babul N, Darke AC. Disposition of morphine and its glucuronide metabolites after oral and rectal administration: evidence of route specificity. *Clin Pharmacol Ther* 1993; **54:** 286–92.

BUCCAL ROUTE. Conflicting results from studies on buccal morphine may reflect differences in formulation[1] and hence absorption. Some[2] reported equivalent analgesia with buccal and intramuscular morphine although others[3] found marked interindividual variability with mean peak serum concentrations of morphine some eight times lower after a buccal tablet

than after an intramuscular injection and occurring a mean of 4 hours later. Morphine sulfate in aqueous solution has been reported to be moderately well absorbed from the buccal mucosa.[4] Absolute bioavailability for morphine was estimated to be 23.8% after an oral solution, 22.4% after a modified-release oral tablet (*MST Continus; Napp, UK*), and 20.2% after a modified-release buccal tablet, with maximum plasma-morphine concentrations at 45 minutes, 2.5 hours, and 6 hours respectively; mean ratios of area under the plasma concentration-time curve for morphine-6-glucuronide to morphine in plasma were 11:1 after buccal and oral morphine compared with 2:1 for intravenous morphine.[5] There was considerable inter-subject variation in plasma concentrations of the morphine metabolites, morphine-3-glucuronide and morphine-6-glucuronide after buccal doses of morphine as a modified-release formulation,[6] and lack of pain relief was subsequently reported with this buccal formulation.[7] Poor absorption of morphine from modified-release buccal tablets when compared with intramuscular injection was also reported;[8] bitterness of the tablets, leading to their premature removal, and poor dissolution may have contributed.

1. Calvey TN, Williams NE. Pharmacokinetics of buccal morphine. *Br J Anaesth* 1990; **64:** 256.
2. Bell MDD, *et al.* Buccal morphine—a new route for analgesia? *Lancet* 1985; **i:** 71–3.
3. Fisher AP, *et al.* Serum morphine concentrations after buccal and intramuscular morphine administration. *Br J Clin Pharmacol* 1987; **24:** 685–7.
4. Al-Sayed-Omar O, *et al.* Influence of pH on the buccal absorption of morphine sulphate and its major metabolite, morphine-3-glucuronide. *J Pharm Pharmacol* 1987; **39:** 934–5.
5. Hoskin PJ, *et al.* The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *Br J Clin Pharmacol* 1989; **27:** 499–505.
6. Manara AR, *et al.* Pharmacokinetics of morphine following administration by the buccal route. *Br J Anaesth* 1989; **62:** 498–502.
7. Manara AR, *et al.* Analgesic efficacy of perioperative buccal morphine. *Br J Anaesth* 1990; **64:** 551–5.
8. Simpson KH, *et al.* An investigation of premedication with morphine given by the buccal or intramuscular route. *Br J Clin Pharmacol* 1989; **27:** 377–80.

Children. The pharmacokinetics of morphine in *children* are generally considered similar to those in adults;[1-3] in both an elimination half-life of about 2 hours has been reported after intravenous administration of morphine. In *neonates*, however, clearance is generally reduced[4-7] and pharmacokinetics are more variable.[8-10] Studies[7,11] have found significantly higher plasma concentrations of morphine and a significantly lower morphine-6-glucuronide to morphine ratio in neonates when compared with older infants and children; however, the morphine-6-glucuronide to morphine-3-glucuronide ratio remains constant irrespective of age.[7] Elimination half-lives of 6.7 and 10 hours have been reported in term and preterm infants, respectively after a single intravenous dose of morphine, with nearly 80% of the dose remaining unbound.[10] The reduced clearance, which is dependent on gestational age and birth weight,[12,13] and higher morphine concentrations are probably due to reduced metabolism in neonates as well as immature renal function: the capacity to conjugate morphine by glucuronidation is reduced in preterm infants,[6,8,9] and some premature neonates may lack the capacity entirely.[9]

1. Dahlström B, *et al.* Morphine kinetics in children. *Clin Pharmacol Ther* 1979; **26:** 354–65.
2. Stanski DR, *et al.* Kinetics of high-dose intravenous morphine in cardiac surgery patients. *Clin Pharmacol Ther* 1976; **19:** 752–6.
3. Olkkola KT, *et al.* Clinical pharmacokinetics and pharmacodynamics of opioid analgesics in infants and children. *Clin Pharmacokinet* 1995; **5:** 385–404.
4. Koren G, *et al.* Postoperative morphine infusion in newborn infants: assessment of disposition characteristics and safety. *J Pediatr* 1985; **107:** 963–7.
5. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. *Anesthesiology* 1987; **66:** 136–9.
6. Choonara IA, *et al.* Morphine metabolism in children. *Br J Clin Pharmacol* 1989; **28:** 599–604.
7. Bouwmeester NJ, *et al.* Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. *Br J Anaesth* 2003; **90:** 642–52.
8. Hartley R, *et al.* Pharmacokinetics of morphine infusion in premature neonates. *Arch Dis Child* 1993; **69:** 55–8.
9. Bhat R, *et al.* Morphine metabolism in acutely ill preterm newborn infants. *J Pediatr* 1992; **120:** 795–9.
10. Bhat R, *et al.* Pharmacokinetics of a single dose of morphine in preterm infants during the first week of life. *J Pediatr* 1990; **117:** 477–81.
11. Bouwmeester NJ, *et al.* Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Med* 2003; **29:** 2009–15.
12. Scott CS, *et al.* Morphine pharmacokinetics and pain assessment in premature newborns. *J Pediatr* 1999; **135:** 423–9.
13. Saarenmaa E, *et al.* Morphine clearance and effects in newborn infants in relation to gestational age. *Clin Pharmacol Ther* 2000; **68:** 160–6.

The elderly. The pharmacokinetics of morphine were compared[1] in 7 healthy elderly (60 to 69 years) and 13 healthy young (24 to 28 years) subjects, after a single intravenous injection of morphine sulfate 10 mg per 70 kg. Although the terminal rate of drug disappearance from plasma was faster in the elderly group, apparent volume of distribution at steady state was about half that of the young group and plasma clearance was reduced.

1. Owen JA, *et al.* Age-related morphine kinetics. *Clin Pharmacol Ther* 1983; **34:** 364–8.

Hepatic impairment. The liver is a major site of morphine metabolism and therefore hepatic impairment could be expected to affect elimination (see under Precautions, above). There is some evidence that in cirrhosis glucuronidation might be relatively spared compared with other metabolic processes and that some extrahepatic metabolism may occur. Several studies have served to illustrate these points:

- Hepatic extraction of morphine was impaired in cirrhotic patients, but less than expected[1]
- Morphine metabolism was minimal during the anhepatic phase of liver transplantation, but increased markedly when the new liver was reperfused[2]
- Morphine metabolism was virtually complete after liver transplantation with only 4.5% unchanged morphine being excreted in the urine 24 hours after administration[3]
- Morphine elimination was reduced when hepatic blood flow was impaired[4]

1. Crotty B, *et al.* Hepatic extraction of morphine is impaired in cirrhosis. *Eur J Clin Pharmacol* 1989; **36:** 501–6.
2. Bodenham A, *et al.* Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* 1989; **63:** 380–4.
3. Shelly MP, *et al.* Pharmacokinetics of morphine in patients following orthotopic liver transplantation. *Br J Anaesth* 1989; **63:** 375–9.
4. Manara AR, *et al.* Morphine elimination and liver blood flow: a study in patients undergoing distal splenorenal shunt. *Br J Hosp Med* 1989; **42:** 148 (abstract).

Renal impairment. Only a small amount of morphine is excreted unchanged in the urine. There are conflicting reports of morphine accumulation in patients with renal impairment; some for,[1,2] others against.[3-5] It does seem clear though that morphine metabolites accumulate in such patients[5-9] including those on peritoneal dialysis;[10] the half-life of the active metabolite morphine-6-glucuronide was reported to be prolonged and its clearance reduced when morphine-6-glucuronide was given to patients with renal impairment.[11] Opioid intoxication[12] and a prolonged opioid effect[13] in patients with renal failure has been associated with morphine-6-glucuronide (see also under Precautions, above).

1. Ball M, *et al.* Renal failure and the use of morphine in intensive care. *Lancet* 1985; **i:** 784–6.
2. Osborne R, *et al.* The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993; **54:** 158–67.
3. Säwe J, *et al.* Kinetics of morphine in patients with renal failure. *Lancet* 1985; **ii:** 211.
4. Woolner DF, *et al.* Renal failure does not impair the metabolism of morphine. *Br J Clin Pharmacol* 1986; **22:** 55–9.
5. Chauvin M, *et al.* Morphine pharmacokinetics in renal failure. *Anesthesiology* 1987; **66:** 327–31.
6. Säwe J, Odar-Cederlöf I. Kinetics of morphine in patients with renal failure. *Eur J Clin Pharmacol* 1987; **32:** 377–82.
7. Wolff J, *et al.* Influence of renal function on the elimination of morphine and morphine glucuronides. *Eur J Clin Pharmacol* 1988; **34:** 353–7.
8. Sear JW, *et al.* Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites. *Br J Anaesth* 1989; **62:** 28–32.
9. Peterson GM, *et al.* Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration. *Eur J Clin Pharmacol* 1990; **38:** 121–4.
10. Pauli-Magnus C, *et al.* Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 1999; **14:** 903–9.
11. Hanna MH, *et al.* Morphine-6-glucuronide disposition in renal impairment. *Br J Anaesth* 1993; **70:** 511–14.
12. Osborne RJ, *et al.* Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *BMJ* 1986; **292:** 1548–9.
13. Bodd E, *et al.* Morphine-6-glucuronide might mediate the prolonged opioid effect of morphine in acute renal failure. *Hum Exp Toxicol* 1990; **9:** 317–21.

Uses and Administration

Morphine, a phenanthrene derivative, is the main alkaloid of opium (p.105). It is now commonly obtained from whole opium poppies (*Papaver somniferum*) which are harvested as poppy straw; a concentrate of poppy straw is known as CPS.

Morphine is an opioid analgesic (p.104) with agonist activity mainly at μ opioid receptors and perhaps at κ and δ receptors. It acts mainly on the CNS and smooth muscle. Although morphine is mainly a CNS depressant it has some central stimulant actions which result in nausea and vomiting and miosis. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts.

Morphine may produce both physical and psychological dependence (see p.101) and should therefore be used with discrimination. Tolerance may also develop.

Morphine is used for the relief of moderate to severe pain, especially that associated with cancer, myocardial infarction, and surgery. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain and it is useful as a hypnotic where sleeplessness is due to pain. It is also used in the management of neonatal abstinence syndrome (see Administration in Children, below).

Morphine reduces intestinal motility but its role, if any, in the symptomatic treatment of diarrhoea is very limited. It also relieves dyspnoea associated with various conditions, including that due to pulmonary oedema resulting from left ventricular failure. It is an effective cough suppressant, but codeine is usually preferred as there is less risk of dependence; morphine may however be necessary to control intractable cough associated with terminal lung cancer. Morphine has been used pre-operatively as an adjunct to anaesthesia for pain relief and to allay anxiety. It has also been used in high doses as a general anaesthetic in specialised procedures such as open-heart surgery.

Morphine is usually **administered** as the sulfate, although the hydrochloride and the tartrate are used in similar doses. Doses are expressed as the salts. Dosage routes include the oral, subcutaneous, intramuscular, intravenous, intraspinal, and rectal routes. Subcutaneous injections are considered unsuitable for oedematous patients. Parenteral doses may be intermittent injections or continuous or intermittent infusions adjusted according to individual analgesic requirements.

Doses should generally be reduced in the elderly or debilitated or in patients with hepatic or renal impairment (see also under Precautions, above).

For **pain**:

- *Oral* doses are usually in the range of 5 to 20 mg every 4 hours and may be given as an aqueous solution of the hydrochloride or sulfate, as modified-release granules or tablets, or as tablets. With modified-release preparations the 24-hour dose is usually given as a single dose or in 2 divided doses; in the USA, a modified-release preparation (*MS Contin, Purdue*) that allows dosing every 8 or 12 hours is also available. With all modified-release preparations, additional doses of a conventional formulation may be needed if breakthrough pain occurs. As with the other routes, high oral doses may be required for effective analgesia in palliative care.
- Morphine is sometimes given *rectally* generally as suppositories in doses of 10 to 30 mg every 4 hours. Oral modified-release preparations have also been used rectally although such use is unlicensed in the UK and is generally not recommended except, possibly, in some emergency situations.
- The usual dose by *subcutaneous* or *intramuscular* injection is 10 mg every 4 hours but may range from 5 to 20 mg.
- Doses of up to 15 mg have been given by slow *intravenous* injection, sometimes as a loading dose for continuous or patient-controlled infusion. For continuous intravenous administration maintenance doses have generally ranged from 0.8 to 80 mg/hour, although some patients have required and been given much higher doses. Similar doses have been given by continuous subcutaneous infusion.
- For myocardial infarction, the *BNF* recommends that 10 mg may be given by intravenous injection at a rate of 2 mg/minute followed by a further 5 to 10 mg if necessary; half this dose should be used in elderly or debilitated patients.
- Intraspinal doses are in the region of 5 mg for an initial *epidural* injection; if pain relief is unsatisfactory after one hour, further doses of 1 to 2 mg may be given up to a total dose of 10 mg per 24 hours. The recommended initial dose for continuous epidural infusion is 2 to 4 mg per 24 hours increased if necessary by further doses of 1 to 2 mg. A modified-release formulation of liposomal morphine sulfate for lumbar epidural use is also available for the treatment of pain after major surgery; doses range from

10 to 20 mg, depending on the type of surgery, and should be given before the operation, or after clamping of the umbilical cord if used during caesarean section. It is intended for single-use only and no other drugs should be administered into the epidural space for at least the next 48 hours.

- *Intrathecal* use of morphine and its salts has tended to be less common than epidural. Doses of 200 micrograms to 1 mg have been injected intrathecally on a single occasion.

For details of doses in children see below.

In **acute pulmonary oedema** 5 to 10 mg may be given by intravenous injection at a rate of 2 mg/minute.

For the control of intractable **cough** associated with terminal lung cancer, morphine oral solution is given in an initial dose of 5 mg every 4 hours.

Administration. ***CONTINUOUS INFUSION.*** Both acute and chronic pain have been controlled satisfactorily by continuous intravenous or subcutaneous infusions of morphine sulfate[1-3] but diamorphine hydrochloride or hydromorphone hydrochloride may be preferred for subcutaneous infusion because their greater solubility in water allows a smaller dose volume. Continuous subcutaneous infusions may be preferred to continuous intravenous infusions.[4] Continuous subcutaneous infusion may be less effective than epidural morphine for relief of postoperative pain;[5] however, it was still considered to provide simple and relatively effective analgesia with a low rate of adverse effects.

See also Patient-controlled Analgesia, below.

1. Waldmann CS, *et al.* Serum morphine levels: a comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients. *Anaesthesia* 1984; **39:** 768–71.
2. Goudie TA, *et al.* Continuous subcutaneous infusion of morphine for postoperative pain relief. *Anaesthesia* 1985; **40:** 1086–92.
3. Stuart GJ, *et al.* Continuous intravenous morphine infusions for terminal pain control: a retrospective review. *Drug Intell Clin Pharm* 1986; **20:** 968–72.
4. Drexel H. Long-term continuous subcutaneous and intravenous opioid infusions. *Lancet* 1991; **337:** 979.
5. Hindsholm KB, *et al.* Continuous subcutaneous infusion of morphine—an alternative to extradural morphine for postoperative pain relief. *Br J Anaesth* 1993; **71:** 580–2.

INTRA-ARTICULAR ROUTE. Intra-articular injection of morphine into the knee at the end of arthroscopy has been reported to provide some degree of postoperative pain relief;[1,2] such pain relief may be more pronounced than that produced by the same dose given intravenously[1] or intramuscularly.[2] The effect appears to be due to the action of morphine on peripheral opioid receptors[2] although a systemic effect has not been completely excluded.[1]

There have been conflicting results on whether addition of morphine to intra-articular bupivacaine improves analgesia[3,4] and a systematic review[5] concluded that from the few well-controlled studies there was no evidence of an added analgesic effect of morphine compared with saline alone.

Doses of morphine reported to have been injected intra-articularly have ranged from 1 to 10 mg.

1. Gupta A, *et al.* A systematic review of the peripheral analgesic effects of intraarticular morphine. *Anesth Analg* 2001; **93:** 761–70.
2. Raj N, *et al.* Comparison of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy. *Eur J Anaesthesiol* 2004; **21:** 932–7.
3. Laurent SC, *et al.* Addition of morphine to intra-articular bupivacaine does not improve analgesia after day-case arthroscopy. *Br J Anaesth* 1994; **72:** 170–3.
4. Heine MF, *et al.* Intra-articular morphine after arthroscopic knee operation. *Br J Anaesth* 1994; **73:** 413–15.
5. Rosseland LA. No evidence for analgesic effect of intra-articular morphine after knee arthroscopy: a qualitative systematic review. *Reg Anesth Pain Med* 2005; **30:** 83–98.

INTRANASAL ROUTE. An intranasal formulation of morphine is under investigation for the relief of acute pain.

INTRASPINAL ROUTE. Morphine is given epidurally and intrathecally to relieve both acute and chronic pain. However, reviews on the role of spinal opioids have generally concluded that they should be reserved for pain not controlled by more conventional routes.[1-3] When converting from conventional routes it has been suggested that 1% of the total daily dose could be tried as the daily intrathecal dose and 10% as the epidural dose.[3] Conversion from intrathecal to oral dosage has also been investigated.[4]

Intrathecal morphine may be delivered continuously via an implanted programmable infusion pump for the long-term management of chronic non-malignant and cancer pain.

See also Patient-controlled Analgesia, below.

1. Anonymous. Spinal opiates revisited. *Lancet* 1986; **i:** 655–6.
2. Gustafsson LL, Wiesenfeld-Hallin Z. Spinal opioid analgesia: a critical update. *Drugs* 1988; **35:** 597–603.
3. McQuay HJ. Opioids in chronic pain. *Br J Anaesth* 1989; **63:** 213–26.
4. Sylvester RK, *et al.* The conversion challenge: from intrathecal to oral morphine. *Am J Hosp Palliat Care* 2004; **21:** 143–7.

PATIENT-CONTROLLED ANALGESIA. Morphine is one of the most frequently used opioid analgesics for patient-controlled analgesia (see p.4). Most experience has been with the intravenous route, but the intramuscular, subcutaneous, oral, pulmonary, and epidural[1] routes have also been used. Reasonable initial settings recommended for intravenous use have been a demand dose of 1 to 2 mg of morphine sulfate (or its equivalent) and a lockout interval of 5 to 10 minutes.[2]

1. Sjöström S, *et al.* Patient-controlled analgesia with extradural morphine or pethidine. *Br J Anaesth* 1988; **60:** 358–66.
2. Grass JA. Patient-controlled analgesia. *Anesth Analg* 2005; **101** (suppl): S44–S61.

PULMONARY ROUTE. For reference to the use of nebulised morphine see Dyspnoea, below.

TOPICAL ROUTE. Morphine has been applied topically for local analgesia in oral mucositis[1,2] and cutaneous ulceration[3-6] including epidermolysis bullosa.[7]

1. Cerchietti LC, *et al.* Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer* 2000; **95:** 2230–6. Correction. *ibid.* 2003; **97:** 1137.
2. Cerchietti L. Morphine mouthwashes for painful mucositis. *Support Care Cancer* 2007; **15:** 115–16.
3. Twillman RK, *et al.* Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage* 1999; **17:** 288–92.
4. Krajnik M, *et al.* Potential uses of topical opioids in palliative care–report of 6 cases. *Pain* 1999; **80:** 121–5.
5. Zeppetella G, *et al.* Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage* 2003; **25:** 555–8.
6. Zeppetella G, Ribeiro MDC. Morphine in Intrasite gel applied topically to painful ulcers. *J Pain Symptom Manage* 2005; **29:** 118–19.
7. Watterson G, *et al.* Peripheral opioids in inflammatory pain. *Arch Dis Child* 2004; **89:** 679–81.

Administration in children. Opioid analgesics are used in children in the management of moderate to severe **pain** (see p.3); morphine is the most widely used opioid for severe pain in children and is the standard against which other opioids are compared. Morphine may be given to children requiring acute analgesia as a result of surgery or invasive procedures. It may also be given for chronic non-malignant pain and is the opioid of choice for the oral treatment of severe pain in palliative care. Its analgesic and sedative properties are useful in the management of children in intensive care (see p.957); morphine is considered to be a more rational choice than fentanyl in settings where long-term infusions are required. Respiratory depression with morphine treatment is a risk in all children; however, neonates (and particularly those who are breathing spontaneously) may have an enhanced susceptibility because of the pharmacokinetic differences of morphine in this age group (see above).

The following initial doses are recommended by the *BNFC*; doses should thereafter be adjusted according to response:

- By subcutaneous or intramuscular injection, neonates may be given 100 micrograms/kg every 6 hours; those aged 1 to 6 months, 100 to 200 micrograms/kg every 6 hours; 6 months to 2 years, 100 to 200 micrograms/kg every 4 hours; 2 to 12 years, 200 micrograms/kg every 4 hours; 12 to 18 years, 2.5 to 10 mg every 4 hours
- By intravenous injection over at least 5 minutes, neonates may be given 50 micrograms/kg every 6 hours; those aged 1 to 6 months, 100 micrograms/kg every 6 hours; 6 months to 12 years, 100 micrograms/kg every 4 hours; 12 to 18 years, 2.5 mg every 4 hours

  The following doses given by slow intravenous injection are suggested as loading doses for continuous intravenous infusion: neonates may be given 25 to 100 micrograms/kg; those aged 1 to 6 months, 100 to 200 micrograms/kg; 6 months to 12 years, 100 to 200 micrograms/kg; 12 to 18 years, 2.5 to 10 mg. The loading dose may be followed by an infusion given in a dose dependent on the patient's age: neonates, 5 to 40 micrograms/kg per hour; 1 to 6 months, 10 to 30 micrograms/kg per hour; 6 months to 18 years, 20 to 30 micrograms/kg per hour
- By mouth or rectum, infants aged 1 to 12 months may be given 80 to 200 micrograms/kg every 4 hours; those aged 1 to 2 years, 200 to 400 micrograms/kg every 4 hours; 2 to 12 years, 200 to 500 micrograms/kg, to a maximum of 20 mg, every 4 hours; 12 to 18 years, 5 to 20 mg every 4 hours. In *palliative care*, modified-release oral preparations may be used; they are given as a single daily dose or in 2 divided doses
- By continuous subcutaneous infusion, children aged 1 to 3 months may be given 10 micrograms/kg per hour; those aged 3 months to 18 years, 20 micrograms/kg per hour

Intraspinal doses of morphine that have been tried[1] in children are as follows:

- Caudal epidural block, 100 micrograms/kg
- Thoracic or lumbar epidural block, 50 micrograms/kg
- Intrathecal doses of 20 or 30 micrograms/kg have provided satisfactory postoperative pain relief, but respiratory depression occurred in 10 and 25%, respectively

Guidelines[2] for analgesia in children in Accident and Emergency departments in the UK recommend the use of intravenous morphine as an alternative to, or after initial treatment with, intranasal diamorphine for *severe pain* such as that associated with large burns, long bone dislocation, appendicitis, or sickle-cell crisis, but it should be used with caution if there is risk of depression of airway, breathing, or circulation.

In the UK, morphine is also used in the management of **neonatal abstinence syndrome** (p.102) under specialist supervision. The *BNFC* recommends an initial oral dose of 40 micrograms/kg (increase dose if necessary) every 4 hours until symptoms are controlled; the dosage frequency should be reduced gradually over 6 to 10 days until a dose of 40 micrograms/kg once daily is achieved after which the drug should be stopped.

1. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; **64:** 85–104.
2. 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)

Cancer pain. Morphine is the opioid of choice for moderate to severe cancer pain (p.5); guidelines for its use issued by the European Association for Palliative Care[1] include:

- the optimal route for use is by mouth. For best effect, both conventional (for dose titration) and modified-release (for maintenance) dosage forms are required
- the simplest method of dose titration is with conventional morphine dosage every 4 hours, and the same dose for breakthrough pain. This 'rescue dose' may be given as often as required, up to hourly. The total daily dose of morphine should be reviewed each day and the regular dose adjusted to take into account the amount needed for breakthrough pain
- if pain returns consistently before the next dose is due the regular dose should be increased. Conventional formulations do not generally need to be given more often than every 4 hours, and modified-release products should be given according to the intended duration of the preparation (usually every 12 or 24 hours). Patients stabilised on regular oral morphine require continued access to a rescue dose for breakthrough pain
- if a conventional formulation of morphine is not available and treatment is started with modified-release morphine, changes to the regular dose should not be made more often than every 48 hours, which means that dose titration will be prolonged
- for patients taking conventional morphine preparations every 4 hours, a double dose at bedtime is effective to prevent pain disturbing sleep
- if patients are unable to take morphine orally the preferred alternative route is subcutaneous. There is no indication for intramuscular morphine for cancer pain since subcutaneous dosage is simpler and less painful
- when converting dosage, the relative potency of oral to subcutaneous morphine is between about 1:2 and 1:3, so 20 to 30 mg of oral morphine is equianalgesic to 10 mg by subcutaneous injection
- in patients who need continuous parenteral morphine the preferred route is by subcutaneous infusion. However, intravenous infusion may be preferred:

  in patients who already have an indwelling intravenous line

  in those with generalised oedema

  if erythema, soreness, or sterile abscess develop during subcutaneous dosage

  in patients with coagulation disorders

  where peripheral circulation is poor
- when converting dosage, the relative potency of oral to intravenous morphine is also between about 1:2 and 1:3
- the buccal, sublingual, and nebulised routes of administration are not recommended in the absence of evidence for clinical advantage over more usual routes
- a small proportion of patients develop intolerable adverse effects with oral morphine (in conjunction with adjuvant non-opioid analgesics as appropriate) before achieving adequate pain relief. In such patients a change to an alternative opioid, or a change in the route should be considered. Although switching between opioids complicates pain management, adequate pain relief for some may depend on the use of alternative drugs, the use of intraspinal routes, or non-drug methods of pain control

Similar recommendations are given in guidelines issued by the US National Comprehensive Cancer Network.[2]

1. Hanks GW, *et al.* Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001; **84:** 587–93.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: adult cancer pain (version 1.2008). Available at: http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf (accessed 26/06/08)

Dyspnoea. In the treatment of dyspnoea (p.104), doses of morphine tend to be smaller than those used for pain relief. Morphine hydrochloride or sulfate may be given as an oral solution in carefully titrated doses, starting at a dose of 5 mg every 4 hours; as little as 2.5 mg every 4 hours may be sufficient for opioid-naive patients.[1] In acute pulmonary oedema, 5 to 10 mg may be given

by slow intravenous injection. In patients already receiving morphine for pain relief the following doses have been suggested:[2]

- mild dyspnoea: 25 to 50% of usual analgesic dose
- moderate dyspnoea: 50 to 100% of usual analgesic dose
- severe dyspnoea: 100% or more of usual analgesic dose

Patients have also obtained relief from subcutaneous injection.[3]

Although it has been reported that a low dose of nebulised morphine (mean dose 1.7 mg) improved exercise endurance in patients with dyspnoea due to advanced chronic lung disease,[4] several subsequent studies[5-7] have failed to obtain significant improvements with doses up to 40 mg. It is considered that current evidence does not support the use of nebulised morphine for breathlessness.[1,8-10] Furthermore, bronchospasm can be a problem, particularly at high doses, and there is no consensus on the optimal dose, schedule, or method of dose titration.

1. Davis CL. ABC of palliative care: breathlessness, cough, and other respiratory problems. *BMJ* 1997; **315:** 931–4.
2. Twycross R, Wilcock A. *Palliative Care Formulary.* 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 280.
3. Bruera E, *et al.* Subcutaneous morphine for dyspnea in cancer patients. *Ann Intern Med* 1993; **119:** 906–7.
4. Young IH, *et al.* Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax* 1989; **44:** 387–90.
5. Beauford W, *et al.* Effects of nebulized morphine sulfate on the exercise tolerance of the ventilatory limited COPD patients. *Chest* 1993; **104:** 175–8.
6. Noseda A, *et al.* Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. *Eur Respir J* 1997; **10:** 1079–83.
7. Jankelson D, *et al.* Lack of effect of high doses of inhaled morphine on exercise endurance in chronic obstructive pulmonary disease. *Eur Respir J* 1997; **10:** 2270–4.
8. Polosa R, *et al.* Nebulised morphine for severe interstitial lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 26/06/08).
9. Foral PA, *et al.* Nebulized opioids use in COPD. *Chest* 2004; **125:** 691–4.
10. Brown SJ, *et al.* Nebulized morphine for relief of dyspnea due to chronic lung disease. *Ann Pharmacother* 2005; **39:** 1088–92.

Preparations

BP 2008: Chloroform and Morphine Tincture; Morphine and Atropine Injection; Morphine Sulphate Injection; Morphine Suppositories; Morphine Tablets; Prolonged-release Morphine Tablets;
USP 31: Morphine Sulfate Extended-Release Capsules; Morphine Sulfate Injection; Morphine Sulfate Suppositories.

Proprietary Preparations (details are given in Part 3)
Arg.: Algedol; Amidiaz; Analmorph; Duramorph; GNO; MST Continus; Neocalmans; ***Austral.:*** Anamorph; Kapanol; MS Contin; MS Mono; Ordine; Sevredol; ***Austria:*** Compensan; Kapabloc; Kapanol; M-Dolor; Morapid; Mundidol; Substitol; Vendal; ***Belg.:*** Docmorfine; Kapanol; MS Contin; MS Direct; Oramorph; Stellorphinad; Stellorphine; ***Braz.:*** Dimorf; Dolo Moff; MS-Long†; MST Continus†; ***Canad.:*** Kadian; M-Eslon; Morphitec†; MOS; MS Contin; MSIR; Oramorph†; Statex†; ***Chile:*** M-Eslon; ***Cz.:*** Doltard†; M-Eslon; MST Continus; MST Uno†; Oramorph†; Sevredol; Skenan†; Slovalgin; Vendal; ***Denm.:*** Contalgin; Depolan; Doltard; ***Fin.:*** Depolan; Dolcontin; ***Fr.:*** Actiskenan; Kapanol; Moscontin; Oramorph; Sevredol; Skenan; ***Ger.:*** Capros; Kapanol; M-beta; M-Dolor†; M-long; M-Stada; Mogetic†; Morph; Morphanton; MSI; MSR; MST; Onkomorphin†; Oramorph; Painbreak; Sevredol; ***Hong Kong:*** M-Eslon; MST Continus; ***Hung.:*** M-Eslon; Moretal; MST Continus; Sevredol; ***India:*** Morcontin; ***Indon.:*** MST; ***Irl.:*** Morstel†; MST Continus; MXL; Oramorph; Sevredol; Slo-Morph†; ***Israel:*** Kapanol†; MCR; MIR; Morphex; MSP; ***Ital.:*** MS Contin; Oramorph; Skenan†; Ticinan; Twice; ***Jpn:*** MS Contin; ***Malaysia:*** MST Continus; ***Mex.:*** Analfin; Duralmor†; Graten; ***Neth.:*** Kapanol; MS Contin; Noceptin†; Oramorph; Sevredol; Skenan; ***Norw.:*** Dolcontin; ***NZ:*** Kapanol; LA Morph; M-Eslon; MST Continus†; MST Mono†; RA Morph; Sevredol; ***Philipp.:*** M-Dolor; MST Continus; Relimal; ***Pol.:*** MST Continus; Sevredol; Vendal; ***Port.:*** Ethirfin; MST; MXL†; Oramorph; Sevredol; Skenan; ***S.Afr.:*** MST Continus; SRM-Rhotard; ***Singapore:*** MST Continus; SRM-Rhotard†; Statex; ***Spain:*** MST Continus; MST Unicontinus; Oglos†; Oramorph; Sevredol; Skenan; ***Swed.:*** Depolan; Dolcontin; ***Switz.:*** Kapanol; M-retard; MST Continus; Sevre-Long; Sevredol; ***Turk.:*** M-Eslon; Vendal; ***UK:*** Filnarine; Morcap†; Morphgesic; MST Continus; MXL; Oramorph; Rhotard; Sevredol; Zomorph; ***USA:*** Astramorph; Avinza; DepoDur; Duramorph; Infumorph; Kadian; MS Contin; MSIR; Oramorph; RMS; Roxanol; ***Venez.:*** MS Contin.

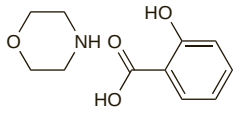
Multi-ingredient: ***Austral.:*** Morphalgin†; ***Austria:*** Modiscop; ***Belg.:*** Spasma†; ***Irl.:*** Cyclimorph; ***Ital.:*** Cardiostenol; ***Pol.:*** Doltard; ***S.Afr.:*** Chloropect; Cyclimorph; Enterodyne; Pectrolyte; ***Swed.:*** Spasmofen; ***Switz.:*** Spasmosol; ***UK:*** Collis Browne's; Cyclimorph; Diocalm Dual Action; Opazimes.

Morpholine Salicylate

Morfoliinsalisylaatti; Morfolinsalicylat; Morpholini Salicylas; Salicilato de morfolinio. 2-Hydroxybenzoic acid compounded with morpholine (1 : 1).

Морфолин Салицилат

$C_{11}H_{15}NO_4$ = 225.2.
CAS — 147-90-0.
ATC — N02BA08.
ATC Vet — QN02BA08.



Profile

Morpholine salicylate is a salicylic acid derivative (see Aspirin, p.20) that has been used for musculoskeletal disorders.

Preparations

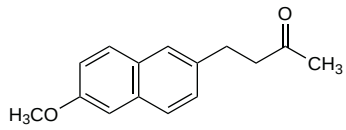
Proprietary Preparations (details are given in Part 3)
Israel: Dolical.

Nabumetone *(BAN, USAN, rINN)*

BRL-14777; Nabumeton; Nabumetona; Nabumetonas; Nabumétone; Nabumetoni; Nabumetonum. 4-(6-Methoxy-2-naphthyl)butan-2-one.

Набуметон

$C_{15}H_{16}O_2$ = 228.3.
CAS — 42924-53-8.
ATC — M01AX01.
ATC Vet — QM01AX01.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in acetone; slightly soluble in methyl alcohol. Protect from light.
USP 31 (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96. Nabumetone is contra-indicated in patients with severe hepatic impairment.

Effects on the gastrointestinal tract. Like other NSAIDs nabumetone can produce adverse effects on the gastrointestinal tract, although some studies have produced favourable comparisons with ibuprofen[1] or naproxen.[2] A recent review[3] noted that limited comparative data suggest that nabumetone has a similar gastrointestinal adverse effect profile to that of selective COX-2 inhibitors. It has been suggested[4] that nabumetone may be a preferential inhibitor of cyclo-oxygenase-2 (COX-2) but the significance of this in determining its adverse effects is uncertain.

1. Roth SH, *et al.* A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen plus misoprostol on the upper gastrointestinal tract mucosa. *Arch Intern Med* 1993; **153:** 2565–71.
2. Roth SH, *et al.* A longterm endoscopic evaluation of patients with arthritis treated with nabumetone vs naproxen. *J Rheumatol* 1994; **21:** 1118–23.
3. Bannwarth B. Safety of the nonselective NSAID nabumetone: focus on gastrointestinal tolerability. *Drug Safety* 2008; **31:** 485–503.
4. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; **33:** 403–16.

Effects on the lungs. Pulmonary fibrosis developed in a 68-year-old woman taking nabumetone 1.5 g; symptoms appeared after 2 weeks of therapy and worsened during the next 6 weeks.[1] There was rapid resolution on stopping nabumetone and treatment with oral corticosteroids.

1. Morice A, *et al.* Pulmonary fibrosis associated with nabumetone. *Postgrad Med J* 1991; **67:** 1021–2.

Effects on the skin. Pseudoporphyria characterised by blistering on the neck and hands developed in a 36-year-old woman taking nabumetone and auranofin for rheumatoid arthritis.[1] Stopping auranofin had no effect on the blistering which only resolved once nabumetone was withdrawn. The authors of the report stated that the UK CSM had received 3 additional reports of pseudoporphyria suspected to be caused by nabumetone.

1. Varma S, Lanigan SW. Pseudoporphyria caused by nabumetone. *Br J Dermatol* 1998; **138:** 549–50. Correction. *ibid.* **139:** 759. [dose]

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Nabumetone is well absorbed from the gastrointestinal tract. Plasma concentrations after oral doses are too small to be measured, as it undergoes rapid and extensive first-pass metabolism in the liver to the principal active compound 6-methoxy-2-naphthylacetic acid (6-MNA) and other inactive metabolites. 6-MNA is more than 99% bound to plasma proteins. It diffuses into synovial fluid, crosses the placenta, and is distributed into breast milk. There is considerable interindividual variation in the plasma elimination half-life of 6-MNA, especially in the elderly; some reported mean values at steady state include 22 to about 27 hours for young adults and about 25 and 34 hours in elderly patients. 6-MNA eventually undergoes further metabolism by *O*-methylation and conjugation. About 80% of a dose is excreted in the urine as inactive or conjugated metabolites and less than 1% as unchanged 6-MNA.

◊ References.

1. Brier ME, *et al.* Population pharmacokinetics of the active metabolite of nabumetone in renal dysfunction. *Clin Pharmacol Ther* 1995; **57:** 622–7.
2. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; **33:** 403–16.

Uses and Administration

Nabumetone is a non-active prodrug whose major metabolite is an NSAID (p.99) structurally similar to naproxen (p.92). It is used for the relief of pain and inflammation associated with osteoarthritis and rheumatoid arthritis in a usual oral dose of 1 g taken as a single dose in the evening; if necessary 0.5 to 1 g may be given additionally in the morning. It has been recommended that a dose of 1 g daily should not be exceeded in elderly patients and that 500 mg daily may be satisfactory in some cases.

◊ References.

1. Friedel HA, *et al.* Nabumetone: a reappraisal of its pharmacology and therapeutic use in rheumatic diseases. *Drugs* 1993; **45:** 131–56.
2. Proceedings of a symposium: continuing developments with nabumetone: an investigators' update. *Am J Med* 1993; 95 (suppl 2A): 1S–45S.
3. Dahl SL. Nabumetone: a "nonacidic" nonsteroidal antiinflammatory drug. *Ann Pharmacother* 1993; **27:** 456–63.
4. Hedner T, *et al.* Nabumetone: therapeutic use and safety profile in the management of osteoarthritis and rheumatoid arthritis. *Drugs* 2004; **64:** 2315–43.

Preparations

BP 2008: Nabumetone Oral Suspension; Nabumetone Tablets;
USP 31: Nabumetone Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Relifex†; ***Canad.:*** Relafen; ***Cz.:*** Relifex; Rodanol S†; ***Denm.:*** Relifex; ***Fin.:*** Relifex; ***Fr.:*** Nabucox; ***Gr.:*** Akratol; Anfer; Ethyfen†; Flogmed; Mevedal; Nabuton; Naditone; Relifex; ***Hong Kong:*** Relifex†; ***Hung.:*** Relifex; Rodanol S†; ***India:*** Nabuflam; ***Indon.:*** Goflex; ***Irl.:*** Relifex; Religer; ***Israel:*** Nabuco; Relifex; ***Ital.:*** Artaxan; Nabuser; ***Jpn:*** Relifen; ***Mex.:*** Naflam; Relifex; ***Neth.:*** Mebutan; ***Norw.:*** Relifex; ***Philipp.:*** Relifex; ***Pol.:*** Coxalgan; Coxeton; Nabuton; Relifex; Rodanol S; ***Port.:*** Balmox; Elitar; ***Rus.:*** Rodanol (Роданол); ***S.Afr.:*** Relifen; Relisan; Relitone; ***Spain:*** Listran; Relif; ***Swed.:*** Relifex; ***Switz.:*** Balmox; ***Thai.:*** Aflex; Anfer†; Bumetone; Nabone; Nabonet; Naflex; Nametone; No-Ton†; Relifex; ***Turk.:*** Relifex; ***UK:*** Relifex; ***USA:*** Relafen†.

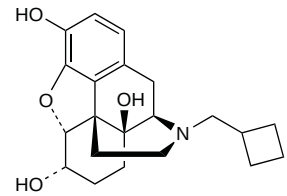
Nalbuphine Hydrochloride

(BANM, USAN, rINNM)

EN-2234A; Hidrocloruro de nalbufina; Nalbufine Hydrochloride; Nalbuphine, Chlorhydrate de; Nalbuphini Hydrochloridum. 17-Cyclobutylmethyl-7,8-dihydro-14-hydroxy-17-normorphine hydrochloride; (−)-(5*R*,6*S*,14*S*)-9a-Cyclobutylmethyl-4,5-epoxymorphinan-3,6,14-triol hydrochloride.

Налбуфина Гидрохлорид

$C_{21}H_{27}NO_4$,HCl = 393.9.
CAS — 20594-83-6 (nalbuphine); 23277-43-2 (nalbuphine hydrochloride).
ATC — N02AF02.
ATC Vet — QN02AF02.



(nalbuphine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of nalbuphine hydrochloride:
Nubian.

Incompatibility. Incompatibility has been reported between injections of nalbuphine hydrochloride and nafcillin sodium,[1] diazepam,[2] pentobarbital sodium,[2] or thiethylperazine maleate.[2] US licensed product information states that nalbuphine is also physically incompatible with ketorolac.

1. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462–4.
2. Jump WG, *et al.* Compatibility of nalbuphine hydrochloride with other preoperative medications. *Am J Hosp Pharm* 1982; **39:** 841–3.