liquid. Very slightly soluble in water; miscible with alcohol, and with fatty and essential oils. Protect from light.

USNF 26 (Methyl Salicylate). It is produced synthetically or is obtained from the leaves of *Gaultheria procumbens* (Ericaceae) [wintergreen] or from the bark of *Betula lenta* (Betulaceae) [sweet or black birch]. The source of the methyl salicylate must be indicated on the label.

A colourless, yellowish, or reddish liquid having the characteristic odour of wintergreen. Slightly soluble in water; soluble in alcohol and in glacial acetic acid. Store in airtight containers.

Storage. Certain plastic containers, such as those made from polystyrene, are unsuitable for liniments or ointments containing methyl salicylate.

Adverse Effects, Treatment, and Precautions

Salicylate intoxication can occur after ingestion or topical application of methyl salicylate (see Overdosage, below).

Overdosage. Ingestion of methyl salicylate poses the threat of severe, rapid-onset salicylate poisoning because of its liquid concentrated form and lipid solubility.[1] It is readily absorbed from the gastrointestinal tract and most is rapidly hydrolysed to free salicylate. The symptoms, which may appear within 2 hours of ingestion, are similar to those of salicylate poisoning in general (see Adverse Effects of Aspirin, p.20), although methyl salicylate is expected to be more toxic because of its lipid solubility. There have been reports of fatalities after ingestion of as little as 4 mL in a child and 6 mL in an adult, although the adult lethal dose is estimated to be 30 mL.[1] Topical Chinese herbal medicinal preparations may contain methyl salicylate in variable amounts, and salicylate poisoning has been reported in a 40-year-old man after a total body application of such a preparation.[2] Salicylate poisoning has also been reported in a woman who had attempted suicide by ingesting Red Flower Oil, a topical Chinese herbal oil.[3] The authors also noted that some patients took small amounts of this preparation orally in an attempt to enhance its analgesic effects.

1. Chan TYK. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol* 1996; **15:** 747–50.
2. Bell AJ, Duggin G. Acute methyl salicylate toxicity complicating herbal skin treatment for psoriasis. *Emerg Med (Fremantle)* 2002; **14:** 188–90.
3. Chan TH, *et al.* Severe salicylate poisoning associated with the intake of Chinese medicinal oil ('Red Flower Oil'). *Aust N Z J Med* 1995; **25:** 57.

Percutaneous absorption. Like other salicylates, methyl salicylate may be absorbed through intact skin.[1] Percutaneous absorption is enhanced by exercise, heat, occlusion, or disruption of the integrity of the skin. The amount absorbed will also be increased by application to large areas of skin.

Results from a study in healthy subjects showed that a considerable amount of salicylic acid may be absorbed through the skin after topical application of products containing methyl salicylate.[2] Both the rate and extent of absorption increased after repeated application; the bioavailability of the ointment preparation used in the study increased from 15% after the second dose to 22% after the third to eighth dose. The authors recommend that topical analgesic preparations containing methyl salicylate or other salicylates should be used with caution in patients at increased risk of developing salicylate adverse effects (see Precautions of Aspirin, p.22).

Results from another study[3] showing high tissue to plasma ratios after topical application of a methyl salicylate formulation suggest that direct penetration and not recirculation in the blood is responsible for the salicylate concentrations found. The results also showed that methyl salicylate is extensively metabolised to salicylic acid in the dermal and subcutaneous tissues after topical application.

However, for a study suggesting limited absorption from a patch preparation containing camphor, menthol, and methyl salicylate, see Menthol, p.2340.

1. Chan TYK. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol* 1996; **15:** 747–50.
2. Morra P, *et al.* Serum concentrations of salicylic acid following topical applied salicylate derivatives. *Ann Pharmacother* 1996; **30:** 935–40.
3. Cross SE, *et al.* Is there tissue penetration after application of topical salicylate formulations? *Lancet* 1997; **350:** 636.

Interactions

Absorption of methyl salicylate through the skin can occur after excessive topical application (see above), and interactions would be expected to be as for other salicylates (see Interactions of Aspirin, p.23).

Anticoagulants. Potentiation of *warfarin* anticoagulation has been reported[1-3] after topical application of methyl salicylate preparations.

1. Littleton F. Warfarin and topical salicylates. *JAMA* 1990; **263:** 2888.
2. Tam LS, *et al.* Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil. *Aust N Z J Med* 1995; **25:** 258.
3. Joss JD, LeBlond RF. Potentiation of warfarin anticoagulation associated with topical methyl salicylate. *Ann Pharmacother* 2000; **34:** 729–33.

Uses and Administration

Methyl salicylate is a salicylic acid derivative that is irritant to the skin and is used topically in rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders. It is also used for minor peripheral vascular disorders such as chilblains and as an ingredient in inhalations for the symptomatic relief of upper respiratory-tract disorders.

Wintergreen oil is also used in aromatherapy.

Preparations

BP 2008: Kaolin Poultice; Methyl Salicylate Liniment; Methyl Salicylate Ointment; Surgical Spirit.

Proprietary Preparations (details are given in Part 3)
Arg.: Aspi-Rub†; Rati Salil Gel; ***Austral.:*** Linsal†; ***Canad.:*** Deep Heating; ***Chile:*** Parche Calorub; ***Ger.:*** Hewedolor N; ***India:*** Dolocide Plus; ***Mex.:*** Balsamo Nordin; Friccion Don Juan; Tolan; ***S.Afr.:*** Thermo-Rub; ***Thai.:*** Mygesal; ***UK:*** Numark Muscle Rub; ***USA:*** Argesic†; Exocaine†; Gordogesic; ***Venez.:*** Novofric†; Ultrafil†.

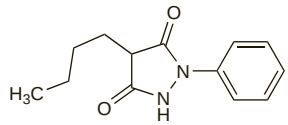
Multi-ingredient: numerous preparations are listed in Part 3.

Mofebutazone *(rINN)*

Mofebutatsoni; Mofebutazon; Mofebutazona; Mofébutazone; Mofebutazonum; Monobutazone; Monophenylbutazone. 4-Butyl-1-phenylpyrazolidine-3,5-dione.

Мофебутазон

$C_{13}H_{16}N_2O_2$ = 232.3.
CAS — 2210-63-1.
ATC — M01AA02; M02AA02.
ATC Vet — QM01AA02; QM02AA02.



Profile

Mofebutazone, a derivative of phenylbutazone (p.117), is an NSAID (p.96). It has been used in the management of musculoskeletal and joint disorders. The sodium salt has been given by intramuscular injection.

Preparations

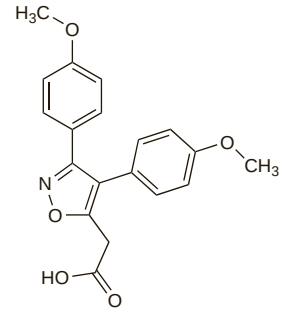
Proprietary Preparations (details are given in Part 3)
Ger.: Mofesal N†.

Mofezolac *(rINN)*

Mofézolac; Mofezolaco; Mofezolacum; N-22. 3,4-Bis(*p*-methoxyphenyl)-5-isoxazoleacetic acid.

Мофезолак

$C_{19}H_{17}NO_5$ = 339.3.
CAS — 78967-07-4.



Profile

Mofezolac is an NSAID (p.96) given orally in the management of pain and musculoskeletal and joint disorders.

Preparations

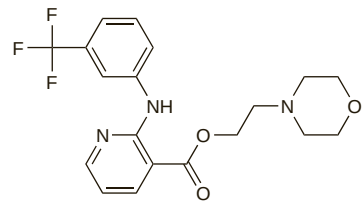
Proprietary Preparations (details are given in Part 3)
Jpn: Disopain.

Morniflumate *(USAN, rINN)*

Morniflumato; Morniflumatum; UP-164. 2-Morpholinoethyl 2-(α,α,α-trifluoro-*m*-toluidino)nicotinate.

Морнифлумат

$C_{19}H_{20}F_3N_3O_3$ = 395.4.
CAS — 65847-85-0.
ATC — M01AX22.
ATC Vet — QM01AX22.



Profile

Morniflumate, the morpholinoethyl ester of niflumic acid (p.95), is an NSAID (p.96). It has been used in inflammatory conditions in doses of 700 mg given twice daily by mouth or rectally as suppositories.

Preparations

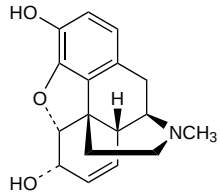
Proprietary Preparations (details are given in Part 3)
Fr.: Nifluril; ***Ital.:*** Flomax; Flumarin; Morniflu; Niflam; ***Spain:*** Niflactol.

Morphine *(BAN)* ⊗

Morfiini; Morfin; Morfina; Morphinum. 7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol.

Морфин

$C_{17}H_{19}NO_3$ = 285.3.
CAS — 57-27-2 (anhydrous morphine); 6009-81-0 (morphine monohydrate).
ATC — N02AA01.
ATC Vet — QN02AA01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of morphine:
Adolf; Block; China White; Cube; Dreamer; Drug store dope; Drugstore dope; Emsel; First line; German boy; God's drug; Goma; Hard stuff; Hospital Heroin; Hows; Hydrogen Bomb; M; Miss Emma; Mister blue; Mojo; Monf; Monkey; Morf; Morfs; Morfa; Morphia; Morphina; Morpho; Morphy; Mr. Blue; M.S.; MS; Mud; Murphy; Nasty; Nazi; Sweet Jesus; Sweet Morpheus; Tar; Unkie; White Stuff.

Morphine Hydrochloride *(BANM)* ⊗

Morfiinihydrokloridi; Morfin Hidroklorür; Morfina, hidrocloruro de; Morfin-hidroklorid; Morfin-hydrochlorid trihydrát; Morfinhydroklorid; Morfino hidrochloridas; Morfiny chlorowodorek; Morphine, chlorhydrate de; Morphini hydrochloridum; Morphini Hydrochloridum Trihydricum; Morphinii Chloridum; Morphinum Chloratum.

Морфина Гидрохлорид

$C_{17}H_{19}NO_3$,HCl,3H_2O = 375.8.
CAS — 52-26-6 (anhydrous morphine hydrochloride); 6055-06-7 (morphine hydrochloride trihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *Viet.*
Ph. Eur. 6.2 (Morphine Hydrochloride). Colourless, silky needles, cubical masses or a white or almost white, crystalline powder. It is efflorescent in a dry atmosphere. Soluble in water; slightly soluble in alcohol; practically insoluble in toluene. Protect from light.

Incompatibility. See under Morphine Sulfate, below.

Morphine Sulfate ⊗

Morfiinisulfaatti; Morfin Sülfat; Morfina, sulfato de; Morfino sulfatas; Morfinsulfat; Morfin-sulfát pentahydrát; Morfin-szulfát; Morfiny siarczan; Morphine, sulfate de; Morphine Sulphate *(BANM)*; Morphini sulfas; Morphini Sulfas Pentahydricus.

Морфина Сульфат

($C_{17}H_{19}NO_3)_2$,H_2SO_4,5H_2O = 758.8.
CAS — 64-31-3 (anhydrous morphine sulfate); 6211-15-0 (morphine sulfate pentahydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Morphine Sulphate). A white or almost white, crystalline powder. Soluble in water; very slightly soluble in alcohol; practically insoluble in toluene. Protect from light.
USP 31 (Morphine Sulfate). White, feathery, silky crystals, cubical masses of crystals, or a white crystalline powder. Is odourless and when exposed to air it gradually loses water of hy-

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.