including erythema multiforme and Stevens-Johnson syndrome (5). No patients died from skin reactions and most recovered after meloxicam was withdrawn. Other frequently reported reactions were neurological (mostly headache), cardiovascular (oedema and palpitations), dizziness, flushing, and fatigue. A prescription event monitoring study has also analysed events reported with meloxicam use.[2] In a cohort of 19 087 patients who had received meloxicam some time between December 1996 and March 1997, 203 patients had had 252 events considered to be suspected adverse reactions. The majority of reactions were not serious or were labelled adverse effects of meloxicam. Rare, serious suspected adverse reactions included 2 reports of thrombocytopenia and 1 each of interstitial nephritis and idiosyncratic liver abnormality. The most frequent gastrointestinal event was dyspepsia; other more serious gastrointestinal events occurring during meloxicam exposure included upper gastrointestinal bleeding (33 reports) and peptic ulcer (19 reports). However it was considered that the incidence of gastrointestinal disturbance was low in the absence of gastrointestinal risk factors. Adverse drug reactions reported during the first year of marketing of meloxicam to the Swedish Medical Products Agency suggested a similar safety profile to other NSAIDs.[3] Of the 15 reports, 6 were for gastrointestinal disturbances and 5 involved skin reactions.

1. CSM/MCA. Meloxicam (Mobic): gastrointestinal and skin reactions. *Current Problems* 1998; **24:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
2. Martin RM, *et al.* The incidence of adverse events and risk factors for upper gastrointestinal disorders associated with meloxicam use amongst 19 087 patients in general practice in England: cohort study. *Br J Clin Pharmacol* 2000; **50:** 35–42.
3. Anonymous. Meloxicam safety similar to other NSAIDs. *WHO Drug Information* 1998; **12:** 147.

Effects on the gastrointestinal tract. It is generally accepted that inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of NSAIDs, and that selective inhibition of the other isoform, COX-2, by NSAIDs such as meloxicam may cause less gastrotoxicity than that seen with the non-selective inhibition of traditional NSAIDs. However, there has been little convincing evidence that the risk of severe gastrointestinal events is lower with meloxicam than with other NSAIDs at equi-effective doses.[1] Two large multicentre studies[2,3] have reported a lower incidence of gastrointestinal adverse effects with meloxicam than with non-selective cyclo-oxygenase inhibitors (diclofenac[2] or piroxicam[3]) but in one of these[2] the dose of meloxicam given also appeared to be less effective than the reference drug. A more recent systematic review[4] also found a lower risk of serious gastrointestinal toxicity with meloxicam 7.5 mg daily when compared with diclofenac (100 or 150 mg daily), naproxen (500 mg twice daily), or piroxicam (20 mg daily); however, when given at a dose of 15 mg daily, the risk of toxicity with meloxicam was significantly lower only when compared with piroxicam.

Individual case reports of gastrointestinal toxicity with meloxicam included one of ischaemic colitis associated with high-dose (15 mg daily) meloxicam treatment.[5]

1. Anonymous. Meloxicam—a safer NSAID? *Drug Ther Bull* 1998; **36:** 62–4.
2. Hawkey C, *et al.* Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. *Br J Rheumatol* 1998; **37:** 937–45.
3. Dequeker J, *et al.* Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the safety and efficacy large-scale evaluation of COX-inhibiting therapies (SELECT) trial in osteoarthritis. *Br J Rheumatol* 1998; **37:** 946–51.
4. Singh G, *et al.* Risk of serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam. *Am J Med* 2004; **117:** 100–106.
5. Garcia B, *et al.* Ischaemic colitis in a patient taking meloxicam. *Lancet* 2001; **357:** 690.

Precautions

As for NSAIDs in general, p.98.

Meloxicam should be avoided in severe hepatic impairment, in bleeding disorders, and in patients with renal failure unless receiving dialysis. Rectal use should be avoided in patients with a history of proctitis, haemorrhoids, or rectal bleeding.

Renal impairment. The pharmacokinetics of meloxicam were not substantially altered in patients with a creatinine clearance (CC) of 41 to 60 mL/minute compared with those with normal renal function.[1] In those with a CC of 20 to 40 mL/minute, total plasma-meloxicam concentrations were lower but meloxicam free fractions were higher. Such free meloxicam concentrations were similar to the other groups. On the basis of these results, it was suggested that it was not necessary to reduce meloxicam doses in patients with a CC greater than 20 mL/minute.

1. Boulton-Jones JM, *et al.* Meloxicam pharmacokinetics in renal impairment. *Br J Clin Pharmacol* 1997; **43:** 35–40.

Interactions

For interactions associated with NSAIDs, see p.99.

Colestyramine increases the clearance and decreases the half-life of meloxicam.

Pharmacokinetics

Meloxicam is well absorbed after oral or rectal doses with peak plasma concentrations reached in up to 6 hours. It is 99% bound to plasma proteins. Meloxicam has a plasma-elimination half-life of about 20 hours. It is extensively metabolised, mainly by oxidation to its major metabolite, 5′-carboxymeloxicam. *In vitro* studies suggest that the cytochrome P450 isoenzyme CYP2C9 plays an important role in the metabolism of meloxicam with CYP3A4 involved to a lesser degree. Meloxicam, in the form of metabolites, is excreted in similar amounts in the urine and in the faeces; less than 5% of a dose is excreted unchanged. The volume of distribution is increased in renal failure.

◊ References.

1. Narjes H, *et al.* Pharmacokinetics and tolerability of meloxicam after i.m. administration. *Br J Clin Pharmacol* 1996; **41:** 135–9.
2. Türck D, *et al.* Clinical pharmacokinetics of meloxicam. *Arzneimittelforschung* 1997; **47:** 253–8.
3. Davies NM, Skjodt NM. Clinical pharmacokinetics of meloxicam: a cyclooxygenase-2 preferential nonsteroidal anti-inflammatory drug. *Clin Pharmacokinet* 1999; **36:** 115–26.
4. Meineke I, Türck D. Population pharmacokinetic analysis of meloxicam in rheumatoid arthritis patients. *Br J Clin Pharmacol* 2003; **55:** 32–8.
5. Burgos-Vargas R, *et al.* Pharmacokinetics of meloxicam in patients with juvenile rheumatoid arthritis. *J Clin Pharmacol* 2004; **44:** 866–72.

Renal impairment. For reference to the pharmacokinetics of meloxicam in renal impairment, see under Precautions, above.

Uses and Administration

Meloxicam, an oxicam derivative, is an NSAID (p.99). It is reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). Meloxicam is used in the management of rheumatoid arthritis, for the short-term symptomatic treatment of acute exacerbations of osteoarthritis, and for the symptomatic treatment of ankylosing spondylitis. It may also be used in the treatment of juvenile idiopathic arthritis.

In the treatment of rheumatoid arthritis and ankylosing spondylitis, meloxicam is given in a usual oral dose of 15 mg daily as a single dose. Those with an increased risk of adverse reactions should be started on 7.5 mg daily. A dose of 7.5 mg daily is recommended for long-term treatment in the elderly. In the treatment of acute exacerbations of osteoarthritis the usual oral daily dose of meloxicam is 7.5 mg, increased if necessary to a maximum of 15 mg daily given as a single dose.

For dosage details in children see below.

Meloxicam may be given by rectal suppository in doses similar to those used orally but use should be limited to the shortest time possible.

For the dose of meloxicam in patients with renal impairment, see below.

Administration in children. In the USA, meloxicam is used in the treatment of juvenile idiopathic arthritis in children aged 2 years and over. The recommended oral dose is 125 micrograms/kg once daily, up to a maximum of 7.5 mg daily. In the UK, licensed product information states that meloxicam should not be used in children aged under 15 years; however, the *BNFC* has suggested the following oral doses, according to body-weight, in those aged 12 to 18 years who are intolerant of other NSAIDs:

- less than 50 kg: 7.5 mg once daily
- over 50 kg: 15 mg once daily

Administration in renal impairment. Meloxicam is normally contra-indicated in patients with severe renal impairment. However, in dialysed patients, meloxicam may be given in a dose of 7.5 mg daily by mouth or by rectal suppository. No dose reduction is required in those with mild to moderate renal impairment (creatinine clearance of greater than 25 mL/min).

Musculoskeletal and joint disorders. Meloxicam is used in the treatment of osteoarthritis (see p.11), rheumatoid arthritis (see p.11) including juvenile idiopathic arthritis (p.10), and ankylosing spondylitis (see Spondyloarthropathies, p.13). However, in the UK, the use of meloxicam and other selective cyclo-oxygenase-2 (COX-2) inhibitors is limited to those patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID (see p.97).

References.

1. Lemmel EM, *et al.* Efficacy and safety of meloxicam in patients with rheumatoid arthritis. *J Rheumatol* 1997; **24:** 282–90.
2. Yocum D, *et al.* Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. *Arch Intern Med* 2000; **160:** 2947–54.
3. Combe B, *et al.* Comparison of intramuscular and oral meloxicam in rheumatoid arthritis patients. *Inflamm Res* 2001; **50** (suppl 1): S10–16.
4. Fleischmann R, *et al.* Meloxicam. *Expert Opin Pharmacother* 2002; **3:** 1501–12.

Veterinary use. For the suggestion that meloxicam should be used as an alternative to diclofenac in cattle in South Asia (to reduce toxicity to vultures who may consume their carcasses), see under Precautions of Diclofenac, p.45

Preparations

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

Proprietary Preparations (details are given in Part 3)
Arg.: Bronax; Dominadol; Flexidol; Flexium; Loxitenk; Meloxid†; Merapiran†; Mextran; Miogesil†; Miolox; Mobic; Skudal†; Telaroid; Tenaron; ***Austral.:*** Mobic; Movalis; Moxicam; ***Austria:*** Melodyn; Meloxistad; Metosan; Movalis; ***Belg.:*** Docmeloxi; Mobic; ***Braz.:*** Alivian; Artritec†; Bioflac; Diatec†; Dormelox; Flamatec; Inicox; Leutrol; Lonaflam†; Loxam; Loxiflan; Melocox; Melonan†; Melonax†; Melotec; Meloxigran; Meloxil; Mevamox; Movacox†; Movatec; Movoxicam; ***Canad.:*** Mobicox; ***Chile:*** Anposel; Ecax; Hyflex; Isox; Melic; Melodol; Mexan; Mexilal; Mibloc FT; Mobex; Sition; Tenaron; Zix†; ***Cz.:*** Artrilom; Duplicam; Galoxiway; Melobax; Melocox; Melovis; Meloxistad; Movalis; Recoxa; ***Denm.:*** Mobic; ***Fin.:*** Latonid; Mobic; ***Fr.:*** Mobic; ***Ger.:*** Mobec; ***Gr.:*** Arsitec; Arthrox; Auroxicam; Brosiral; Doctinon; Examel; Farmelox; Flumidon; Iamaxicam; Iaten; Iconal; Infomel; Loxitan; Mecalox; Medoxicam; Melice; Melocalm; Melock; Melocox; Melodin; Meloprol; Melorilif; Melotec; Melotop; Meloxil; Meloxitor; Meomel; Movatec; Movaxin; Moxalid; Notpel; Partial; Philipon-S; Rentilox; Reumotec; Reumotherm; Sanetron; Saniflam; Starmelox; Supercad; Transantor; Tropofin; Valoxin; Vexicam; Zametrixal; Zerelin; ***Hong Kong:*** Melflam; Melox; Mobic; ***Hung.:*** Camelox; Melodyn; Melogen; Meloxan; Meloxep; Movalis; Moxicam; Noflamen; ***India:*** Mel-OD; Melflam; Melstar†; ***Indon.:*** Artrilox; Flamoxi; Loxinic; Mecox; Meloxin; Mevilox; Mexpharm; Mobiflex; MoviCox; Movix; Moxam; Moxic; Nulox; Ostelox; Velcox; X-Cam; ***Irl.:*** Areloger; Melcam; Mobic; Mobiglan; Movox; ***Ital.:*** Leutrol; Mobic; ***Jpn:*** Mobic; ***Malaysia:*** Mel-OD; Melocam; Melox; Mobic; Rafree; ***Mex.:*** Aflamid; Anflatox†; Anpre; Auricam; Dolocam; Exel; Flexiver; Flexol; Lexpram; Loxam; Loxibach; Loxibest; Masflex†; Mavicam; Maxoflam; Meflen; Melarthryl; Melican; Melosteral; Menflixil; Mobicox; Promotion; Reosan; Retoflam; ***Neth.:*** Movalis; Movicox; ***Norw.:*** Mobic; ***NZ:*** Mobic; ***Philipp.:*** Melora; Mobic; ***Pol.:*** Aglan; Aspicam; Lormed; Meloksam; Melokssia; Meloxic; MeloxiLek; Meloxistad; Movalis; ***Port.:*** Marlex; Melpor; Movalis; Ziloxican†; ***Rus.:*** Lem (Лем); Melokan (Мелокан); Melox (Мелокс); Mirlox (Мирлокс); Movalis (Мовалис); Movasin (Мовасин); ***S.Afr.:*** Coxflam; Flexocam; Loxiflam; Melflam; Mobic; ***Singapore:*** Melox; Mobic; ***Spain:*** Aliviodol; Movalis; Parocin; Uticox; ***Swed.:*** Latonid†; Mobic; ***Switz.:*** Mobicox; Zilutrol†; ***Thai.:*** Melcam; Melobic; Melox; Mobic; ***Turk.:*** Exen; Melox; Mobic; Zeloxim; ***UK:*** Mobic; ***USA:*** Mobic; ***Venez.:*** Biomelox; Calmox†; Mecox†; Melonax; Melovax; Mobic; Mowin†; Taucaron.

Multi-ingredient: ***Arg.:*** Flexidol Relax; Mextran Flex; ***India:*** Melodol; ***Mex.:*** Dolocam Plus; Dolocartigen; Dorsal; Flexamol; Nuro-B; Retoflam F.

Meptazinol Hydrochloride

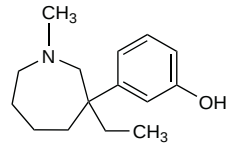
(BANM, USAN, rINNM)

Hidrocloruro de meptazinol; IL-22811 (meptazinol); Meptazinol, Chlorhydrate de; Meptazinoli Hydrochloridum; Wy-22811 (meptazinol). 3-(3-Ethyl-1-methylperhydroazepin-3-yl)phenol hydrochloride.

Мептазинола Гидрохлорид

$C_{15}H_{23}NO,HCl$ = 269.8.

CAS — 54340-58-8 (meptazinol); 59263-76-2 (meptazinol hydrochloride); 34154-59-1 (±-meptazinol hydrochloride).



(meptazinol)

Pharmacopoeias. In *Br.*

BP 2008 (Meptazinol Hydrochloride). A white or almost white powder. Very soluble in water and in methyl alcohol; freely soluble in alcohol; very slightly soluble in acetone; dissolves in dilute solutions of alkali hydroxides. Store at a temperature not exceeding 25°.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

◊ In assessing the dependence potential of meptazinol, a WHO expert committee[1] noted in 1989 that abrupt discontinuation of chronic meptazinol use precipitated only slight withdrawal signs in *animals* and that meptazinol did not suppress opioid withdrawal signs and symptoms in humans dependent on morphine. Abuse had not been reported. They considered that the likelihood of abuse was moderate and that international control was not warranted at that time.

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 26/06/08)

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

Gastrointestinal adverse effects are commonly reported with meptazinol and include abdominal pain, constipation, dyspepsia, diarrhoea, and nausea and vomiting. Meptazinol is claimed to have a low incidence of respiratory depression; nonetheless, UK licensed prod-

uct information states that it should not be used in patients with acute respiratory depression. There have been occasional reports of psychiatric disorders such as hallucinations, confusion, and depression. As meptazinol has both antagonist and agonist properties its effects may be only partially reversed by naloxone, but use of the latter is still recommended in overdosage.

Meptazinol has the potential to precipitate withdrawal symptoms if given to patients who are physically dependent on opioids.

Abuse. See under Dependence and Withdrawal, above.

Effects on the respiratory system. Meptazinol is said to have a relatively low potential for respiratory depression and in healthy subjects was reported to produce substantially less respiratory depression than morphine or pentazocine at usual analgesic doses.[1] However, respiratory depression does occur in anaesthetised patients given meptazinol[2] and the effects on respiration may be similar to those of morphine[3,4] or pethidine.[5,6] Compensatory mechanisms may come into play after repeated doses of meptazinol but the intravenous use of meptazinol during anaesthesia should be viewed with as much caution as with any other opioid.[6]

Respiratory arrest occurred after an *overdose* of 50 meptazinol 200-mg tablets and a quarter of a bottle of whisky.[7] Full recovery eventually followed supportive measures although spontaneous respiration was not re-established by naloxone intravenously to a cumulative total dose of 10 mg.

1. Jordan C, *et al.* A comparison of the respiratory effects of meptazinol, pentazocine and morphine. *Br J Anaesth* 1979; **51:** 497–502.
2. Hardy PAJ. Meptazinol and respiratory depression. *Lancet* 1983; **ii:** 576.
3. Frater RAS, *et al.* Analgesia-induced respiratory depression: comparison of meptazinol and morphine in the postoperative period. *Br J Anaesth* 1989; **63:** 260–5.
4. Verborgh C, Camu F. Post-surgical pain relief with zero-order intravenous infusions of meptazinol and morphine: a double-blind placebo-controlled evaluation of their effects on ventilation. *Eur J Clin Pharmacol* 1990; **38:** 437–42.
5. Wilkinson DJ, *et al.* Meptazinol—a cause of respiratory depression in general anaesthesia. *Br J Anaesth* 1985; **57:** 1077–84.
6. Lee A, Drummond GB. Ventilatory effects of meptazinol and pethidine in anaesthetised patients. *Br J Anaesth* 1987; **59:** 1127–33.
7. Davison AG, *et al.* Meptazinol overdose producing near fatal respiratory depression. *Hum Toxicol* 1987; **6:** 331.

Interactions

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

Plasma concentrations of meptazinol may be increased by ritonavir and use together should be avoided (see also p.103).

Pharmacokinetics

After oral doses of meptazinol peak plasma concentrations have been achieved within 0.5 to 2 hours, but bioavailability is low since it undergoes extensive first-pass metabolism. Systemic availability is improved after rectal doses. Peak plasma concentrations have been achieved 30 minutes after rectal or intramuscular use. Plasma protein binding has averaged only about 27%. Elimination half-lives of about 2 hours have been reported. Meptazinol is extensively metabolised in the liver and is excreted mainly in the urine as the glucuronide conjugate. Less than 10% of a dose has been recovered from the faeces. Meptazinol crosses the placenta.

◊ References.

1. Franklin RA, *et al.* Studies on the metabolism of meptazinol, a new analgesic drug. *Br J Clin Pharmacol* 1976; **3:** 497–502.
2. Franklin RA, *et al.* Studies on the absorption and disposition of meptazinol following rectal administration. *Br J Clin Pharmacol* 1977; **4:** 163–7.
3. Davies G, *et al.* Pharmacokinetics of meptazinol in man following repeated intramuscular administration. *Eur J Clin Pharmacol* 1982; **23:** 535–8.
4. Norbury HM, *et al.* Pharmacokinetics of the new analgesic, meptazinol, after oral and intravenous administration to volunteers. *Eur J Clin Pharmacol* 1983; **25:** 77–80.
5. Murray GR, *et al.* The systemic availability of meptazinol in man after oral and rectal doses. *Eur J Clin Pharmacol* 1989; **36:** 279–82.

The elderly. A lower clearance and longer elimination half-life has been reported for meptazinol in elderly patients, but dosage reduction was not considered warranted on pharmacokinetic grounds. Mean half-lives in elderly and young subjects were 3.39 and 1.94 hours, respectively after single oral doses[1] and 2.93 and 2.06 hours, respectively after intravenous doses.[2]

1. Norbury HM, *et al.* Pharmacokinetics of meptazinol after single and multiple oral administration to elderly patients. *Eur J Clin Pharmacol* 1984; **27:** 223–6.
2. Murray GR, *et al.* Pharmacokinetics of meptazinol after parenteral administration in the elderly. *Eur J Clin Pharmacol* 1987; **31:** 733–6.

Hepatic impairment. Oral bioavailability of meptazinol appeared to be enhanced in patients with liver disease. After a single oral dose of meptazinol mean peak plasma concentrations were 184 nanograms/mL, 131 nanograms/mL, and 53 nanograms/mL in cirrhotic patients, patients with non-cirrhotic liver disease, and patients with normal liver function, respectively, although there was no evidence of accumulation after chronic dosing.[1] There were no significant differences in plasma clearance after an intravenous dose. Reduced oral doses of meptazinol might be advisable in cirrhotic patients.

1. Birnie GG, *et al.* Enhanced oral bioavailability of meptazinol in cirrhosis. *Gut* 1987; **28:** 248–54.

Pregnancy. In women given an intramuscular injection of 100 to 150 mg during labour, meptazinol was found to cross the placenta readily but was rapidly eliminated from the neonate.[1] This contrasted with pethidine which was known to be excreted very slowly from neonates. As in the adult, elimination of meptazinol by the neonate appeared to take place mainly by conjugation with glucuronic acid.[2] A half-life of 3.4 hours, similar to that in adults, has been reported in the neonate,[3] in contrast to 22.7 hours for pethidine in neonates.

Disposition of meptazinol appears not to be significantly affected by pregnancy. Mean half-lives of 1.36 and 1.68 hours were reported in pregnant and non-pregnant women, respectively,[4] compared with 2.06 hours in men.

1. Franklin RA, *et al.* Preliminary studies on the disposition of meptazinol in the neonate. *Br J Clin Pharmacol* 1981; **12:** 88–90.
2. Dowell PS, *et al.* Routes of meptazinol conjugation in the neonate. *Br J Clin Pharmacol* 1982; **14:** 748–9.
3. Jackson MBA, Robson PJ. Preliminary clinical and pharmacokinetic experiences in the newborn when meptazinol is compared with pethidine as an obstetric analgesic. *Postgrad Med J* 1983; **59** (suppl 1): 47–51.
4. Murray GR, *et al.* The disposition of meptazinol after single and multiple intravenous administration to pregnant and non-pregnant women. *Eur J Clin Pharmacol* 1989; **36:** 273–7.

Uses and Administration

Meptazinol is a mixed opioid agonist and antagonist with partial opioid agonist activity at the μ_1 opioid receptor (see p.104); it also has cholinergic activity. Meptazinol is used in the treatment of moderate to severe pain. It has a shorter duration of action than morphine.

Meptazinol hydrochloride is given orally or by intramuscular or intravenous injection; doses are expressed in terms of the base. Meptazinol hydrochloride 115.6 mg is equivalent to about 100 mg of meptazinol. For the short-term treatment of moderate pain meptazinol is given in an oral dose of 200 mg every 3 to 6 hours, as required. The intramuscular dose is 75 to 100 mg given every 2 to 4 hours, as required; for obstetric pain a dose of 2 mg/kg (100 to 150 mg) may be used. Meptazinol is also given by slow intravenous injection in doses of 50 to 100 mg every 2 to 4 hours, as required.

Administration. ***EPIDURAL ROUTE.*** Epidural meptazinol 90 mg for postoperative pain was reported to be superior to an intramuscular dose of 90 mg.[1] However, in another study[2] a 30-mg dose was ineffective and associated with an unacceptable incidence of adverse effects. A 60-mg dose was also found to be ineffective because of its short duration of action.[3]

UK licensed product information states that the injectable formulation is not suitable for epidural or intrathecal use.

1. Verborgh C, *et al.* Meptazinol for postoperative pain relief in man: comparison of extradural and im administration. *Br J Anaesth* 1987; **59:** 1134–9.
2. Francis RI, Lockhart AS. Epidural meptazinol. *Anaesthesia* 1986; **41:** 88–9.
3. Birks RJS, Marsh DRG. Epidural meptazinol. *Anaesthesia* 1986; **41:** 883.

Administration in hepatic impairment. See under Pharmacokinetics, above for a suggestion that doses may need to be reduced in patients with cirrhosis.

Preparations

BP 2008: Meptazinol Injection; Meptazinol Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Meptidol†; ***Ger.:*** Meptid; ***Irl.:*** Meptid; ***UK:*** Meptid.

Methadone Hydrochloride

(BANM, pINNM) ⊗

Amidine Hydrochloride; Amidone Hydrochloride; Hidrocloruro de amidina; Hidrocloruro de metadona; Metadon Hidroklorür; Metadon-hidroklorid; Metadonhydroklorid; Metadonihydroklorid; Metadono hidrochloridas; Metadonu chlorowodorek; Methadon hydrochlorid; Méthadone, chlorhydrate de; (±)-Methadone Hydrochloride; Methadoni hydrochloridum; Phenadone. (±)-6-Dimethylamino-4,4-diphenylheptan-3-one hydrochloride.

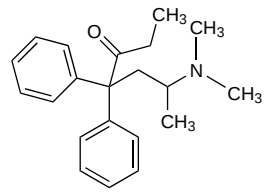
Метадона Гидрохлорид

$C_{21}H_{27}NO,HCl$ = 345.9.

CAS — 76-99-3 (methadone); 297-88-1 (±methadone); 1095-90-5 (methadone hydrochloride); 125-56-4 (±methadone hydrochloride).

ATC — N07BC02.

ATC Vet — QN07BC02.



(methadone)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methadone:
Amidone; Balloons; Breeze; Burdock; Buzz bomb; Dollies; Dolls; Done; Doses; Fizzies; Juice; Jungle juice; Junk; Meta; Mud; Phy; Phyamps; Tootsie roll.

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

Ph. Eur. 6.2 (Methadone Hydrochloride). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Methadone Hydrochloride). Odourless colourless crystals or white crystalline powder. Soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether and in glycerol. pH of a 1% solution in water is between 4.5 and 6.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. There appears to be adequate evidence that stable solutions containing methadone hydrochloride and hydroxybenzoate esters can be formulated but the risk of precipitation exists if syrup preserved with hydroxybenzoates is used to extemporaneously prepare a methadone mixture 1 mg/mL to the DTF formula.[1] An oral formulation of methadone hydrochloride 5 mg/mL containing methyl hydroxybenzoate 0.1% as preservative rather than chloroform has been reported stable for at least 4 months at room temperature.[2]

1. *PSGB Lab Report P/80/1* 1980.
2. Ching MS, *et al.* Stability of methadone mixture with methyl hydroxybenzoate as a preservative. *Aust J Hosp Pharm* 1989; **19:** 159–61.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Methadone withdrawal symptoms are similar to, but more prolonged than, those produced by morphine or diamorphine. They develop more slowly and do not usually appear until 3 to 4 days after the last dose.

Methadone is used for substitution therapy in the management of opioid dependence (see Uses and Administration, below) including neonatal abstinence syndrome (see Administration in Children, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Methadone has a more prolonged effect than morphine and readily accumulates with repeated doses. It may have a relatively greater respiratory depressant effect than morphine and, although reported to be less sedating, repeated doses of methadone may result in marked sedation. QT prolongation and torsade de pointes have been reported rarely with methadone use, particularly at doses above 100 mg daily. After gross overdosage symptoms are similar to those of morphine poisoning. Pulmonary oedema after overdosage is a common cause of fatalities among addicts.

Methadone causes pain at injection sites; subcutaneous injection causes local tissue irritation and induration.