with an analgesic, in the management of muscle spasm (p.1887) and painful musculoskeletal disorders but such use is no longer considered appropriate.

The usual anxiolytic dose is 400 mg orally three or four times daily to a maximum of 2.4 g daily. In elderly patients, no more than half the usual adult dose has been suggested.

Preparations

USP 31: Meprobamate Oral Suspension; Meprobamate Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Cyrpon; Epikur; Microbamat; Miltaun; ***Belg.:*** Pertranquil†; Reposo-Mono†; ***Fr.:*** Equanil; ***Ger.:*** Visano N†; Visano-mini N†; ***Hung.:*** Andaxin; ***Israel:*** Mepro; ***Ital.:*** Quanil; ***S.Afr.:*** Equanil; ***Switz.:*** Meprodil; ***USA:*** Miltown†; Neuramate†.

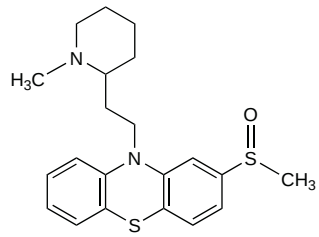
Multi-ingredient: ***Arg.:*** Hidromens†; ***Canad.:*** 282 Mep†; ***Chile:*** Butartrol; ***Fin.:*** Anervan; Crampiton; Potentol†; ***Fr.:*** Kaologeais; Mepronizine; Palpipax†; Precyclan; ***Indon.:*** Deparon; ***Mex.:*** Artrilan; ***Norw.:*** Anervan; ***Port.:*** Vitasma†; ***S.Afr.:*** Adco-Payne; Antipyn Forte; Ban Pain; Briscopyn; Equagesic; Fevapar; Go-Pain; Medipyn; Megapyn; Meprogesic; Mepromol; Micro-Gesic; Nopyn†; Noralget†; Painagon; Painrite; Pynmed; Salterpyn; Spectrapain Forte; Stilpane; Stopayne; Supragesic; Synaleve; Tenston; Trinagesic; Vacudol Forte; Xeramax†; Xerogesic†; ***Swed.:*** Anervan; ***UK:*** Paxidal; ***USA:*** Equagesic; Micrainin†.

Mesoridazine *(BAN, USAN, rINN)*

Mesoridatsiini; Mesoridazin; Mesoridazina; Mésoridazine; Mesoridazinum; Mesuridazine; Mezoridazin; NC-123; TPS-23. 10-[2-(1-Methyl-2-piperidyl)ethyl]-2-(methylsulphinyl)phenothiazine.

Мезоридазин

$C_{21}H_{26}N_2OS_2$ = 386.6.
CAS — 5588-33-0.
ATC — N05AC03.
ATC Vet — QN05AC03.



Mesoridazine Besilate *(BANM, rINNM)*

Bencenosulfonato de mesoridazina; Mesoridazine Benzenesulphonate; Mésoridazine, Bésilate de; Mesoridazine Besylate; Mesoridazini Besilas; Mesuridazine Benzenesulphonate.

Мезоридазина Безилат

$C_{21}H_{26}N_2OS_2,C_6H_6O_3S$ = 544.7.
CAS — 32672-69-8 (mesoridazine besilate).
ATC — N05AC03.
ATC Vet — QN05AC03.

Pharmacopoeias. In *US.*
USP 31 (Mesoridazine Besylate). A white to pale yellowish powder having not more than a faint odour. Soluble 1 in 1 of water, 1 in 11 of alcohol, 1 in 3 of chloroform, and 1 in 6300 of ether; freely soluble in methyl alcohol. pH of a freshly prepared 1 in 100 solution is between 4.2 and 5.7. Store in airtight containers. Protect from light.

Profile

Mesoridazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperidine side-chain and is a metabolite of thioridazine (p.1031). Mesoridazine has usually been given as the besilate, orally or by intramuscular injection.

Mesoridazine has been shown to prolong the QT interval in a dose-related manner which increases the risk of life-threatening arrhythmias such as torsade de pointes and sudden death; consequently its use in schizophrenia has been restricted. Details of these restrictions are given under Precautions of Thioridazine, the parent drug of mesoridazine (see p.1031). Its use in other psychiatric disorders was abandoned after it was felt that there was an unacceptable balance of risks and benefits as a result of its cardiotoxic potential, and it is no longer available in many countries.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of mesoridazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Preparations

USP 31: Mesoridazine Besylate Injection; Mesoridazine Besylate Oral Solution; Mesoridazine Besylate Tablets.

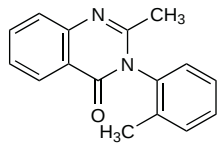
Proprietary Preparations (details are given in Part 3)
Turk.: Lidanil; ***USA:*** Serentil†.

Methaqualone *(BAN, USAN, rINN)*

CI-705; CN-38703; Metacualona; Metakvalon; Metakvalonas; Metakvaloni; Methachalonum; Methakvalon; Méthaqualone; Methaqualonum; QZ-2; R-148; TR-495. 2-Methyl-3-*o*-tolylquinazolin-4-(3*H*)-one.

Метахалон

$C_{16}H_{14}N_2O$ = 250.3.
CAS — 72-44-6 (methaqualone); 340-56-7 (methaqualone hydrochloride).
ATC — N05CM01.
ATC Vet — QN05CM01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methaqualone:
300's; 714; 714s; Bandits; Beiruts; Blou Bulle; Blue Balls; Blue bulls; Disco biscuits; Down and dirtys; Drunfos; Drunken Monkey; Ewings; Flamingos; Flowers; Four-strokes; Fuckers; Genuines; Germans; Golfsticks; Gorilla Biscuits; Humbles; Joe Fridays; Knoppies; Lemmon 714; Lemons; Lennons; Lewds; Lizards; Loss-of-memory; Love drug; Lovers; Ludes; Luds; Lula; Magwheels; Pressouts; Pupumala; Q; Qua; Quaa; Quaalude; Quaaludes; Quaas; Quack; Quad; Quads; Quas; Seven fourteens; Shiny Tops; Soaper; Sopor; Sopors; Sporos; Strawberries; Super Sopors; Supers; Supper; Three hundreds; Vitamin Q; Wagon Wheels; Wallbangers; Whore pills.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Methaqualone). A white or almost white, crystalline powder. Very slightly soluble in water; soluble in alcohol; dissolves in dilute sulfuric acid. Protect from light.

Profile

Methaqualone is a quinazoline derivative with hypnotic and sedative properties. It has been given orally in the short-term management of insomnia but the use of methaqualone for this purpose is no longer considered appropriate. It has also been given with diphenhydramine for an enhanced effect.

Methaqualone has been withdrawn from the market in many countries because of problems with abuse.

Adverse effects and symptoms of overdosage are similar to those of barbiturates (see Amobarbital, p.962) although cardiac and respiratory depression reportedly occur less frequently.

Abuse. Although oral abuse of methaqualone has greatly declined in developed countries after the widespread withdrawal of the tablets, smoking of (usually illicitly manufactured) methaqualone, generally in combination with cannabis and tobacco, is a major public health problem in South Africa, and some other parts of Africa and India. Although diazepam has been used to manage dependence, controlled studies to inform the management of the condition are lacking.[1]

1. McCarthy G, *et al.* Treatment for methaqualone dependence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 11/05/06).

Preparations

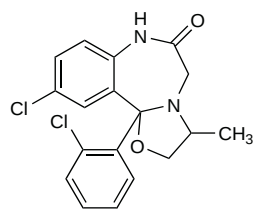
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Switz.:*** Toquilone compositum†.

Mexazolam *(rINN)*

CS-386; Methylcloxazolam; Mexazolamum. 10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro-3-methyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

Мексазолам

$C_{18}H_{16}Cl_2N_2O_2$ = 363.2.
CAS — 31868-18-5.



Profile

Mexazolam is a benzodiazepine with general properties similar to those of diazepam (p.986). It has been given by mouth for its anxiolytic and sedative properties.

Preparations

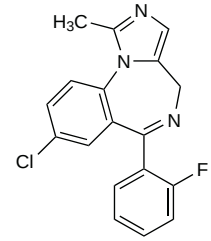
Proprietary Preparations (details are given in Part 3)
Port.: Sedoxil.

Midazolam *(BAN, rINN)*

Midatsolaami; Midazolám; Midazolamas; Midazolamum; Ro-21-3971. 8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine.

Мидазолам

$C_{18}H_{13}ClFN_3$ = 325.8.
CAS — 59467-70-8.
ATC — N05CD08.
ATC Vet — QN05CD08.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Midazolam). A white or yellowish crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; soluble in methyl alcohol.

Midazolam Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de midazolam; Midazolam, Chlorhydrate de; Midazolami Hydrochloridum; Ro-21-3981/003.

Мидазолама Гидрохлорид

$C_{18}H_{13}ClFN_3,HCl$ = 362.2.
CAS — 59467-96-8.
ATC — N05CD08.
ATC Vet — QN05CD08.

Incompatibility. The visual compatibility of midazolam hydrochloride with a range of drugs was studied over a period of 4 hours.[1] A white precipitate was formed immediately with dimenhydrinate, pentobarbital sodium, perphenazine, prochlorperazine edisilate, and ranitidine hydrochloride. Similar incompatibility has been reported[2,3] with furosemide, thiopental, and parenteral nutrition solutions. Other workers[4] have reported that a precipitate is formed with midazolam hydrochloride if the resultant mixture has a pH of 5 or more.

1. Forman JK, Souney PF. Visual compatibility of midazolam hydrochloride with common preoperative injectable medications. *Am J Hosp Pharm* 1987; **44:** 2298–9.
2. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
3. Trissel LA, *et al.* Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1295–300.
4. Swart EL, *et al.* Compatibility of midazolam hydrochloride and lorazepam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 2020–2.

Stability. Licensed product information states that solutions of midazolam hydrochloride in sodium chloride 0.9%, glucose 5%, or glucose 4% with sodium chloride 0.18% are stable at room temperature for up to 24 hours, and similar solutions containing the equivalent of 0.5 mg/mL of the base were stable for 36 days[1] when stored in glass bottles at temperatures of 4° to 6°, 24° to 26°, and 39° to 41°. Other workers[2] found that a solution containing midazolam hydrochloride equivalent to 1 mg/mL of the base in sodium chloride 0.9% was stable for at least 10 days when stored in PVC bags. The product information advises against admixture with Compound Sodium Lactate Intravenous Infusion (Hartmann's solution) as the potency of midazolam is reduced.

1. Pramar YV, *et al.* Stability of midazolam hydrochloride in syringes and i.v. fluids. *Am J Health-Syst Pharm* 1997; **54:** 913–15.
2. McMullin ST, *et al.* Stability of midazolam hydrochloride in polyvinyl chloride bags under fluorescent light. *Am J Health-Syst Pharm* 1995; **52:** 2018–20.

Midazolam Maleate *(BANM, USAN, rINNM)*

Maleato de midazolam; Midazolam, Maléate de; Midazolami Maleas; Ro-21-3981/001.

Мидазолама Малеат

$C_{18}H_{13}ClFN_3,C_4H_4O_4$ = 441.8.
CAS — 59467-94-6.
ATC — N05CD08.
ATC Vet — QN05CD08.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ Withdrawal symptoms occurred[1] in 2 children after stopping midazolam, which had been used for sedation during mechanical ventilation.

1. van Engelen BGM, *et al.* Benzodiazepine withdrawal reaction in two children following discontinuation of sedation with midazolam. *Ann Pharmacother* 1993; **27:** 579–81.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987. There have been reports of life-threatening adverse respiratory and cardiovascular events occurring after use of midazolam; when giving midazolam the precautions given below should be observed to lessen the risk of such reactions. Pain, tenderness, and thrombophlebitis have occurred after injection of midazolam. Hiccups have been reported.

Incidence of adverse effects. Death due to respiratory depression, hypotension, or cardiac arrest has been reported in patients given intravenous midazolam for conscious sedation.[1] Within about 6 months of its introduction in the USA in May 1986, 13 fatalities due to cardiorespiratory depression had been reported (higher doses were used initially in the USA than those in the UK). By January 1988, 66 deaths had been reported, although in November 1987 the adult dosage recommendation had been reduced to 70 micrograms/kg and to 50 micrograms/kg for elderly patients. Fatalities have also occurred in the UK [where the dose is 70 micrograms/kg, reduced in the elderly] with 4 deaths reported to the UK CSM by November 1987.

While it appears that midazolam and diazepam produce very similar degrees of hypoventilation and oxygen desaturation when used in equivalent doses,[2] the sedative end-point does appear to be reached more abruptly with midazolam.[3] Appropriate precautions should therefore be taken:

- facilities for resuscitation should always be available when intravenous midazolam is used
- respiratory and cardiac function should be monitored continuously
- the dose of midazolam should be carefully titrated against the response of the patient and the product recommendations concerning dosage rate be observed
- particular care, including a reduction in midazolam dosage, is required in patients also receiving opioid analgesics, in the elderly and children, and in patients with compromised cardiorespiratory function
- similar warnings apply to the use of oral midazolam where it is available

The availability of the benzodiazepine antagonist, flumazenil, should not be an encouragement to use larger doses of midazolam.[1]

Since endoscopy of the upper gastrointestinal tract can itself reduce oxygen saturation, some workers have advocated the prophylactic use of nasal oxygen during this procedure for those patients at particular risk as outlined above.

1. Anonymous. Midazolam—is antagonism justified? *Lancet* 1988; **ii:** 140–2.
2. Bell GD. Review article: premedication and intravenous sedation for upper gastrointestinal endoscopy. *Aliment Pharmacol Ther* 1990; **4:** 103–22.
3. Ryder W, Wright PA. Dental sedation: a review. *Br Dent J* 1988; **165:** 207–16.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of midazolam on breast-fed infants is unknown its use by mothers during breast feeding may be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Midazolam could not be detected in breast milk from 11 mothers the morning after either the first or the fifth nightly 15-mg oral dose.[2] Additional study of 2 mothers found that midazolam and its hydroxy-metabolite disappeared rapidly from milk with undetectable concentrations at 4 hours. The mean milk to plasma ratio for midazolam was 0.15 in 6 paired samples.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Matheson I, *et al.* Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; **30:** 787–93.

Children. An intravenous bolus injection of midazolam in children already receiving intravenous morphine after cardiac surgery produced an undesirable transient fall in cardiac output.[1] It was suggested that for patients already receiving other drugs that provide sedation the use of midazolam in the early postoperative period should be limited to a continuous infusion. Similarly, it has been recommended[2] that bolus intravenous doses of midazolam should be avoided in neonates due to the occurrence of hypotension.

The initial dosage of midazolam used for continuous intravenous sedation may need to be reduced in critically ill children under 3 years of age since the plasma clearance of midazolam appears to be reduced in these patients.[3]

1. Shekerdemian L, *et al.* Cardiovascular effects of intravenous midazolam after open heart surgery. *Arch Dis Child* 1997; **76:** 57–61.
2. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31:** 423–43.
3. Hughes J, *et al.* Steady-state plasma concentrations of midazolam in critically ill infants and children. *Ann Pharmacother* 1996; **30:** 27–30.

Effects on mental function. For discussion of the adverse effects of benzodiazepines on mental function, including reports of sexual fantasies in women sedated with intravenous midazolam, see Diazepam, p.987.

Effects on the nervous system. For reference to acute dystonia associated with use of midazolam, see Diazepam, p.988.

Encephalopathy. For a report of prolonged use of midazolam with fentanyl being associated with encephalopathy in infants sedated under intensive care, see Diazepam, p.988.

Myoclonus. Myoclonic twitching of all four limbs was noted[1] in 6 of 102 neonates who received a continuous intravenous infusion of midazolam at a rate of 30 to 60 micrograms/kg per hour. Myoclonus ceased a few hours after stopping the infusion and never recurred. No ictal activity was detected in EEGs recorded during the myoclonus.

1. Magny JF, *et al.* Midazolam and myoclonus in neonate. *Eur J Pediatr* 1994; **153:** 389–90.

The elderly. Sedation with midazolam in elderly subjects needed only about half the dose necessary to produce comparable effects in younger subjects.[1] Pharmacodynamic differences due to age suggested an increase in sensitivity of the CNS to midazolam in the elderly subjects.

1. Albrecht S, *et al.* The effect of age on the pharmacokinetics and pharmacodynamics of midazolam. *Clin Pharmacol Ther* 1999; **65:** 630–9.

Hepatic impairment. For the precautions to be observed in patients with impaired liver function, see under Pharmacokinetics, below.

Renal impairment. Five patients with severe renal impairment experienced prolonged sedation when given midazolam; this was attributed to accumulation of conjugated metabolites.[1]

1. Bauer TM, *et al.* Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet* 1995; **346:** 145–7.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Absorption of midazolam is rapid, peak plasma concentrations being achieved within 20 to 60 minutes of a dose, depending on the route. Extensive first-pass metabolism results in a low systemic bioavailability after oral doses. Bioavailability is higher, but variable, after intramuscular injection; figures of more than 90% are often cited.

Midazolam is lipophilic at physiological pH. It crosses the placenta and is distributed into breast milk (but see above). Midazolam is about 96% bound to plasma proteins.

Midazolam usually has a short elimination half-life of about 2 hours although half-lives longer than 7 hours have been reported in some patients. The half-life of midazolam is also prolonged in neonates, in the elderly, and in patients with liver disorders.

Midazolam is metabolised in the liver via the cytochrome P450 isoenzyme CYP3A4. The major metabolite, 1-hydroxymidazolam (alpha-hydroxymidazolam) has some activity; its half-life is less than 1 hour. Midazolam metabolites are excreted in the urine, mainly as glucuronide conjugates.

◊ References.

1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; **16:** 337–64.
2. Swart EL, *et al.* Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol* 2004; **57:** 135–45.

Children. In a study[1] of the pharmacokinetics of midazolam in children the bioavailability of a dose of 0.15 mg/kg was 100, 87, 27, and 18% when given by the intravenous, intramuscular, oral, and rectal routes, respectively. The oral bioavailability was reduced to 16 and 15% after increasing the dose to 0.45 and 1 mg/kg, respectively. There was bioequivalence between the 0.15 mg/kg intramuscular dose and the 0.45 mg/kg oral dose from 45 to 120 minutes after dosage. Absorption from the rectal route gave lower serum-midazolam concentrations than the oral route at the 0.15 mg/kg dose.

Midazolam appears to be absorbed rapidly when given intranasally to children with mean maximum plasma concentrations being achieved within about 12 minutes;[2-4] values of 30% and 55% have been reported for the bioavailability[3,4] but methods to optimise nasal delivery have resulted in higher bioavailability in studies in adults (see below). A study comparing intranasal, intravenous, and rectal dosage of midazolam in children found that plasma concentrations from 45 minutes after intranasal and intravenous doses were similar; those after rectal doses were consistently less than after these other 2 routes.[2] Possible reasons suggested by the authors for this included the effect that the wide interindividual variations in rectal pH may have had on the absorption of midazolam.

Another study has investigated the relationship between intravenous dose and plasma-midazolam concentrations in children.[5]

See also Children under Precautions, above.

1. Payne K, *et al.* The pharmacokinetics of midazolam in paediatric patients. *Eur J Clin Pharmacol* 1989; **37:** 267–72.
2. Malinovsky J-M, *et al.* Plasma concentrations of midazolam after iv, nasal or rectal administration in children. *Br J Anaesth* 1993; **70:** 617–20.
3. Rey E, *et al.* Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. *Eur J Clin Pharmacol* 1991; **41:** 355–7.
4. Kauffman RE, *et al.* Intranasal absorption of midazolam. *Clin Pharmacol Ther* 1995; **57:** 209.
5. Tolia V, *et al.* Pharmacokinetic and pharmacodynamic study of midazolam in children during esophagogastroduodenoscopy. *J Pediatr* 1991; **119:** 467–71.

Neonates. References to the pharmacokinetics of midazolam in neonates. See also Children under Precautions, above.

1. Jacqz-Aigrain E, *et al.* Pharmacokinetics of midazolam in critically ill neonates. *Eur J Clin Pharmacol* 1990; **39:** 191–2.
2. Jacqz-Aigrain E, *et al.* Pharmacokinetics of midazolam during continuous infusion in critically ill neonates. *Eur J Clin Pharmacol* 1992; **42:** 329–32.
3. Burtin P, *et al.* Population pharmacokinetics of midazolam in neonates. *Clin Pharmacol Ther* 1994; **56:** 615–25.
4. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31:** 423–43.
5. Harte GJ, *et al.* Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. *J Paediatr Child Health* 1997 **33:** 335–8.
6. Lee TC, *et al.* Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics. *Anesthesiology* 1999; **90:** 451–7.
7. de Wildt SN, *et al.* Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. *Clin Pharmacol Ther* 2001; **70:** 525–31.

Half-life. Data collected from 7 studies involving 90 subjects has suggested that the prolonged midazolam half-lives reported in a small number of patients are secondary to increases in the volume of distribution and not a result of alterations in clearance and metabolism.[1] Prolongation of the half-life of midazolam has been reported[2] in 2 patients after sustained infusion for status epilepticus.

1. Wills RJ, *et al.* Increased volume of distribution prolongs midazolam half-life. *Br J Clin Pharmacol* 1990; **29:** 269–72.
2. Naritoku DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. *Neurology* 2000 **54:** 1366–8.

Intranasal administration. Plasma concentrations of midazolam sufficient to induce conscious sedation are rapidly attained after intranasal doses.[1] Although bioavailability of up to 55% had previously been obtained in children after intranasal use (see above), slow administration and other methods to optimise nasal delivery had resulted in a bioavailability of 83% in adults.[2,3]

1. Burstein AH, *et al.* Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration. *J Clin Pharmacol* 1997; **37:** 711–18.
2. Björkman S, *et al.* Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients. *Br J Anaesth* 1997; **79:** 575–80.
3. Knoester PD, *et al.* Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray: a study in healthy volunteers. *Br J Clin Pharmacol* 2002; **53:** 501–7.

Liver disorders. The pharmacokinetics of midazolam in patients with advanced cirrhosis of the liver were characterised by an increase in oral systemic bioavailability[1] and by a decrease in clearance with consequent prolongation of elimination half-life.[1,2] Dosage may need to be reduced. However, metabolism of midazolam has been found in the anhepatic period of liver transplantation indicating extrahepatic metabolism (see below).

1. Pentikäinen PJ, *et al.* Pharmacokinetics of midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. *J Clin Pharmacol* 1989; **29:** 272–7.
2. MacGilchrist AJ, *et al.* Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. *Gut* 1986; **27:** 190–5.

Metabolism. For a discussion of the metabolism of benzodiazepines, see Diazepam, p.992. Midazolam appears to be metabolised by at least 3 different cytochrome P450 isoenzymes found in the liver and in the kidney.[1] Variations in the activity of these enzymes might account for some of the interindividual differences in pharmacokinetics and pharmacodynamics seen with midazolam.[2] However, a study[3] in patients undergoing liver transplantation has indicated that the small intestine is a significant site for

the first-pass metabolism of midazolam, metabolism presumably being catalysed by the cytochrome P450 isoenzyme CYP3A4 found in intestinal mucosa.

1. Wandel C, *et al.* Midazolam is metabolized by at least three different cytochrome P450 enzymes. *Br J Anaesth* 1994; **73:** 658–61.
2. Lown KS, *et al.* The erythromycin breath test predicts the clearance of midazolam. *Clin Pharmacol Ther* 1995; **57:** 16–24.
3. Paine MF, *et al.* First-pass metabolism of midazolam by the human intestine. *Clin Pharmacol Ther* 1996; **60:** 14–24.

Sublingual administration. High bioavailability (about 75%) and reliable plasma concentrations have been achieved after sublingual doses of midazolam.[1]

1. Schwagmeier R, *et al.* Midazolam pharmacokinetics following intravenous and buccal administration. *Br J Clin Pharmacol* 1998; **46:** 203–6.

Uses and Administration

Midazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992), except that it has a more potent amnestic action. It is mainly used for sedation (p.956) in minor surgical or investigative procedures and in intensive care, for premedication, and for induction of general anaesthesia. It is also used as a hypnotic in the short-term management of insomnia. When midazolam is used as a premedicant or for conscious sedation, onset of sedation occurs at about 15 minutes after intramuscular injection reaching a peak at 30 to 60 minutes, and within about 3 to 5 minutes after intravenous injection. When given intravenously as an anaesthetic induction agent, anaesthesia is induced in about 2 to 2.5 minutes; onset of action is more rapid when premedication with an opioid analgesic has been given.

Since the sedative end-point is reached abruptly with midazolam, dosage must be titrated carefully against the response of the patient; lower doses of midazolam are required when it is used with opioid analgesics. Respiratory and cardiac function should be monitored continuously, and facilities for resuscitation should always be available. It is advisable to keep the patient supine during intravenous use and throughout the procedure. The doses given below are, except where specified, the usual adult doses: midazolam should be given in reduced doses to **elderly** or **debilitated patients**.

Midazolam is used as the hydrochloride for oral, parenteral, and rectal dosage; the maleate may also be given orally. All doses are given in terms of the base; midazolam hydrochloride 8.3 mg or midazolam maleate 10.2 mg are both equivalent to about 7.5 mg of midazolam.

A usual total **sedative** dose for dental and minor surgical and other procedures ranges from 2.5 to 7.5 mg (about 70 micrograms/kg) *intravenously*; an initial dose of 2 mg over 30 seconds has been suggested, with further incremental doses of 0.5 to 1 mg at intervals of 2 minutes if required until the desired end-point is reached. In the USA a suggested initial dose of up to 2.5 mg is given intravenously over at least 2 minutes and repeated if necessary after an additional 2 minutes or more to a usual maximum total dose of 5 mg.

Sedation in children aged 6 months and over may be achieved orally. A single *oral* dose of 250 to 500 micrograms/kg, up to a maximum of 20 mg, is recommended although younger patients (6 months to less than 6 years) may require up to 1 mg/kg. If the *intravenous* route is more suitable, doses of 50 to 100 micrograms/kg up to a total dose of 600 micrograms/kg (but not exceeding 6 mg) are recommended in children aged 6 months to 5 years; children aged 6 to 12 years may be given 25 to 50 micrograms/kg up to a total dose of 400 micrograms/kg (or a maximum of 10 mg). Initial doses should be given over 2 to 3 minutes and an additional interval of at least 2 minutes is recommended before giving further doses. In some countries including the UK, the injection may be used *rectally* for sedation in children over 6 months of age; doses range from 300 to 500 micrograms/kg as a single dose. The injection solution may be diluted with Water for Injections up to a total volume of 10 mL if the volume is too small. The *intramuscular* route should only be used in children in exceptional cases as such injections are painful; usual doses ranging from 50 to 150 micrograms/kg have been suggested for intramuscular use in children aged 1 to 15 years. In the UK, although midazolam is not licensed for sedation of children under 6 months of age, the *BNFC* suggests that it may be given orally or intravenously to those aged 1 month and over in doses similar to those used in children aged 6 months and over (see above). Although also unlicensed, it further suggests that midazolam may be given *buccally* to children 6 months to 10 years of age in doses of 200 to 300 micrograms/kg (maximum of 5 mg); those aged 10 to 18 years may be given 6 to 7 mg (maximum of 8 mg if weighing 70 kg or over). The injection solution has been given *intranasally* to children aged 1 month and over; however, severe irritation of the nasal mucosa may occur (see Administration, below) and use of this route is not recommended in the *BNFC*.

Patients in **intensive care** who require continuous sedation (p.957) can be given midazolam by *intravenous infusion*. An initial loading dose of 30 to 300 micrograms/kg may be given by intravenous infusion over 5 minutes to induce sedation; in the USA a lower dose of 10 to 50 micrograms/kg is recommended. The maintenance dose required varies considerably but a dose of between 20 and 200 micrograms/kg per hour has been suggested. The loading dose should be reduced or omitted, and the maintenance dose reduced, for patients with hypovolaemia, vasoconstriction, or hypothermia. The need for continuous infusion should be reassessed on a daily basis to reduce the risk of accumulation and prolonged recovery. Sedation can also be achieved by giving intermittent *intravenous bolus injections* of midazolam; doses of 1 to 2 mg may be given, and repeated, until the desired level of sedation has been reached.

Midazolam is also used in children in intensive care who require sedation. In those aged over 6 months, an initial loading dose of 50 to 200 micrograms/kg is given by *slow intravenous injection*; maintenance doses are given as an intravenous infusion and range from 60 to 120 micrograms/kg per hour. Neonates with a gestational age of greater than 32 weeks and infants aged up to 6 months may be given midazolam by intravenous infusion in a dose of 60 micrograms/kg per hour; neonates with a gestational age of less than 32 weeks should be started on 30 micrograms/kg per hour. Loading doses are not recommended in infants aged under 6 months.

Abrupt withdrawal should be avoided after prolonged use.

Midazolam is given *intramuscularly* as a **premedicant** about 20 to 60 minutes before surgery. The usual dose is about 5 mg; doses range from 70 to 100 micrograms/kg. Children aged 6 months and over may be premedicated with *oral* midazolam in similar doses to those used for sedation (see above). The *rectal* route is used for premedication in some countries; total doses recommended in the UK in children aged over 6 months range from 300 to 500 micrograms/kg. The *intramuscular* route is also licensed in children aged 1 to 15 years in doses of 80 to 200 micrograms/kg; however, as before, this route should only be used in exceptional circumstances.

The usual dose of midazolam for **induction of anaesthesia** (p.1780) is about 150 to 200 micrograms/kg by slow *intravenous injection* in premedicated patients and at least 300 micrograms/kg in those who have not received a premedicant. Additional doses may be needed to complete induction; up to 600 micrograms/kg has been used in resistant cases. Further incremental doses of midazolam of about 25% of the induction dose have also been given as a component of the regimens used for the maintenance of anaesthesia during short surgical procedures. A dose of 150 micrograms/kg has been recommended for the induction of anaesthesia in children over 7 years of age; however, the *BNFC* notes that such use is rare and suggests a maximum total dose of 500 micrograms/kg (not exceeding 25 mg) in those aged up to 18 years.

Midazolam is also given for sedation in **combined anaesthesia** by *intravenous injection* in a dose of 30 to 100 micrograms/kg repeated as required or by *intravenous infusion* in a dose of 30 to 100 micrograms/kg every hour.

Midazolam maleate is also given *orally* for the short-term management of **insomnia**; the usual dose is the equivalent of midazolam 7.5 to 15 mg at night.

◊ References.

1. Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* 1998; **35:** 37–47.
2. Marshall J, *et al.* Pediatric pharmacodynamics of midazolam oral syrup. *J Clin Pharmacol* 2000; **40:** 578–89.

Administration. The rectal,[1] intranasal,[1-5] buccal,[6-8] and sublingual[1,9] routes have all been proposed as alternatives to parenteral use of midazolam.

Intranasal midazolam has caused intense burning, irritation, and lachrymation on instillation, and use of a lidocaine nasal spray has been advocated before giving midazolam to children.[10] The use of midazolam spray intranasally in adults would be impractical and uncomfortable because of the large volume required. It has therefore been tried as a nebulised solution.[11]

1. Wong L, McQueen KD. Midazolam routes of administration. *DICP Ann Pharmacother* 1991; **25:** 476–7.
2. Theroux MC, *et al.* Efficacy of intranasal midazolam in facilitating suturing of lacerations in preschool children in the emergency department. *Pediatrics* 1993; **91:** 624–7.
3. Louon A, *et al.* Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. *Br J Ophthalmol* 1993; **77:** 529–30.
4. Bates BA, *et al.* A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. *Ann Emerg Med* 1994; **24:** 646–51.
5. Ljungman G, *et al.* Midazolam nasal spray reduces procedural anxiety in children. *Pediatrics* 2000; **105:** 73–8.
6. Body R, Ijaz M. Buccal midazolam as an alternative to rectal diazepam for prolonged seizures in childhood and adolescence. *Emerg Med J* 2005; **22:** 364–5.
7. McIntyre J, *et al.* Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005; **366:** 205–10.
8. Baysun S, *et al.* A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. *Clin Pediatr (Phila)* 2005; **44:** 771–6.
9. Karl HW, *et al.* Transmucosal administration of midazolam for premedication of pediatric patients: comparison of the nasal and sublingual routes. *Anesthesiology* 1993; **78:** 885–91.
10. Lugo RA, *et al.* Complication of intranasal midazolam. *Pediatrics* 1993; **92:** 638.
11. Hodgson PE, *et al.* Administration of nebulized intranasal midazolam to healthy adult volunteers: a pilot study. *Br J Anaesth* 1994; **73:** 719P.

INTRATHECAL. See Pain, below.

Conversion and dissociative disorders. For reference to the use of midazolam in the diagnosis of conversion disorders, such as hysterical paralysis, see p.993.

Convulsions. Benzodiazepines such as diazepam or lorazepam given parenterally are often tried first to control status epilepticus (p.469). Midazolam has been used as an alternative.[1] It may be of value when intravenous access is difficult as effective concentrations of midazolam can be obtained after intramuscular injection.[2,3] The *BNF* considers it to be the benzodiazepine of choice when a continuous subcutaneous infusion is required for the control of convulsions, such as in palliative care, and states that it may be given in an initial dose of 20 to 40 mg every 24 hours. Intravenous midazolam has been used in some centres[4] for status epilepticus refractory to diazepam, lorazepam, or phenytoin but reviews of the literature[5] reveal that evidence of efficacy is limited mainly to uncontrolled studies and anecdotal reports.

The intranasal[6,7] and buccal[8] routes have also been used for the management of seizures, and UK guidelines[9] consider buccal midazolam an alternative to rectal diazepam for initial management of status epilepticus in the home setting or where intravenous access is not possible. In addition, a recent study[10] found that buccal midazolam was more effective than rectal diazepam for treatment of children with seizures in the hospital setting and did not appear to increase the risk of respiratory depression. The *BNF* states that a dose of midazolam 10 mg, repeated once if necessary, may be given by the buccal route to adults and children aged over 10 years.

The *BNFC* suggests giving a single buccal dose of 300 micrograms/kg to neonates. It suggests giving the following buccal doses, which may be repeated once if necessary, according to age: 1 to 6 months, 300 micrograms/kg (maximum of 2.5 mg); 6 months to 1 year, 2.5 mg; 1 to 5 years, 5 mg; 5 to 10 years, 7.5 mg. Alternatively, 1 microgram/kg per minute by continuous intravenous infusion may be given to neonates, children, and adolescents after an initial loading dose of 150 to 200 micrograms/kg. This may be increased by 1 microgram/kg per minute every 15 minutes until the seizure is controlled or until a maximum of 5 micrograms/kg per minute is reached.

1. Hanley DF, *et al.* Use of midazolam in the treatment of refractory status epilepticus. *Clin Ther* 1998; **20:** 1093–1105.

2. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
3. Towne AR, DeLorenzo RJ. Use of intramuscular midazolam for status epilepticus. *J Emerg Med* 1999; **17:** 323–8.
4. Bebin M, Bleck TP. New anticonvulsant drugs: focus on flunarizine, fosphenytoin, midazolam and stiripentol. *Drugs* 1994; **48:** 153–71.
5. Denzel D, Burstein AH. Midazolam in refractory status epilepticus. *Ann Pharmacother* 1996; **30:** 1481–3.
6. Wallace SJ. Nasal benzodiazepines for management of acute childhood seizures? *Lancet* 1997; **349:** 222.
7. Lahat E, *et al.* Intranasal midazolam for childhood seizures. *Lancet* 1998; **352:** 620.
8. Scott RC, *et al.* Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999; **353:** 623–6.
9. NICE. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (issued October 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/CG020NICEguideline.pdf (accessed 21/08/08)
10. McIntyre J, *et al.* Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005; **366:** 205–10.

Disturbed behaviour. For a discussion of the palliative treatment of terminal restlessness with benzodiazepines such as midazolam, see p.954.

Dyspnoea. Midazolam has been suggested[1] as an alternative to chlorpromazine in patients with advanced cancer and intractable dyspnoea (p.104) to relieve air hunger and to sedate dying patients who have unrelieved distress. Suggested[2] initial doses are 2.5 to 5 mg subcutaneously or 10 mg given by infusion over a period of 24 hours, increased as necessary. It may be combined successfully with morphine.[3]

1. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342:** 450–1.
2. Davis CL. ABC of palliative care: breathlessness, cough, and other respiratory problems. *BMJ* 1997; **315:** 931–4.
3. Navigante AH, *et al.* Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. *J Pain Symptom Manage* 2006; **31:** 38–47.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976. Midazolam given intravenously or subcutaneously has been reported[1] to have been effective in 2 patients with metastatic cancer who had hiccups unresponsive to conventional treatment. However, it has been noted[1,2] that benzodiazepines such as midazolam may exacerbate or precipitate hiccups.

1. Wilcock A, Twycross R. Midazolam for intractable hiccup. *J Pain Symptom Manage* 1996; **12:** 59–61.
2. Rousseau P. Hiccups. *South Med J* 1995; **88:** 175–81.

Insomnia. For discussion of the management of insomnia including limitations on the use of benzodiazepines and a recommendation that the period of treatment with midazolam should be limited to 2 weeks, see p.957.

References.

1. Monti JM, *et al.* The effect of midazolam on transient insomnia. *Eur J Clin Pharmacol* 1993; **44:** 525–7.

Pain. The conventional use of benzodiazepines in pain management is as muscle relaxants to relieve pain associated with skeletal muscle spasm (see under Choice of Analgesic, p.2). Midazolam has been studied[1-5] for use as an intrathecal analgesic but efficacy has been inconsistent.

1. Cripps TP, Goodchild CS. Intrathecal midazolam and the stress response to upper abdominal surgery. *Clin J Pain* 1988; **4:** 125–8.
2. Serrao JM, *et al.* Intrathecal midazolam for the treatment of chronic mechanical low back pain: a controlled comparison with epidural steroid in a pilot study. *Pain* 1992; **48:** 5–12.
3. Baaijens PFJ, *et al.* Intrathecal midazolam for the treatment of chronic mechanical low back pain: a randomized double-blind placebo-controlled study. *Br J Anaesth* 1995; **74** (suppl 1): 143.
4. Valentine JMJ, *et al.* The effect of intrathecal midazolam on post-operative pain. *Eur J Anaesthesiol* 1996; **13:** 589–93.
5. Batra YK, *et al.* Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery. *Int J Clin Pharmacol Ther* 1999; **37:** 519–23.

Premedication and sedation. Midazolam is used as a premedicant (p.1780) and as a sedative for therapeutic and investigative procedures such as dental treatment (p.956) and endoscopy (see below). It is also used to provide continuous sedation in patients in intensive care (p.957) although a systematic review has raised concerns about such use in neonates.

References.

1. Sandler ES, *et al.* Midazolam versus fentanyl as premedication for painful procedures in children with cancer. *Pediatrics* 1992; **89:** 631–4.
2. Stenhammar L, *et al.* Intravenous midazolam in small bowel biopsy. *Arch Dis Child* 1994; **71:** 558.
3. Jacqz-Aigrain E, *et al.* Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. *Lancet* 1994; **344:** 646–50.
4. Mitchell V, *et al.* Comparison of midazolam with trimeprazine as an oral premedicant for paediatric anaesthesia. *Br J Anaesth* 1995; **74** (suppl 1): 94–5.
5. McCarver-May DG, *et al.* Comparison of chloral hydrate and midazolam for sedation of neonates for neuroimaging studies. *J Pediatr* 1996; **128:** 573–6.
6. Zedie N, *et al.* Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. *Clin Pharmacol Ther* 1996; **59:** 341–8.
7. McErlean M, *et al.* Midazolam syrup as a premedication to reduce the discomfort associated with pediatric intravenous catheter insertion. *J Pediatr* 2003; **142:** 429–30.
8. TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *BMJ* 2003; **327:** 708–11.
9. Ng E, *et al.* Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 24/03/06).
10. Averley PA, *et al.* An RCT pilot study to test the effects of intravenous midazolam as a conscious sedation technique for anxious children requiring dental treatment: an alternative to general anaesthesia. *Br Dent J* 2004; **197:** 553–8.

ENDOSCOPY. Intravenous benzodiazepines such as diazepam or midazolam are often the preferred drugs for sedation in patients undergoing endoscopy (p.956). They are sometimes used with opioid analgesics for sedation.[1]

A reduced dose of midazolam was required for endoscopy when it was given as a bolus intravenous injection rather than as a slow intravenous titration. A study in 788 patients undergoing endoscopy found that a mean dose of 4.65 mg of midazolam given as a bolus intravenous injection was safe and effective in patients under 70 years of age whereas a mean dose of 1.89 mg was sufficient for patients over 70 years of age.[2] Furthermore, topical pharyngeal anaesthesia was not required with these doses of midazolam. Intravenous boluses were also easier to give and associated with less oxygen desaturation than titrating the dose.[3] Another study found that even lower doses of midazolam (35 micrograms/kg) were effective as premedication before gastroscopy, and were associated with fewer complications than higher doses (70 micrograms/kg).[4]

Intranasal[5] and oral[6] midazolam have also been tried for sedation before endoscopy, particularly in children.

1. Bahal-O'Mara N, *et al.* Sedation with meperidine and midazolam in pediatric patients undergoing endoscopy. *Eur J Clin Pharmacol* 1994; **47:** 319–23.
2. Smith MR, *et al.* Small bolus injections of intravenous midazolam for upper gastrointestinal endoscopy: a study of 788 consecutive cases. *Br J Clin Pharmacol* 1993; **36:** 573–8.
3. Morrow JB, *et al.* Sedation for colonoscopy using a single bolus is safe, effective, and efficient: a prospective, randomized, double-blind trial. *Am J Gastroenterol* 2000; **95:** 2242–7.
4. Campo R, *et al.* Efficacy of low and standard midazolam doses for gastroscopy: a randomized, double-blind study. *Eur J Gastroenterol Hepatol* 2000; **12:** 187–90.
5. Fishbein M, *et al.* Evaluation of intranasal midazolam in children undergoing esophagogastroduodenoscopy. *J Pediatr Gastroenterol Nutr* 1997; **25:** 261–6.
6. Martinez JL, *et al.* A comparison of oral diazepam versus midazolam, administered with intravenous meperidine, as premedication to sedation for pediatric endoscopy. *J Pediatr Gastroenterol Nutr* 2002; **35:** 51–8.

Preparations

BP 2008: Midazolam Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Dalam; Dormicum; Dormid; Drimnorth; Gobbizolam; Ormir†; Rem; Ukel; ***Austral.:*** Hypnovel; ***Austria:*** Dormicum; ***Belg.:*** Dormicum; ***Braz.:*** Dormire; Dormium; Dormonid; Hipnazolam; Zolidan†; ***Canad.:*** Versed†; ***Chile:*** Dormonid; Noctura; Terap; Zolmid; ***Cz.:*** Dormicum; Fulsed; ***Denm.:*** Dormicum; ***Fin.:*** Dormicum; ***Fr.:*** Hypnovel; Versed; ***Ger.:*** Dormicum; Midaselect†; ***Gr.:*** Damizol; Dormicum; Dormixal; ***Hong Kong:*** Dormicum; ***Hung.:*** Dormicum; ***India:*** Fulsed; ***Indon.:*** Dormicum; Fortanest; Miloz; ***Irl.:*** Hypnovel; ***Israel:*** Dormicum; Midazol; Midolam; ***Ital.:*** Ipnovel; ***Malaysia:*** Dormicum; Fulsed†; Mizolam; ***Mex.:*** Dormicum; ***Neth.:*** Dormicum; ***Norw.:*** Dormicum; ***NZ:*** Hypnovel; ***Philipp.:*** Dormicum; ***Pol.:*** Dormicum; Midanium; Sopodorm; ***Port.:*** Dormicum; Zolamid; ***S.Afr.:*** Dormicum; Midacum; Midanium; ***Singapore:*** Dormicum; Fulsed; ***Spain:*** Dormicum; ***Swed.:*** Dormicum; ***Switz.:*** Dormicum; ***Thai.:*** Dormicum; Midazol†; ***Turk.:*** Dormicum; ***UK:*** Hypnovel; ***USA:*** Versed†; ***Venez.:*** Benzosed; Doricum; Midazepin.

Molindone Hydrochloride *(BANM, USAN, rINNM)*

EN-1733A; Hidrocloruro de molindona; Molindone, Chlorhydrate de; Molindoni Hydrochloridum. 3-Ethyl-1,5,6,7-tetrahydro-2-methyl-5-(morpholinomethyl)indol-4-one hydrochloride.

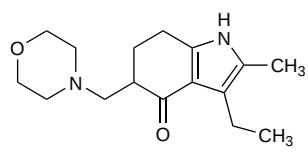
Молиндона Гидрохлорид

$C_{16}H_{24}N_2O_2$,HCl = 312.8.

CAS — 7416-34-4 (molindone); 15622-65-8 (molindone hydrochloride).

ATC — N05AE02.

ATC Vet — QN05AE02.



(molindone)

Pharmacopoeias. In *US.*

USP 31 (Molindone Hydrochloride). pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Molindone hydrochloride is less likely to cause hypotension than chlorpromazine, and extrapyramidal effects may be frequent but less severe. The incidence of sedation is intermediate between that of chlorpromazine and of phenothiazines with a piperazine side-chain. Weight gain or loss may occur, but weight loss appears to be more prominent (see p.970).

Effects on the liver. A report of hepatotoxicity, associated with a flu-like syndrome, in a patient given molindone.[1] Symptoms and liver-enzyme values returned to normal on stopping the drug and recurred on rechallenge with low doses. The effect was probably due to a hypersensitivity reaction.

1. Bhatia SC, *et al.* Molindone and hepatotoxicity. *Drug Intell Clin Pharm* 1985; **19:** 744–6.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Molindone is readily absorbed after oral doses, with peak concentrations of unchanged molindone occurring within about 1.5 hours. It is rapidly and extensively metabolised and a large number of metabolites have been identified. It is excreted in the urine and faeces mainly as metabolites and less than 2 to 3% as unchanged drug. The pharmacological effect from a single oral dose is reported to last for 24 to 36 hours.

◊ References.

1. Zetin M, *et al.* Bioavailability of oral and intramuscular molindone hydrochloride in schizophrenic patients. *Clin Ther* 1985; **7:** 169–75.

Uses and Administration

Molindone is an indole derivative with general properties similar to those of the phenothiazine, chlorpromazine (p.975). It is given as the hydrochloride for the treatment of psychoses including schizophrenia (p.955).

The usual oral dose of molindone hydrochloride is 50 to 75 mg daily initially, increased in 3 or 4 days to 100 mg daily; in severe or resistant conditions doses of up to 225 mg daily may be required. The maintenance dose can range from 15 to 225 mg daily according to severity of symptoms. The daily dose is usually divided into 3 or 4 portions.

Molindone should be given in reduced dosage to elderly or debilitated patients.

Psychiatric disorders. A systematic review[1] found that, based on limited data, molindone appeared to be effective in schizophrenia and other severe psychoses but evidence of differences from other classical antipsychotics was lacking.

1. Bagnall A, *et al.* Molindone for schizophrenia and severe mental illness. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 19/03/08).

Preparations

USP 31: Molindone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Moban.

Moperone Hydrochloride *(rINNM)*

Hidrocloruro de moperona; Methylperidol Hydrochloride; Mopérone, Chlorhydrate de; Moperoni Hydrochloridum; R-1658 (moperone). 4′-Fluoro-4-(4-hydroxy-4-*p*-tolylpiperidino)butyrophenone hydrochloride.

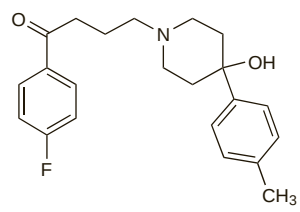
Моперона Гидрохлорид

$C_{22}H_{26}FNO_2$,HCl = 391.9.

CAS — 1050-79-9 (moperone); 3871-82-7 (moperone hydrochloride).

ATC — N05AD04.

ATC Vet — QN05AD04.



(moperone)

Profile

Moperone is a butyrophenone with general properties similar to those of haloperidol (p.1000). It has been given orally for the treatment of psychoses.

Preparations

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