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.

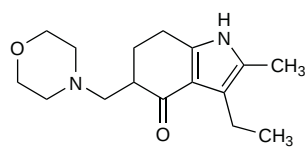
Молиндона Гидрохлорид

$C_{16}H_{24}N_2O_2$,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.

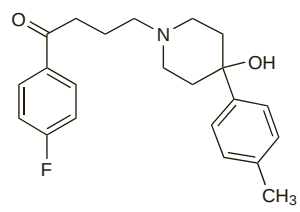
Моперона Гидрохлорид

$C_{22}H_{26}FNO_2$,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.