Cyclobarbital *(BAN, rINN)*

Ciclobarbital; Cyclobarbitalum; Cyclobarbitone; Cyklobarbital; Ethylhexabital; Hexemalum; Syklobarbitaali. 5-(Cyclohex-1-enyl)-5-ethylbarbituric acid.

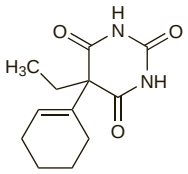
Циклобарбитал

$C_{12}H_{16}N_2O_3$ = 236.3.

CAS — 52-31-3.

ATC — N05CA10.

ATC Vet — QN05CA10.



NOTE. The name ciclobarbital has sometimes been applied to hexobarbital.

Cyclobarbital Calcium *(BANM, rINNM)*

Calcii Cyclobarbitalum; Ciclobarbital cálcico; Ciclobarbital Calcium; Cyclobarbital Calcique; Cyclobarbitalum Calcicum; Cyclobarbitone Calcium; Cyklobarbital wapniowy; Hexemalcalcium. Calcium 5-(cyclohex-1-enyl)-5-ethylbarbiturate.

Кальций Циклобарбитал

$(C_{12}H_{15}N_2O_3)_2Ca$ = 510.6.

CAS — 5897-20-1.

ATC — N05CA10.

ATC Vet — QN05CA10.

Pharmacopoeias. In *Pol.*

Profile

Cyclobarbital is a barbiturate with general properties similar to those of amobarbital (p.961). The calcium salt has been used as a hypnotic but barbiturates are no longer considered appropriate for such purposes.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Rus.:* Reladorm (Реладорм).

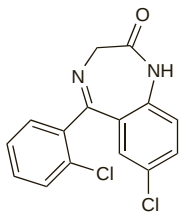
Delorazepam *(pINN)*

Chlordesmethyldiazepam; Clordesmethyldiazepam; Délorazépam; Delorazepamum. 7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Делоразепам

$C_{15}H_{10}Cl_2N_2O$ = 305.2.

CAS — 2894-67-9.



Profile

Delorazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It has been used in the short-term treatment of anxiety disorders, insomnia, and epilepsy, and for premedication.

Administration in hepatic or renal impairment. The pharmacokinetics of total delorazepam were unchanged in patients with renal failure undergoing haemodialysis compared with controls.[1] However, the apparent volume of distribution of unbound drug was smaller and the clearance slower. The volume of distribution and clearance of unchanged drug was also reduced in patients with liver disease.[2]

1. Sennesael J, *et al.* Pharmacokinetics of intravenous and oral chlordesmethyldiazepam in patients on regular haemodialysis. *Eur J Clin Pharmacol* 1991; **41:** 65–8.
2. Bareggi SR, *et al.* Effects of liver disease on the pharmacokinetics of intravenous and oral chlordesmethyldiazepam. *Eur J Clin Pharmacol* 1995; **48:** 265–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Dadumir; En.

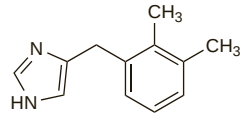
Detomidine Hydrochloride *(BANM, USAN, rINNM)*

Demotidini Hydrochloridum; Detomidiinihydrokloridi; Detomidin hydrochlorid; Détomidine, chlorhydrate de; Detomidin-hidroklorid; Detomidinhydroklorid; Detomidini hydrochloridum; Hidrocloruro de detomidina; MPV-253-All. 4-(2,3-Dimethylbenzyl)imidazole hydrochloride.

Детомидина Гидрохлорид

$C_{12}H_{14}N_2$,HCl = 222.7.

CAS — 76631-46-4 (detomidine); 90038-01-0 (detomidine hydrochloride).



(detomidine)

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.

Ph. Eur. 6.2 (Detomidine Hydrochloride for Veterinary Use; Detomide Hydrochloride BP(Vet) 2008). A white or almost white, hygroscopic, crystalline powder. Soluble in water; freely soluble in alcohol; practically insoluble in acetone; very slightly soluble in dichloromethane. Protect from moisture.

Profile

Detomidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties. It is used as the hydrochloride in veterinary medicine.

Dexmedetomidine Hydrochloride

(BANM, USAN, rINNM)

Deksmedetomidin Hidroklorür; Dexmédétomidine, Chlorhydrate de; Dexmedetomidini Hydrochloridum; Hidrocloruro de dexmedetomidina; MPV-1440 (dexmedetomidine). (*S*)-4-[1-(2,3-Xylyl)ethyl]imidazole hydrochloride.

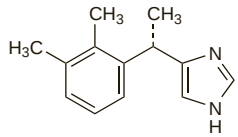
Дексмедетомидина Гидрохлорид

$C_{13}H_{16}N_2$,HCl = 236.7.

CAS — 113775-47-6 (dexmedetomidine); 145108-58-3 (dexmedetomidine hydrochloride).

ATC — N05CM18.

ATC Vet — QN05CM18.



(dexmedetomidine)

Adverse Effects and Precautions

The most frequently observed adverse effect with dexmedetomidine is hypotension. Other common adverse effects include hypertension, nausea and vomiting, bradycardia, tachycardia, fever, hypoxia, and anaemia. Patients should be continuously monitored during use. Dexmedetomidine should be used with caution in patients with advanced heart block, or hepatic or renal impairment, or in the elderly.

Interactions

The effects of other CNS depressants may be enhanced by dexmedetomidine. Dexmedetomidine may also increase the effects of other vasodilators or drugs such as cardiac glycosides, that have negative chronotropic effects.

Pharmacokinetics

Dexmedetomidine is about 94% protein bound, but this has been reported to be significantly decreased in patients with hepatic impairment. Dexmedetomidine is almost completely metabolised by direct glucuronidation or by cytochrome P450 isoenzymes. It is excreted mainly as metabolites in the urine and faeces. The terminal elimination half-life is about 2 hours.

◊ References.

1. Scheinin H, *et al.* Pharmacodynamics and pharmacokinetics of intramuscular dexmedetomidine. *Clin Pharmacol Ther* 1992; **52:** 537–46.
2. Kivistö KT, *et al.* Pharmacokinetics and pharmacodynamics of transdermal dexmedetomidine. *Eur J Clin Pharmacol* 1994; **46:** 345–9.
3. De Wolf AM, *et al.* The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. *Anesth Analg* 2001; **93:** 1205–9.
4. Anttila M, *et al.* Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. *Br J Clin Pharmacol* 2003; **56:** 691–3.

Uses and Administration

Dexmedetomidine is a selective alpha$_2$-adrenergic receptor agonist with anxiolytic, analgesic, and sedative properties. It is used for the sedation of mechanically ventilated patients in intensive care. Dexmedetomidine is given as the hydrochloride, but doses are expressed in terms of the base. Dexmedetomidine hydrochloride 118 micrograms is equivalent to about 100 micrograms of dexmedetomidine.

It is given in sodium chloride 0.9% by intravenous infusion in a loading dose equivalent to 1 microgram/kg of dexmedetomidine over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 micrograms/kg per hour for up to 24 hours. Reduced doses may be necessary in patients with hepatic or renal impairment, or in the elderly.

The racemate, medetomidine (p.1006), is used as the hydrochloride in veterinary medicine.

◊ References.

1. Venn RM, *et al.* Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* 1999; **54:** 1136–42.
2. Bhana N, *et al.* Dexmedetomidine. *Drugs* 2000; **59:** 263–8.
3. Coursin DB, *et al.* Dexmedetomidine. *Curr Opin Crit Care* 2001; **7:** 221–6.
4. Bekker A, Sturaitis MK. Dexmedetomidine for neurological surgery. *Neurosurgery* 2005; **57** (suppl): 1–10.
5. Szumita PM, *et al.* Sedation and analgesia in the intensive care unit: evaluating the role of dexmedetomidine. *Am J Health-Syst Pharm* 2007; **64:** 37–44.
6. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. *Ann Pharmacother* 2007; **41:** 245–53. Correction. *ibid.*; 530–1.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Precedex; ***Austral.:*** Precedex; ***Braz.:*** Precedex; ***Cz.:*** Precedex; ***Hong Kong:*** Precedex; ***Israel:*** Precedex; ***Malaysia:*** Precedex; ***Mex.:*** Precedex; ***NZ:*** Precedex; ***Pol.:*** Precedex; ***Singapore:*** Precedex†; ***Thai.:*** Precedex; ***Turk.:*** Precedex; ***USA:*** Precedex; ***Venez.:*** Precedex†.

Diazepam *(BAN, USAN, rINN)*

Diatsepaami; Diazépam; Diazepám; Diazepamas; Diazepamum; LA-III; NSC-77518; Ro-5-2807; Wy-3467. 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

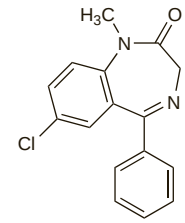
Диазепам

$C_{16}H_{13}ClN_2O$ = 284.7.

CAS — 439-14-5.

ATC — N05BA01.

ATC Vet — QN05BA01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of diazepam:
Benzo; Blue; Blues; Drunk pills; La Roche; Ludes; Mother's little helper; Mother's little helpers; Pami; Roaches; Roachies; Roche; V; V's blues; Vallies; Vals.

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

Ph. Eur. 6.2 (Diazepam). A white or almost white, crystalline powder. Very slightly soluble in water; soluble in alcohol. Protect from light.

USP 31 (Diazepam). An off-white to yellow, practically odourless, crystalline powder. Soluble 1 in 333 of water, 1 in 16 of alcohol, 1 in 2 of chloroform, and 1 in 39 of ether. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between diazepam and several other drugs. Manufacturers of diazepam injection (*Roche* and others) have advised against its admixture with other drugs.

Sorption. Substantial adsorption of diazepam onto some plastics may cause problems when giving the drug by continuous intravenous infusion. More than 50% of diazepam in solution may be adsorbed onto the walls of PVC infusion bags and their use should, therefore, be avoided. Giving sets should contain the minimum amount of PVC tubing and should not contain a cellulose propionate volume-control chamber. Suitable materials for infusion containers, syringes, and giving sets for diazepam include glass, polyolefin, polypropylene, and polyethylene.

References.

1. Cloyd JC, *et al.* Availability of diazepam from plastic containers. *Am J Hosp Pharm* 1980; **37:** 492–6.
2. Parker WA, MacCara ME. Compatibility of diazepam with intravenous fluid containers and administration sets. *Am J Hosp Pharm* 1980; **37:** 496–500.

3. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.
4. Kowaluk EA, *et al.* Factors affecting the availability of diazepam stored in plastic bags and administered through intravenous sets. *Am J Hosp Pharm* 1983; **40:** 417–23.
5. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Stability. Care should be observed when diluting diazepam injections for infusion because of problems of precipitation. The manufacturer's directions should be followed regarding diluent and concentration of diazepam and all solutions should be freshly prepared.

Dependence and Withdrawal

The development of dependence is common after regular use of benzodiazepines, even in therapeutic doses for short periods. Dependence is particularly likely in patients with a history of alcohol or drug abuse and in those with marked personality disorders. Benzodiazepines should therefore be withdrawn by gradual reduction of the dose after regular use for even a few weeks; the time needed for withdrawal can vary from about 4 weeks to a year or more. The extent to which tolerance occurs has been debated but appears to involve psychomotor performance more often than anxiolytic effects. Drug-seeking behaviour is uncommon with therapeutic doses of benzodiazepines. High doses of diazepam and other benzodiazepines, injected intravenously, have been abused for their euphoriant effects.

Benzodiazepine withdrawal syndrome. Development of dependence to benzodiazepines cannot be predicted but risk factors include high dosage, regular continuous use, the use of benzodiazepines with a short half-life, use in patients with dependent personality characteristics or a history of drug or alcohol dependence, and the development of tolerance. The mechanism of dependence is unclear but may involve reduced gamma-aminobutyric acid (GABA) activity resulting from down-regulation of GABA receptors.

Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension. Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines.

Symptoms typical of withdrawal have occurred despite continued use of benzodiazepines and have been attributed either to the development of tolerance or, as in the case of very short-acting drugs such as triazolam, to rapid benzodiazepine elimination. Pseudowithdrawal has been reported in patients who believed incorrectly that their dose of benzodiazepine was being reduced. Benzodiazepine withdrawal syndrome can theoretically be distinguished from these reactions and from rebound phenomena (return of original symptoms at greater than pretreatment severity) by the differing **time course**. A withdrawal syndrome is characterised by its onset, by the development of new symptoms, and by a peak in intensity followed by resolution. Onset of withdrawal symptoms depends on the half-life of the drug and its active metabolites. Symptoms can begin within a few hours after withdrawal of a short-acting benzodiazepine, but may not develop for up to 3 weeks after stopping a longer-acting benzodiazepine. Resolution of symptoms may take several days or months. The dependence induced by short- and long-acting benzodiazepines appears to be qualitatively similar although withdrawal symptoms may be more severe with short-acting benzodiazepines. Rebound effects are also more likely with short-acting benzodiazepines. Rebound and withdrawal symptoms develop particularly rapidly with the very short-acting drug triazolam.

With increased awareness of the problems of benzodiazepine dependence, emphasis has been placed on **prevention** by proper use and careful patient selection. For example, the UK CSM has recommended that benzodiazepines should be reserved for the short-term relief (2 to 4 weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress and is occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness. These recommendations are similar to those of the UK Royal College of Psychiatrists.

Withdrawal from long-term benzodiazepine use should generally be encouraged. Established dependence can be difficult to treat; the patient should have professional and family support and behavioural therapy may be helpful. Withdrawal in a specialist centre may be required for some patients. Since abrupt withdrawal of benzodiazepines may result in severe withdrawal symptoms dosage should be tapered. The *BNF* considers that benzodiazepines can be withdrawn in steps of about one-eighth of the daily dose every fortnight (range one-tenth to one-quarter). There are no comparative studies of the efficacy of various withdrawal schedules and in practice the protocol should be titrated against the response of the patient. Clinicians often favour transferring the patient to an equivalent dose of diazepam given at night and the following rough dosage equivalents to *diazepam 5 mg* have been recommended in the UK:

- chlordiazepoxide 15 mg
- loprazolam 0.5 to 1 mg
- lorazepam 500 micrograms
- lormetazepam 0.5 to 1 mg
- nitrazepam 5 mg
- oxazepam 15 mg
- temazepam 10 mg

The daily dosage of diazepam can then be reduced in steps of 0.5 to 2.5 mg at fortnightly intervals. If troublesome abstinence effects occur the dose should be held level for a longer period before further reduction; increased dosage should be avoided if possible. It is better to reduce too slowly than too quickly. Time required for withdrawal can vary from about 4 weeks to a year or longer. In many cases the rate of withdrawal is best decided by the patient.

Adjuvant therapy should generally be avoided. Although a beta blocker may be given for prominent sympathetic overactivity the *BNF* recommends that this be tried only if other measures fail; antidepressants should be used only for clinical depression or panic attacks. Antipsychotic drugs should be avoided as they may aggravate symptoms.

Symptoms gradually improve after withdrawal but postwithdrawal syndromes lasting for several weeks or months have been described. Continued support may be required for the first year after withdrawal to prevent relapse.

References.
1. CSM. Benzodiazepines, dependence and withdrawal symptoms. *Current Problems 21* 1988. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 21/08/08)
2. Marriott S, Tyrer P. Benzodiazepine dependence: avoidance and withdrawal. *Drug Safety* 1993; **9:** 93–103.
3. Pétursson H. The benzodiazepine withdrawal syndrome. *Addiction* 1994; **89:** 1455–59.
4. Ashton H. The treatment of benzodiazepine dependence. *Addiction* 1994; **89:** 1535–41.
5. The Royal College of Psychiatrists. Benzodiazepines: risks, benefits or dependence—a re-evaluation. *Council Report CR59*; London: January, 1997 [under review]. Available at: http://www.rcpsych.ac.uk/publications/collegereports/cr/cr59.aspx (accessed 31/05/06)
6. DoH. *Drug misuse and dependence: guidelines on clinical management.* London: The Stationery Office, 1999. Available at: http://www.dh.gov.uk/assetRoot/04/07/81/98/04078198.pdf (accessed 28/04/04)
7. Denis C, *et al.* Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/03/08).

Adverse Effects

Drowsiness, sedation, muscle weakness, and ataxia are the most frequent adverse effects of diazepam use. They generally decrease on continued dosage and are a consequence of CNS depression. Less frequent effects include vertigo, headache, confusion, depression (but see Effects on Mental Function, below), slurred speech or dysarthria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation, and amnesia. Some patients may experience a paradoxical excitation which may lead to hostility, aggression, and disinhibition. Jaundice, blood disorders, and hypersensitivity reactions have been reported rarely. Respiratory depression and hypotension occasionally occur with high dosage and parenteral use.

Pain and thrombophlebitis may occur with some intravenous formulations of diazepam; raised liver enzyme values have occurred.

Overdosage can produce CNS depression and coma or paradoxical excitation. However, fatalities are rare when taken alone.

Use of diazepam in the first trimester of pregnancy has occasionally been associated with congenital malformations in the infant but no clear relationship has been established. This topic is reviewed under Pregnancy below. Use of diazepam in late pregnancy has been associated with intoxication of the neonate.

Carcinogenicity. The International Agency for Research on Cancer concluded[1] that there was sufficient evidence from human studies that diazepam did not produce breast cancer, and that there was inadequate data to support its potential carcinogenicity at other sites. For most other benzodiazepines the lack of human studies meant that the carcinogenic risk to humans was not classifiable. However, there appeared to be sufficient evidence of carcinogenicity in *animal* studies for oxazepam to be classified as possibly carcinogenic in humans.

1. IARC/WHO. Some pharmaceutical drugs. *IARC monographs on the evaluation of carcinogenic risks to humans volume 66* 1996. Also available at: http://monographs.iarc.fr/ENG/Monographs/vol66/volume66.pdf (accessed 15/05/06)

Effects on body temperature. Studies in healthy subjects[1,2] indicate that benzodiazepines can reduce body temperature. After a single dose of diazepam 10 mg by mouth in 11 subjects, body temperature on exposure to cold fell to a mean of 36.93° compared with 37.08° on exposure without the drug.[1] An 86-year-old woman developed hypothermia[3] after being given nitrazepam 5 mg. After recovery she was mistakenly given another 5-mg dose of nitrazepam and again developed hypothermia. Midazolam (given as anaesthetic premedication) also produces modest decreases in core body temperature, which can be abolished by atropine,[4] but its effects are negligible compared with other elements of the anaesthetic regimen.[5]

Hypothermia has been reported in the neonates of mothers given benzodiazepines during the late stages of pregnancy.

1. Martin SM. The effect of diazepam on body temperature change in humans during cold exposure. *J Clin Pharmacol* 1985; **25:** 611–13.
2. Matsukawa T, *et al.* I.M. midazolam as premedication produces a concentration-dependent decrease in core temperature in male volunteers. *Br J Anaesth* 1997; **78:** 396–9.
3. Impallomeni M, Ezzat R. Hypothermia associated with nitrazepam administration. *BMJ* 1976; **1:** 223–4.
4. Matsukawa T, *et al.* Atropine prevents midazolam-induced core hypothermia in elderly patients. *J Clin Anesth* 2001; **13:** 504–8.
5. Kurz A, *et al.* Midazolam minimally impairs thermoregulatory control. *Anesth Analg* 1995; **81:** 393–8.

Effects on endocrine function. Galactorrhoea with normal serum-prolactin concentrations has been noted in 4 women taking benzodiazepines.[1] Gynaecomastia has been reported in a man taking up to 140 mg diazepam daily[2] and in 5 men taking diazepam in doses of up to 30 mg daily.[3] Serum-oestradiol concentrations were raised in the latter group. However, raised plasma-testosterone concentrations have also been observed in men taking diazepam 10 to 20 mg daily for 2 weeks.[4]

1. Kleinberg DL, *et al.* Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. *N Engl J Med* 1977; **296:** 589–600.
2. Moerck HJ, Magelund G. Gynaecomastia and diazepam abuse. *Lancet* 1979; **i:** 1344–5.
3. Bergman D, *et al.* Increased oestradiol in diazepam related gynaecomastia. *Lancet* 1981; **ii:** 1225–6.
4. Argüelles AE, Rosner J. Diazepam and plasma-testosterone levels. *Lancet* 1975; **ii:** 607.

Effects on the eyes. Brown opacification of the lens occurred in 2 patients who took diazepam 5 mg or more daily by mouth over several years.[1] Severe visual field loss associated with very high doses (100 mg) of diazepam has also been described.[2]

1. Pau H. Braune scheibenförmige Einlagerungen in die Linse nach Langzeitgabe von Diazepam (Valium). *Klin Monatsbl Augenheilkd* 1985; **187:** 219–20.
2. Elder MJ. Diazepam and its effects on visual fields. *Aust N Z J Ophthalmol* 1992; **20:** 267–70.

Effects on the liver. Cholestatic jaundice[1] and focal hepatic necrosis with intracellular cholestasis[2] have been associated with the use of diazepam.

1. Jick H, *et al.* Drug-induced liver disease. *J Clin Pharmacol* 1981; **21:** 359–64.
2. Tedesco FJ, Mills LR. Diazepam (Valium) hepatitis. *Dig Dis Sci* 1982; **27:** 470–2.

Effects on mental function. The effects of benzodiazepines on psychomotor performance in laboratory tests[1] are not easily extrapolated to the clinical situation. For example postoperative cognitive dysfunction in the elderly does not seem to be related to benzodiazepine concentration in the blood.[2]

Concern has been expressed over the possible effects of long-term benzodiazepine use on the brain. A detailed study[3] found that performance of tasks involving visual-spatial ability and sustained attention was poor in patients taking high doses of benzodiazepines for long periods of time. There was no evidence of impairment in global measures of intellectual functioning such as memory, flexibility, and simple reaction time. The authors could draw no conclusions about the effect of benzodiazepine withdrawal on these changes. A study of 17 long-term users of benzodiazepines has indicated a dose-dependent increase in cerebral ventricle size.[4]

Sexual fantasies have been reported in women sedated with intravenous diazepam or midazolam.[5] These appear to be dose-related.[6]

The view that benzodiazepines can cause depression, albeit infrequently, has been queried.[7]

Adverse effects of alprazolam on behaviour have also been reviewed.[8]

1. Woods JH, *et al.* Abuse liability of benzodiazepines. *Pharmacol Rev* 1987; **39:** 251–413.
2. Rasmussen LS, *et al.* Benzodiazepines and postoperative cognitive dysfunction in the elderly. *Br J Anaesth* 1999; **83:** 585–9.
3. Golombok S, *et al.* Cognitive impairment in long-term benzodiazepine users. *Psychol Med* 1988; **18:** 365–74.
4. Schmauss C, Krieg J-C. Enlargement of cerebrospinal fluid spaces in long-term benzodiazepine abusers. *Psychol Med* 1987; **17:** 869–73.

5. Dundee JW. Fantasies during sedation with intravenous midazolam or diazepam. *Med Leg J* 1990; **58:** 29–34.
6. Brahams D. Benzodiazepine sedation and allegations of sexual assault. *Lancet* 1989; **i:** 1339–40.
7. Patten SB, Love EJ. Drug-induced depression: incidence, avoidance and management. *Drug Safety* 1994; **10:** 203–19.
8. Cole JO, Kando JC. Adverse behavioral events reported in patients taking alprazolam and other benzodiazepines. *J Clin Psychiatry* 1993; **54** (suppl): 49–61.

Effects on the nervous system. There are a few isolated reports of extrapyramidal symptoms in patients taking benzodiazepines.[1-4] Benzodiazepines have been used to treat such symptoms induced by antipsychotics (see Extrapyramidal Disorders under Chlorpromazine, p.971).

1. Rosenbaum AH, De La Fuente JR. Benzodiazepines and tardive dyskinesia. *Lancet* 1979; **ii:** 900.
2. Sandyk R. Orofacial dyskinesias associated with lorazepam therapy. *Clin Pharm* 1986; **5:** 419–21.
3. Stolarek IH, Ford MJ. Acute dystonia induced by midazolam and abolished by flumazenil. *BMJ* 1990; **300:** 614.
4. Joseph AB, Wroblewski BA. Paradoxical akathisia caused by clonazepam, clorazepate and lorazepam in patients with traumatic encephalopathy and seizure disorders: a subtype of benzodiazepine-induced disinhibition? *Behav Neurol* 1993; **6:** 221–3.

ENCEPHALOPATHY. Prolonged use of midazolam with fentanyl has been associated with encephalopathy in infants sedated under intensive care.[1]

1. Bergman I, *et al.* Reversible neurologic abnormalities associated with prolonged intravenous midazolam and fentanyl administration. *J Pediatr* 1991; **119:** 644–9.

Effects on sexual function. The sedative effects of benzodiazepines may reduce sexual arousal and lead to impotence in some patients. Conversely sexual performance may be improved by therapy if it was previously impaired by anxiety.

Increased libido and orgasmic function has been reported in 2 women after withdrawal of long-term benzodiazepine use.[1]

1. Nutt D, *et al.* Increased sexual function in benzodiazepine withdrawal. *Lancet* 1986; **ii:** 1101–2.

Effects on skeletal muscle. In a report[1] of 2 patients who developed rhabdomyolysis secondary to hyponatraemia it was suggested that the use of benzodiazepines might have contributed to the rhabdomyolysis. Of 8 reported cases of rhabdomyolysis associated with hyponatraemia, 5 had received benzodiazepines. Rhabdomyolysis associated with intravenous drug abuse of oral temazepam formulations has also been reported.[2]

1. Fernández-Real JM, *et al.* Hyponatremia and benzodiazepines result in rhabdomyolysis. *Ann Pharmacother* 1994; **28:** 1200–1.
2. Deighan CJ, *et al.* Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse. *Q J Med* 2000; **93:** 29–33.

Effects on the skin. There have been rare reports of cutaneous reactions to benzodiazepines, including contact dermatitis, fixed drug eruptions, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Analysis by the Boston Collaborative Drug Surveillance Program of data on 15 438 patients hospitalised between 1975 and 1982 detected 2 allergic skin reactions attributed to diazepam among 4707 recipients of the drug.[1] A reaction rate of 0.4 per 1000 recipients was calculated from these figures.

1. Bigby M, *et al.* Drug-induced cutaneous reactions. *JAMA* 1986; **256:** 3358–63.

Hypersensitivity. Hypersensitivity reactions including anaphylaxis are very rare after use of diazepam. Reactions have been attributed to the polyoxyl castor oil (p.1918) vehicle used for some parenteral formulations.[1] There is also a report of a type I hypersensitivity reaction to a lipid emulsion formulation of diazepam.[2]

See also under Effects on the Skin, above.

1. Hüttel MS, *et al.* Complement-mediated reactions to diazepam with Cremophor as solvent (Stesolid MR). *Br J Anaesth* 1980; **52:** 77–9.
2. Deardon DJ, Bird GLA. Acute (type 1) hypersensitivity to iv Diazemuls. *Br J Anaesth* 1987; **59:** 391.

Local reactions. Ischaemia and gangrene have been reported after accidental intra-arterial injection of diazepam.[1,2] Clinical signs may not occur until several days after the event. Pain and thrombophlebitis after intravenous use may be similarly delayed. Local reactions after intravenous injection have been attributed to the vehicle, and have been observed more often when diazepam is given as a solution in propylene glycol than in polyethoxylated castor oil.[3] An emulsion of diazepam in soya oil and water has been associated with a lower incidence of local reactions.[3] Pain and phlebitis may also be caused by precipitation of diazepam at the site of infusion.[4] Arterial spasm experienced by a patient given diazepam intravenously was probably due to pressure from a cuff on the arm being inflated causing extravasation of diazepam out of the vein and into the radial artery.[5]

Local irritation has also occurred after rectal use of diazepam.[6]

For a report of the exacerbation of diazepam-induced thrombophlebitis by penicillamine, see p.991.

1. Gould JDM, Lingam S. Hazards of intra-arterial diazepam. *BMJ* 1977; **2:** 298–9.
2. Rees M, Dormandy J. Accidental intra-arterial injection of diazepam. *BMJ* 1980; **281:** 289–90.
3. Olesen AS, Hüttel MS. Local reactions to iv diazepam in three different formulations. *Br J Anaesth* 1980; **52:** 609–11.
4. Hussey EK, *et al.* Correlation of delayed peak concentration with infusion-site irritation following diazepam administration. *DICP Ann Pharmacother* 1990; **24:** 678–80.
5. Ng Wing Tin L, *et al.* Arterial spasm after administration of diazepam. *Br J Anaesth* 1994; **72:** 139.
6. Hansen HC, *et al.* Local irritation after administration of diazepam in a rectal solution. *Br J Anaesth* 1989; **63:** 287–9.

Overdosage. Impairment of consciousness is fairly rapid in poisoning by benzodiazepines.[1] Deep coma or other manifestations of severe depression of brainstem vital functions are rare; more common is a sleep-like state from which the patient can be temporarily roused by appropriate stimuli. There is usually little or no respiratory depression, and cardiac rate and rhythm remain normal in the absence of anoxia or severe hypotension. Since tolerance to benzodiazepines develops rapidly, consciousness is often regained while concentrations of drug in the blood are higher than those which induced coma. Anxiety and insomnia can occur during recovery from acute overdosage, while a full-blown withdrawal syndrome, possibly with major convulsions, can occur in patients who have previously been chronic users.

During the years 1980 to 1989, 1576 fatal poisonings in Britain were attributed to benzodiazepines.[2] Of these, 891 were linked to overdosage with benzodiazepines alone and another 591 to overdosage combined with alcohol. A comparison of these mortality statistics with prescribing data for the same period, to calculate a toxicity index of deaths per million prescriptions, suggested that there were differences between the relative toxicities of individual benzodiazepines in overdosage. A later study of another 303 cases of benzodiazepine poisoning[3] supported these findings of differences in toxicity as well as pointing to the relative safety of the benzodiazepines in overdosage.

1. Ashton CH, *et al.* Drug-induced stupor and coma: some physical signs and their pharmacological basis. *Adverse Drug React Acute Poisoning Rev* 1989; **8:** 1–59.
2. Serfaty M, Masterton G. Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *Br J Psychiatry* 1993; **163:** 386–93.
3. Buckley NA, *et al.* Relative toxicity of benzodiazepines in overdose. *BMJ* 1995; **310:** 219–21.

Treatment of Adverse Effects

The treatment of benzodiazepine overdosage is generally symptomatic and supportive. Activated charcoal may be given orally within one hour of ingestion of more than 100 mg of diazepam (or its equivalent) by adults, or 1 mg/kg by children, provided they are not too drowsy. Gastric lavage is generally not advocated in overdoses of benzodiazepines alone. The specific benzodiazepine antagonist, flumazenil, is rarely required and can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients (see p.1446); the UK Poisons Information Service, contra-indicates its use in mixed overdoses. The *BNF* recommends that flumazenil should be used on expert advice only.

Precautions

Diazepam should be avoided in patients with pre-existing CNS depression or coma, respiratory depression, acute pulmonary insufficiency, myasthenia gravis, or sleep apnoea, and used with care in those with chronic pulmonary insufficiency. Diazepam should be given with care to elderly or debilitated patients who may be more prone to adverse effects. Caution is required in patients with muscle weakness, or those with hepatic or renal impairment, who may require reduced doses; its use should be avoided in severe hepatic impairment. The sedative effects of diazepam are most marked during the first few days of use; affected patients should not drive or operate machinery (see also Driving, below). Monitoring of cardiorespiratory function is generally recommended when benzodiazepines are used for deep sedation.

Diazepam is not appropriate for the treatment of chronic psychosis or for phobic or obsessional states. Diazepam-induced disinhibition may precipitate suicide or aggressive behaviour and it should not, therefore, be used alone to treat depression or anxiety associated with depression; it should also be used with care in patients with personality disorders. Caution is required in patients with organic brain changes particularly arteriosclerosis. In cases of bereavement, psychological adjustment may be inhibited by diazepam.

Many manufacturers of diazepam and other benzodiazepines advise against their use in patients with glaucoma, but the rationale for this contra-indication is unclear.

For warnings on benzodiazepines during pregnancy and breast feeding, see below.

Dependence characterised by a withdrawal syndrome may develop after regular use of diazepam, even in therapeutic doses for short periods (see above); because of the risk of dependence, diazepam should be used with caution in patients with a history of alcohol or drug addiction.

Since hypotension and apnoea may occur when benzodiazepines are given intravenously it has been recommended that this route should only be used when facilities for reversing respiratory depression with mechanical ventilation are available. Patients should remain supine and under medical supervision for at least one hour after intravenous injection. Intravenous infusion is best undertaken in specialist centres with intensive care facilities where close and constant supervision can be undertaken.

Administration. ***INTRAVENOUS.*** Prolonged use of high-dose intravenous infusions of diazepam preparations containing benzyl alcohol can result in benzyl alcohol poisoning.[1] (Such preparations should never be used in neonates—see p.1632.)

1. López-Herce J, *et al.* Benzyl alcohol poisoning following diazepam intravenous infusion. *Ann Pharmacother* 1995; **29:** 632.

Breast feeding. The American Academy of Pediatrics considers that benzodiazepine use by nursing mothers for long periods was a cause for concern; anxiolytic drugs appear in breast milk and could conceivably alter CNS function in the infant both in the short and long term.[1] Similarly, in the UK the CSM has recommended[2] that benzodiazepines should not be given to breast-feeding mothers. In one reviewer's opinion[3] the limited distribution into breast milk did not constitute a hazard to the breast-fed infant but the infant should be monitored for sedation and the inability to suckle. Another group has also reported a low incidence of toxicity and adverse effects in the breast-fed infants of mothers taking psychotropic drugs including benzodiazepines.[4] It has been suggested[5] that if a benzodiazepine must be used during breast feeding it would be preferable to use a short-acting drug with minimal distribution into breast milk and inactive metabolites; oxazepam, lorazepam, alprazolam, or midazolam might be suitable.

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. Committee on Safety of Medicines/Medicines Control Agency. Reminder: avoid benzodiazepines in pregnancy and lactation. *Current Problems* 1997; **23:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
3. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 1994; **8:** 461–75.
4. Birnbaum CS, *et al.* Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. Abstract: *Pediatrics* 1999; **104:** 104. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/1/e11 (accessed 28/04/04)
5. Chisholm CA, Kuller JA. A guide to the safety of CNS-active agents during breastfeeding. *Drug Safety* 1997; **17:** 127–42.

Cardiovascular disorders. See under Respiratory System Disorders, below.

Driving. Most benzodiazepines can adversely affect parameters of driving performance in healthy subjects.[1] It is not entirely clear to what extent benzodiazepines contribute to the risk of driving accidents. A large case-control cohort study[2] in elderly drivers suggested that the risk of accidents was increased in those who took longer-acting benzodiazepines. However, younger drivers are more susceptible to the effects of benzodiazepines or zopiclone as a group;[3,4] the risk is increased by alcohol consumption.[3] Patients affected by drowsiness while taking benzodiazepines should not drive or operate machinery. In the UK, it is an offence to drive while unfit due to the influence of any drug, and benzodiazepines are considered to be the most likely psychotropic medication to impair driving performance, particularly the long-acting compounds.[5] However, it is also noted that drivers with psychiatric illnesses may be safer when well controlled with regular medication than when ill. Drowsiness often becomes less troublesome with continued use of these drugs.

1. Woods JH, *et al.* Abuse liability of benzodiazepines. *Pharmacol Rev* 1987; **39:** 251–413.
2. Hemmelgarn B, *et al.* Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA* 1997; **278:** 27–31.
3. Barbone F, *et al.* Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; **352:** 1331–6.
4. Vanakoski J, *et al.* Driving under light and dark conditions: effects of alcohol and diazepam in young and older subjects. *Eur J Clin Pharmacol* 2000; **56:** 453–8.
5. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (updated February 2008). http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

The elderly. Old age may alter the distribution, elimination, and clearance of benzodiazepines.[1,2] Metabolic clearance of benzodiazepines metabolised principally by oxidation appears to be reduced but not clearance of those biotransformed by glucuronide conjugation or nitroreduction. Prolonged half-life in the elderly may be a result of such a decrease in clearance or of an increase in the volume of distribution. The clinical consequence of these changes depends on factors such as dosage schedule and extent of first-pass extraction by the liver.

Irrespective of pharmacokinetic changes, the elderly may exhibit increased sensitivity to acute doses of benzodiazepines.[1-3] Impairment of memory, cognitive function, and psychomotor performance and behaviour disinhibition may be more common than with younger patients.[4] Long-term use commonly exacerbates underlying dementia in elderly patients.[4]

The upshot of the pharmacokinetic and pharmacodynamic changes of benzodiazepines in the elderly is that adverse effects may be more frequent in these patients and lower doses are commonly required. An epidemiological study of persons 65 years and older found an increased rate of hip fracture among current users of long-acting benzodiazepines (*chlordiazepoxide*, *clorazepate*, *diazepam*, and *flurazepam*), but not among users of short-acting drugs (*alprazolam*, *bromazepam*, *lorazepam*, *oxazepam*, and *triazolam*).[5] A case-control study[6] of patients with falls leading to femur fractures suggested that the most important factor in increasing risk was the dose of benzodiazepine. However, another case-control study[7] found no correlation between hip fracture and benzodiazepines either as a group or according to half-life or to characterisation as an anxiolytic or a hypnotic; there might, though, be an increase in risk with lorazepam. There was also an increased risk associated with use of two or more benzodiazepines. Nonetheless, if use of a benzodiazepine is considered necessary in elderly patients, a short-acting drug is to be preferred. It should also be remembered that the elderly are at increased risk of sleep-related breathing disorders, such as sleep apnoea and the use of hypnotics such as benzodiazepines should be avoided in these patients (see Respiratory System Disorders, below).

1. Greenblatt DJ, *et al.* Implications of altered drug disposition in elderly: studies of benzodiazepines. *J Clin Pharmacol* 1989; **29:** 866–72.
2. Greenblatt DJ, *et al.* Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly: therapeutic considerations. *Clin Pharmacokinet* 1991; **21:** 165–77 and 262–73.
3. Swift CG. Pharmacodynamics: changes in homeostatic mechanisms, receptor and target organ sensitivity in the elderly. *Br Med Bull* 1990; **46:** 36–52.
4. Juergens SM. Problems with benzodiazepines in elderly patients. *Mayo Clin Proc* 1993; **68:** 818–20.
5. Ray WA, *et al.* Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA* 1989; **262:** 3303–7.
6. Herings RMC, *et al.* Benzodiazepines and the risk of falling leading to femur fractures: dosage more important than elimination half-life. *Arch Intern Med* 1995; **155:** 1801–7.
7. Pierfitte C, *et al.* Benzodiazepines and hip fractures in elderly people: case-control study. *BMJ* 2001; **322:** 704–8.

Hangover effects. Long-acting benzodiazepines accumulate in the body to a greater extent than ones with a shorter half-life. Although this might be expected to increase the frequency of daytime sedation and impairment of performance (so-called hangover effects) after a hypnotic dose, such a straightforward relationship has not always been observed in practice.[1]

Anterograde amnesia is more common with short-acting drugs such as triazolam; 'traveller's amnesia' has been used to describe amnesia in persons taking benzodiazepines for sleep disturbances resulting from jet lag.[2]

1. Greenblatt DJ, *et al.* Neurochemical and pharmacokinetic correlates of the clinical action of benzodiazepine hypnotic drugs. *Am J Med* 1990; **88** (suppl 3A): 18S–24S.
2. Meyboom RHB. Benzodiazepines and pilot error. *BMJ* 1991; **302:** 1274–5.

High-altitude disorders. Sleep may be impaired at high altitude due to frequent arousals associated with pronounced oxygen desaturation and periodic breathing. Traditional advice has been that sedatives should not be given at high altitude.[1] Caution may also be warranted at moderate altitudes especially in non-acclimatised climbers.[2] It has been argued that since diazepam, and possibly other sedatives, blunt the hypoxic ventilatory response, sleep hypoxaemia might be exacerbated. A small study[3] has suggested that small doses of a short-acting benzodiazepine, such as temazepam, might actually improve the subjective quality of sleep and reduce episodes of arterial desaturation without changing mean oxygen saturation. However the possibility of an interaction between acetazolamide taken for prophylaxis or treatment of acute mountain sickness and the benzodiazepine should be borne in mind; ventilatory depression in a mountain climber with acute mountain sickness was considered to be due to the potentiation of triazolam by acetazolamide.[4]

1. Sutton JR, *et al.* Insomnia, sedation, and high altitude cerebral oedema. *Lancet* 1979; **i:** 165.
2. Röggla G, *et al.* Effect of temazepam on ventilatory response at moderate altitude. *BMJ* 2000; **320:** 56.
3. Dubowitz G. Effect of temazepam on oxygen saturation and sleep quality at high altitude: randomised placebo controlled crossover trial. *BMJ* 1998; **316:** 587–9.
4. Masuyama S, *et al.* 'Ondine's curse': side effect of acetazolamide? *Am J Med* 1989; **86:** 637.

Neonates. A retrospective review of records from 63 infants given lorazepam or midazolam in a neonatal intensive-care unit indicated that there were 14 cases of adverse effects associated with benzodiazepine use (seizures in 6 cases, hypotension in 5, and respiratory depression in 3).[1] Seven of these were associated with intravenous bolus doses of lorazepam and the remainder with continuous midazolam infusions. Despite the limitations of the study, the incidence of adverse effects in this group seemed high, and the authors recommended that benzodiazepine use in neonates be accompanied by close monitoring.

1. Ng E, *et al.* Safety of benzodiazepines in newborns. *Ann Pharmacother* 2002; **36:** 1150–5.

Nervous system disorders. Benzodiazepines can reduce cerebral perfusion pressure and blood oxygenation to an extent that results in irreversible neurological damage in patients with head injuries. Consequently, they should be given with great care to such patients.[1,2] Their use should be avoided for the control of seizures in patients with head injuries or other acute neurological lesions as these patients can be managed effectively with phenytoin.

1. Eldridge PR, Punt JAG. Risks associated with giving benzodiazepines to patients with acute neurological injuries. *BMJ* 1990; **300:** 1189–90.
2. Papazian L, *et al.* Effect of bolus doses of midazolam on intracranial pressure and cerebral perfusion pressure in patients with severe head injury. *Br J Anaesth* 1993; **71:** 267–71.

Epilepsy. As with other antiepileptic drugs,[1] there have been rare reports of benzodiazepines producing paradoxical exacerbation of seizures in patients with epilepsy.[2-5]

1. Guerrini R, *et al.* Antiepileptic drug-induced worsening of seizures in children. *Epilepsia* 1998; **39** (suppl 3): S2–S10.
2. Prior PF, *et al.* Intravenous diazepam. *Lancet* 1971; **2:** 434–5.
3. Tassinari CA, *et al.* A paradoxical effect: status epilepticus induced by benzodiazepines (Valium and Mogadon). *Electroencephalogr Clin Neurophysiol* 1971; **31:** 182.
4. Di Mario FJ, Clancy RR. Paradoxical precipitation of tonic seizures by lorazepam in a child with atypical absence seizures. *Pediatr Neurol* 1988; **4:** 249–51.
5. Borusiak P, *et al.* Seizure-inducing paradoxical reaction to antiepileptic drugs. *Brain Dev* 2000; **22:** 243–5.

Porphyria. Diazepam has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Intravenous diazepam has been used successfully, however, to control status epilepticus occurring after the acute porphyric attack. For a discussion of the management of seizures associated with acute porphyric attacks, see p.471.

Pregnancy. Benzodiazepines have been widely used in pregnant patients.[1] Use of benzodiazepines in the *third trimester* and during *labour* seems to be associated in some infants with neonatal withdrawal symptoms or the floppy infant syndrome. Also a small number exposed *in utero* to benzodiazepines have shown slow development in the early years but by 4 years of age most had developed normally, and for those that had not it was not possible to prove a cause-effect relationship with benzodiazepine exposure. In a meta-analysis[2] of live births after benzodiazepine use during the *first trimester* of pregnancy, pooled data from cohort studies showed no apparent association between benzodiazepine use and the risk of major malformations or oral cleft alone. There was, however, a small but significantly increased risk of oral cleft according to data from case-control studies. Although benzodiazepines did not appear to be a major human teratogen, use of ultrasonography was advised to rule out visible forms of cleft lip. The UK CSM has recommended[3] that women of child-bearing potential prescribed benzodiazepines should be advised to contact the physician about stopping the drug if they intend to become, or suspect that they are, pregnant.

1. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 1994; **8:** 461–75.
2. Dolovich LR, *et al.* Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 1998; **317:** 839–43.
3. Committee on Safety of Medicines/Medicines Control Agency. Reminder: avoid benzodiazepines in pregnancy and lactation. *Current Problems* 1997; **23:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)

Respiratory system disorders. Benzodiazepines may affect the control of ventilation during sleep and may worsen sleep apnoea or other sleep-related breathing disorders especially in patients with chronic obstructive pulmonary disease or cardiac failure.[1] Risk factors for sleep apnoea, which often goes undiagnosed, include old age, obesity, male sex, postmenopausal status in women, and a history of heavy snoring. Although benzodiazepines may reduce sleep fragmentation, their long-term use may result in conversion from partial to complete obstructive sleep apnoea in heavy snorers or in short repetitive central sleep apnoea in patients with recent myocardial infarction.

1. Guilleminault C. Benzodiazepines, breathing, and sleep. *Am J Med* 1990; **88** (suppl 3A): 25S–28S.

Interactions

Enhanced sedation or respiratory and cardiovascular depression may occur if diazepam or other benzodiazepines are given with other drugs that have CNS-depressant properties; these include alcohol, antidepressants, sedative antihistamines, antipsychotics, general anaesthetics, other hypnotics or sedatives, and opioid analgesics. The sedative effect of benzodiazepines may also be enhanced by cisapride. Adverse effects may also be produced by use with drugs that interfere with the metabolism of benzodiazepines. Drugs that have been reported to alter the pharmacokinetics of benzodiazepines are discussed in detail below but few of these interactions are likely to be of clinical significance. Benzodiazepines such as diazepam that are metabolised primarily by hepatic microsomal oxidation may be more susceptible to pharmacokinetic changes than those eliminated primarily by glucuronide conjugation.

Analgesics. The peak plasma concentration of oxazepam was significantly decreased when *diflunisal* was given to 6 healthy subjects, while the renal clearance of the glucuronide metabolite was reduced and its mean elimination half-life increased from 10 to 13 hours.[1] Diflunisal also displaced oxazepam from plasma protein binding sites *in vitro*. *Aspirin* shortened the time to induce anaesthesia with midazolam in 78 patients also possibly due to competition for plasma protein binding sites.[2] *Paracetamol* produced no significant change in plasma concentrations of diazepam or its major metabolite and only marginal changes in urine concentrations in 4 healthy subjects.[3]

Benzodiazepines such as diazepam, lorazepam, and midazolam may be used with opioid analgesics in anaesthetic or analgesic regimens. An additive sedative effect is to be expected[4] but there are also reports of severe respiratory depression with midazolam and *fentanyl*[5] or sudden hypotension with midazolam and fentanyl[6] or *sufentanil*.[7] The clearance of midazolam appears to be reduced by fentanyl,[8] possibly as a result of competitive inhibition of metabolism by the cytochrome P450 isoenzyme CYP3A. Careful monitoring is therefore required during use of midazolam with these opioids and the dose of both drugs may need to be reduced. Synergistic potentiation of the induction of anaesthesia has been reported between midazolam and fentanyl,[9] but one study has suggested that midazolam can reduce the analgesic effects of sufentanil.[10] Pretreatment with *morphine* or *pethidine* has decreased the rate of oral absorption of diazepam. This has been attributed to the effect of opioid analgesics on gastrointestinal motility.[11]

Dextropropoxyphene prolonged the half-life and reduced the clearance of alprazolam but not diazepam or lorazepam in healthy subjects.[12]

1. Van Hecken AM, *et al.* The influence of diflunisal on the pharmacokinetics of oxazepam. *Br J Clin Pharmacol* 1985; **20:** 225–34.
2. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.
3. Mulley BA, *et al.* Interactions between diazepam and paracetamol. *J Clin Pharm* 1978; **3:** 25–35.
4. Tverskoy M, *et al.* Midazolam-morphine sedative interaction in patients. *Anesth Analg* 1989; **68:** 282–5.
5. Yaster M, *et al.* Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics* 1990; **86:** 463–7.
6. Burtin P, *et al.* Hypotension with midazolam and fentanyl in the newborn. *Lancet* 1991; **337:** 1545–6.
7. West JM, *et al.* Sudden hypotension associated with midazolam and sufentanil. *Anesth Analg* 1987; **66:** 693–4.
8. Hase I, *et al.* I.V. fentanyl decreases the clearance of midazolam. *Br J Anaesth* 1997; **79:** 740–3.
9. Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth* 1990; **64:** 45–7.
10. Luger TJ, Morawetz RF. Clinical evidence for a midazolam-sufentanil interaction in patients with major trauma. *Clin Pharmacol Ther* 1991; **49:** 133.
11. Gamble JAS, *et al.* Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br J Anaesth* 1976; **48:** 1181–5.
12. Abernethy DR, *et al.* Interaction of propoxyphene with diazepam, alprazolam and lorazepam. *Br J Clin Pharmacol* 1985; **19:** 51–7.

Antiarrhythmics. An interaction between clonazepam and existing therapy with *amiodarone* was suspected in a 78-year-old man who experienced symptoms of benzodiazepine toxicity 2 months after starting with clonazepam 500 micrograms given at bedtime for restless leg syndrome;[1] symptoms resolved on withdrawal of clonazepam.

1. Witt DM, *et al.* Amiodarone-clonazepam interaction. *Ann Pharmacother* 1993; **27:** 1463–4.

Antibacterials. Both *erythromycin*[1] and *troleandomycin*[2] have been reported to inhibit the hepatic metabolism of triazolam in healthy subjects. Peak plasma-triazolam concentrations were increased, half-life prolonged, and clearance reduced. Troleandomycin prolonged the psychomotor impairment and amnesia produced by triazolam.[2] Loss of consciousness after erythromycin infusion in a child premedicated with midazolam was attributed to a similar interaction,[3] and increases in peak plasma concentrations of midazolam with profound and prolonged sedation have been reported after use of erythromycin.[4] Use of midazolam with erythromycin should be avoided or the dose of midazolam reduced by 50 to 75%. The clearance of midazolam is also reduced by *clarithromycin*, with an approximate doubling of the benzodiazepine's oral bioavailability.[5] The manufacturers of

quinupristin/dalfopristin state that it too may increase plasma concentrations of midazolam. *Roxithromycin* has been reported[6] to have some effects on the pharmacokinetics and pharmacodynamics of midazolam but these changes were not thought clinically relevant. However, it was recommended that as a precaution the lowest possible effective dose of midazolam should be used when given with roxithromycin. In another study[7] *azithromycin* did not appear to have any effect on the metabolism or psychomotor effects of midazolam.

There is an isolated report of significant rises in steady-state blood-midazolam concentration coinciding with dosage of *ciprofloxacin*.[8] Also ciprofloxacin has been reported to reduce diazepam clearance and prolong its terminal half-life,[9] although psychometric tests did not show any changes in diazepam's pharmacodynamics. However, ciprofloxacin appears to have no effect on the pharmacokinetics or pharmacodynamics of temazepam.[10]

Isoniazid has been reported to increase the half-life of a single dose of diazepam[11] and triazolam[12] but not of oxazepam[12] in healthy subjects. In contrast, *rifampicin* has decreased the half-life of alprazolam,[13] diazepam,[14] midazolam,[15] and nitrazepam[16] and more or less abolishes the effects of triazolam,[17] while *ethambutol* has no effect on diazepam pharmacokinetics.[11] In patients receiving therapy for tuberculosis with isoniazid, rifampicin, and ethambutol the half-life of a single diazepam dose was shortened and its clearance increased.[11] Thus the enzyme-inducing effect of rifampicin appears to predominate over the enzyme-inhibiting effect of isoniazid.

1. Phillips JP, *et al.* A pharmacokinetic drug interaction between erythromycin and triazolam. *J Clin Psychopharmacol* 1986; **6:** 297–9.
2. Warot D, *et al.* Troleandomycin-triazolam interaction in healthy volunteers: pharmacokinetic and psychometric evaluation. *Eur J Clin Pharmacol* 1987; **32:** 389–93.
3. Hiller A, *et al.* Unconsciousness associated with midazolam and erythromycin. *Br J Anaesth* 1990; **65:** 826–8.
4. Olkkola KT, *et al.* A potentially hazardous interaction between erythromycin and midazolam. *Clin Pharmacol Ther* 1993; **53:** 298–305.
5. Gorski JC, *et al.* The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. *Clin Pharmacol Ther* 1998; **64:** 133–43.
6. Backman JT, *et al.* A pharmacokinetic interaction between roxithromycin and midazolam. *Eur J Clin Pharmacol* 1994; **46:** 551–5.
7. Mattila MJ, *et al.* Azithromycin does not alter the effects of oral midazolam on human performance. *Eur J Clin Pharmacol* 1994; **47:** 49–52.
8. Orko R, *et al.* Intravenous infusion of midazolam, propofol and vecuronium in a patient with severe tetanus. *Acta Anaesthesiol Scand* 1988; **32:** 590–2.
9. Kamali F, *et al.* The influence of steady-state ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of diazepam in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44:** 365–7.
10. Kamali F, *et al.* The influence of ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of temazepam in the young and elderly. *J Clin Pharm Ther* 1994; **19:** 105–9.
11. Ochs HR, *et al.* Diazepam interaction with antituberculous drugs. *Clin Pharmacol Ther* 1981; **29:** 671–8.
12. Ochs HR, *et al.* Differential effect of isoniazid on triazolam oxidation and oxazepam conjugation. *Br J Clin Pharmacol* 1983; **16:** 743–6.
13. Schmider J, *et al.* Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics* 1999; **9:** 725–34.
14. Ohnhaus EE, *et al.* The effect of antipyrine and rifampin on the metabolism of diazepam. *Clin Pharmacol Ther* 1987; **42:** 148–56.
15. Backman JT, *et al.* Rifampin drastically reduces plasma concentrations and effects of oral midazolam. *Clin Pharmacol Ther* 1996; **59:** 7–13.
16. Brockmeyer NH, *et al.* Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. *Int J Clin Pharmacol Ther Toxicol* 1990; **28:** 387–93.
17. Villikka K, *et al.* Triazolam is ineffective in patients taking rifampicin. *Clin Pharmacol Ther* 1997; **61:** 8–14.

Anticoagulants. Plasma binding of diazepam and desmethyldiazepam was reduced, and free concentrations increased, immediately following *heparin* intravenously.[1]

Benzodiazepines do not usually interact with oral anticoagulants although there have been rare reports of altered anticoagulant activity.

1. Routledge PA, *et al.* Diazepam and N-desmethyldiazepam redistribution after heparin. *Clin Pharmacol Ther* 1980; **27:** 528–32.

Antidepressants. It has been recommended that the dosage of alprazolam should be reduced when given with *fluvoxamine*, as concomitant use has resulted in doubling of plasma-alprazolam concentrations.[1] Since plasma concentrations of bromazepam[2] and of diazepam[3] also appear to be affected by fluvoxamine, it has been suggested that patients taking fluvoxamine who require a benzodiazepine should preferentially receive one such as lorazepam, which has a different metabolic pathway.[3] Small studies suggest that *fluoxetine* can also increase plasma concentrations of alprazolam.[4,5] Fluoxetine appears to have a similar effect on diazepam but plasma concentrations of diazepam's active metabolite desmethyldiazepam are reduced and it is considered that the overall effect is likely to be minor.[6] The potential for a clinically significant interaction with *sertraline*, *paroxetine*, or *citalopram* is considered to be less.[7]

The US manufacturers have reported that alprazolam may increase the steady-state plasma concentrations of *imipramine* and *desipramine*, although the clinical significance of such changes is unknown. For a suggestion that benzodiazepines may increase the oxidation of *amineptine* to a toxic metabolite, see Effects on the Liver under Adverse Effects of Amitriptyline, p.377.

Nefazodone has been reported to raise concentrations of alprazolam and triazolam, resulting in increased sedation, and impairment of psychomotor performance.[8,9] Nefazodone may inhibit the oxidative metabolism of alprazolam and triazolam. Raised concentrations of midazolam have similarly been seen when given by mouth with nefazodone.[10] No interaction was reported with lorazepam, which is primarily eliminated by conjugation.

For reference to an isolated report of hypothermia after administration of diazepam and *lithium*, see p.405.

There have been occasional reports of sexual disinhibition in patients taking *tryptophan* with benzodiazepines.

1. Fleishaker JC, Hulst LK. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. *Eur J Clin Pharmacol* 1994; **46:** 35–9.
2. Van Harten J, *et al.* Influence of multiple-dose administration of fluvoxamine on the pharmacokinetics of the benzodiazepines bromazepam and lorazepam: a randomized crossover study. *Eur Neuropsychopharmacol* 1992; **2:** 381.
3. Perucca E, *et al.* Inhibition of diazepam metabolism by fluvoxamine: a pharmacokinetic study in normal volunteers. *Clin Pharmacol Ther* 1994; **56:** 471–6.
4. Lasher TA, *et al.* Pharmacokinetic pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. *Psychopharmacology (Berl)* 1991; **104:** 323–7.
5. Greenblatt DJ, *et al.* Fluoxetine impairs clearance of alprazolam but not of clonazepam. *Clin Pharmacol Ther* 1992; **52:** 479–86.
6. Lemberger L, *et al.* The effect of fluoxetine on the pharmacokinetics and psychomotor responses of diazepam. *Clin Pharmacol Ther* 1988; **43:** 412–19.
7. Sproule BA, *et al.* Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997; **33:** 454–71.
8. Greene DS, *et al.* Coadministration of nefazodone (NEF) and benzodiazepines I: pharmacokinetic assessment. *Clin Pharmacol Ther* 1994; **55:** 141.
9. Kroboth P, *et al.* Coadministration of nefazodone and benzodiazepines II: pharmacodynamic assessment. *Clin Pharmacol Ther* 1994; **55:** 142.
10. Lam YWF, *et al.* Effect of antidepressants and ketoconazole on oral midazolam pharmacokinetics. *Clin Pharmacol Ther* 1998; **63:** 229.

Antiepileptics. *Carbamazepine*, *phenobarbital*, and *phenytoin* are all inducers of hepatic drug-metabolising enzymes. Therefore, in patients receiving long-term therapy with these drugs the metabolism of benzodiazepines may be enhanced. For oral midazolam the effects of carbamazepine or phenytoin may be sufficient to virtually abolish the effects of a standard dose, with a more than 90% reduction in peak serum concentrations of the benzodiazepine.[1] Interactions between benzodiazepines and these antiepileptics are further discussed on p.475 (carbamazepine) and p.499 (phenytoin).

Results from a study[2] involving 66 children and adults receiving clobazam as adjunctive therapy for epilepsy showed a significant increase in clobazam clearance, leading to accumulation of its principal active metabolite *N*-desmethylclobazam, in the 16 patients also taking *felbamate*. The metabolism of clobazam and *N*-desmethylclobazam was reduced by *stiripentol*, a potent hepatic enzyme inhibitor, resulting in a threefold increase in the plasma concentrations of this metabolite.[3]

Serum-clonazepam concentrations fell markedly in 4 of 8 children who had *lamotrigine* added to their therapy.[4]

Sodium valproate has been reported to displace diazepam from plasma-protein binding sites.[5] Sporadic reports exist of adverse effects when valproate is given with clonazepam[6,7] with the development of drowsiness and, more seriously, absence status epilepticus, but the existence of an interaction is considered to be unproven.[8] Drowsiness has also been reported when valproate was given with nitrazepam.[9] Use of valproate semisodium with lorazepam has resulted in raised concentrations of lorazepam due to inhibition of glucuronidation of lorazepam.[10]

1. Backman JT, *et al.* Concentrations and effects of oral midazolam are greatly reduced in patients treated with carbamazepine or phenytoin. *Epilepsia* 1996; **37:** 253–7.
2. Contin M, *et al.* Effect of felbamate on clobazam and its metabolite kinetics in patients with epilepsy. *Ther Drug Monit* 1999; **21:** 604–8.
3. Giraud C, *et al.* In vitro and in vivo inhibitory effect of stiripentol on clobazam metabolism. *Drug Metab Dispos* 2006; **34:** 608–11.
4. Eriksson A-S, *et al.* Pharmacokinetic interactions between lamotrigine and other antiepileptic drugs in children with intractable epilepsy. *Epilepsia* 1996; **37:** 769–73.
5. Dhillon S, Richens A. Valproic acid and diazepam interaction in vivo. *Br J Clin Pharmacol* 1982; **13:** 553–60.
6. Watson WA. Interaction between clonazepam and sodium valproate. *N Engl J Med* 1979; **300:** 678.
7. Browne TR. Interaction between clonazepam and sodium valproate. *N Engl J Med* 1979; **300:** 679.
8. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.
9. Jeavons PM, *et al.* Treatment of generalized epilepsies of childhood and adolescence with sodium valproate (Epilim). *Dev Med Child Neurol* 1977; **19:** 9–25.
10. Samara EE, *et al.* Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. *J Clin Pharmacol* 1997; **37:** 442–50.

Antifungals. Both a single dose and multiple doses of *ketoconazole* decreased the clearance of a single intravenous injection of chlordiazepoxide.[1] Studies[2-4] have shown that ketoconazole and *itraconazole* can produce marked pharmacokinetic interactions with midazolam or triazolam and greatly increase the intensity and duration of action of these benzodiazepines. The area under the plasma concentration-time curve for midazolam was increased by 15 times by ketoconazole and by 10 times by itraconazole while peak plasma concentrations of midazolam were increased fourfold and threefold, respectively.[2] The area under the curve for triazolam was increased by 22 times by ketoconazole and by 27 times by itraconazole;[3] peak plasma concentrations of triazolam were increased about threefold by both antifungals. Ketoconazole has also been reported to have a similar effect on alprazolam.[5] One study[6] indicated that the risk of interaction persists for several days after cessation of itraconazole therapy. It is recommended that the use of these antifungals with benzodiazepines should be avoided or that the dose of the benzodiazepine should be greatly reduced. A similar but less pronounced interaction occurs between *fluconazole* and midazolam[7] or triazolam;[8] nonetheless the dosage of the benzodiazepine should be reduced during use together.

1. Brown MW, *et al.* Effect of ketoconazole on hepatic oxidative drug metabolism. *Clin Pharmacol Ther* 1985; **37:** 290–7.
2. Olkkola KT, *et al.* Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; **55:** 481–5.
3. Varhe A, *et al.* Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; **56:** 601–7.
4. Greenblatt DJ, *et al.* Interaction of triazolam and ketoconazole. *Lancet* 1995; **345:** 191.
5. Schmider J, *et al.* Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics* 1999; **9:** 725–34.
6. Neuvonen PJ, *et al.* The effect of ingestion time interval on the interaction between itraconazole and triazolam. *Clin Pharmacol Ther* 1996; **60:** 326–31.
7. Ahonen J, *et al.* Effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. *Eur J Clin Pharmacol* 1997; **51:** 415–19.
8. Varhe A, *et al.* Effect of fluconazole dose on the extent of fluconazole-triazolam interaction. *Br J Clin Pharmacol* 1996; **42:** 465–70.

Antihistamines. A suggestion[1] that a reduction in temazepam metabolism caused by *diphenhydramine* may have contributed to perinatal death after ingestion of these drugs by the mother.

1. Kargas GA, *et al.* Perinatal mortality due to interaction of diphenhydramine and temazepam. *N Engl J Med* 1985; **313:** 1417–18.

Antivirals. The NNRTIs *delavirdine* and *efavirenz*,[1] and HIV-protease inhibitors such as *indinavir, nelfinavir, ritonavir*,[1-3] and *saquinavir*[1,4] may inhibit the hepatic microsomal systems involved in the metabolism of some benzodiazepines. Prolonged use of protease inhibitors may also *induce* these metabolic systems; interactions may therefore be complex and difficult to predict. Monitoring and dosage adjustments for the benzodiazepine may be needed, or the combination should be avoided. Benzodiazepines which should **not** be used with HIV-protease inhibitors include alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, and triazolam.

1. Antoniou T, Tseng AL. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002; **36:** 1598–1613.
2. Greenblatt DJ, *et al.* Extensive impairment of triazolam and alprazolam clearance by short-term low-dose ritonavir: the clinical dilemma of concurrent inhibition and induction *J Clin Psychopharmacol* 1999; **19:** 293–6.
3. Greenblatt DJ, *et al.* Alprazolam-ritonavir interaction: implications for product labeling. *Clin Pharmacol Ther* 2000; **67:** 335–41.
4. Palkama VJ, *et al.* Effect of saquinavir on the pharmacokinetics and pharmacodynamics of oral and intravenous midazolam. *Clin Pharmacol Ther* 1999; **66:** 33–9.

Beta blockers. A clear pattern of interactions between benzodiazepines and beta blockers has not emerged. *Propranolol* may inhibit the metabolism of diazepam[1,2] and bromazepam,[3] and *metoprolol* may inhibit the metabolism of diazepam[1,4] or bromazepam[5] to some extent, although in many cases the effect on pharmacokinetics and pharmacodynamics is unlikely to be of clinical significance. No significant pharmacokinetic interaction has been seen between propranolol and alprazolam,[2] lorazepam,[2] or oxazepam,[6] although the rate of alprazolam absorption may be decreased.[2] Similarly no pharmacokinetic interaction has been seen between *atenolol* and diazepam,[1] *labetalol* and oxazepam,[6] or metoprolol and lorazepam.[5]

1. Hawksworth G, *et al.* Diazepam/β-adrenoceptor antagonist interactions. *Br J Clin Pharmacol* 1984; **17:** 69S–76S.
2. Ochs HR, *et al.* Propranolol interactions with diazepam, lorazepam, and alprazolam. *Clin Pharmacol Ther* 1984; **36:** 451–5.
3. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
4. Klotz U, Reimann IW. Pharmacokinetic and pharmacodynamic interaction study of diazepam and metoprolol. *Eur J Clin Pharmacol* 1984; **26:** 223–6.
5. Scott AK, *et al.* Interaction of metoprolol with lorazepam and bromazepam. *Eur J Clin Pharmacol* 1991; **40:** 405–9.
6. Sonne J, *et al.* Single dose pharmacokinetics and pharmacodynamics of oral oxazepam during concomitant administration of propranolol and labetalol. *Br J Clin Pharmacol* 1990; **29:** 33–7.

Calcium-channel blockers. Peak plasma concentrations of midazolam were doubled and the elimination half-life of midazolam prolonged when given to healthy subjects receiving *diltiazem* or *verapamil*.[1] A similar interaction has been found be-

tween diltiazem and triazolam.[2,3] Concomitant use should be avoided or the dose of these benzodiazepines reduced in such use.

1. Backman JT, *et al.* Dose of midazolam should be reduced during diltiazem and verapamil treatments. *Br J Clin Pharmacol* 1994; **37:** 221–5.
2. Varhe A, *et al.* Diltiazem enhances the effects of triazolam by inhibiting its metabolism. *Clin Pharmacol Ther* 1996; **59:** 369–75.
3. Kosuge K, *et al.* Enhanced effect of triazolam with diltiazem. *Br J Clin Pharmacol* 1997; **43:** 367–72.

Ciclosporin. *In-vitro* studies suggested that ciclosporin could inhibit the metabolism of midazolam.[1] However, blood-ciclosporin concentrations in patients given ciclosporin to prevent graft rejection were considered too low to result in such an interaction.

1. Li G, *et al.* Is cyclosporin A an inhibitor of drug metabolism? *Br J Clin Pharmacol* 1990; **30:** 71–7.

Clonidine. Anxiety was reduced and sedation was enhanced when clonidine was given with flunitrazepam for premedication.[1]

1. Kulka PJ, *et al.* Sedative and anxiolytic interactions of clonidine and benzodiazepines. *Br J Anaesth* 1994; **72** (suppl 1): 81.

Clozapine. For reports of cardiorespiratory collapse and other adverse effects in patients taking benzodiazepines and clozapine, see p.984.

Corticosteroids. The metabolism of midazolam was increased in chronic users of *glucocorticoids*,[1] perhaps due to the induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation. The changes were not considered clinically relevant if midazolam was given intravenously, but might be so if it was given orally.

1. Nakajima M, *et al.* Effects of chronic administration of glucocorticoid on midazolam pharmacokinetics in humans. *Ther Drug Monit* 1999; **21:** 507–13.

Digoxin. For the effects of alprazolam and diazepam on digoxin pharmacokinetics, see p.1262.

Disulfiram. Evidence from healthy and alcoholic subjects suggests that chronic use of disulfiram can inhibit the metabolism of chlordiazepoxide and diazepam leading to a prolonged half-life and reduced clearance; there was little effect on the disposition of oxazepam.[1] No significant pharmacokinetic interaction was observed between disulfiram and alprazolam in alcoholic patients.[2] Temazepam toxicity, attributed to use of disulfiram with temazepam, has been reported.[3]

See also under Disulfiram, p.2297.

1. MacLeod SM, *et al.* Interaction of disulfiram with benzodiazepines. *Clin Pharmacol Ther* 1978; **24:** 583–9.
2. Diquet B, *et al.* Lack of interaction between disulfiram and alprazolam in alcoholic patients. *Eur J Clin Pharmacol* 1990; **38:** 157–60.
3. Hardman M, *et al.* Temazepam toxicity precipitated by disulfiram. *Lancet* 1994; **344:** 1231–2.

Gastrointestinal drugs. *Antacids* have variable effects on the absorption of benzodiazepines[1-6] but any resulting interaction is unlikely to be of major clinical significance.

Several studies, usually involving single doses of diazepam given to healthy subjects, have shown that *cimetidine* can inhibit the hepatic metabolism of diazepam.[7-10] The clearance of diazepam has generally been decreased and the half-life prolonged. Some studies have also shown impaired metabolic clearance of the major metabolite, desmethyldiazepam (nordazepam). Cimetidine has also been reported to inhibit the metabolism of other benzodiazepines (generally those metabolised by oxidation) including alprazolam,[11,12] bromazepam,[13] chlordiazepoxide,[14] clobazam,[15,16] flurazepam,[17] midazolam,[18] nitrazepam,[19] and triazolam.[11,12] Cimetidine does not appear to inhibit the hepatic metabolism of lorazepam,[17] oxazepam,[17] or temazepam.[20] The clinical significance of these interactions between cimetidine and benzodiazepines remains dubious, and little effect on cognitive function or degree of sedation has been shown.

Most studies have failed to find an effect of *ranitidine* on the hepatic metabolism of diazepam,[21-24] although one study[25] reported an increase in the bioavailability of a single oral dose of midazolam, and considered that an effect on hepatic clearance was more likely than an effect on absorption. These results were consistent with those of another study which showed an enhanced sedative effect of midazolam in patients pretreated with ranitidine.[26] Ranitidine has been reported to have no effect on the pharmacokinetics of lorazepam[22] or on the sedative effect of temazepam[26] but has increased the bioavailability of triazolam.[27]

Famotidine[10] or *nizatidine*[24] do not appear to inhibit the hepatic metabolism of diazepam.

Oral diazepam was absorbed more rapidly after intravenous *metoclopramide*.[28] Enhanced motility of the gastrointestinal tract was implicated. *Cisapride* may also accelerate the absorption of diazepam.[29]

Studies of continuous *omeprazole* dosage on the pharmacokinetics of a single intravenous dose of diazepam in healthy subjects indicate inhibition of diazepam metabolism in a similar manner to cimetidine.[30,31] Omeprazole decreases the clearance and prolongs the elimination half-life of diazepam; in addition both the formation and elimination of desmethyldiazepam appear to be decreased. The effects may be greater in rapid than in slow metabolisers of omeprazole[32] and vary between ethnic groups.[33] The clinical significance of the interaction remains to be established. *Lansoprazole*[34] and *pantoprazole*[35] have been reported not to affect the pharmacokinetics of diazepam.

1. Nair SG, *et al.* The influence of three antacids on the absorption and clinical action of oral diazepam. *Br J Anaesth* 1976; **48:** 1175–80.
2. Greenblatt DJ, *et al.* Influence of magnesium and aluminum hydroxide mixture on chlordiazepoxide absorption. *Clin Pharmacol Ther* 1976; **19:** 234–9.
3. Chun AHC, *et al.* Effect of antacids on absorption of clorazepate. *Clin Pharmacol Ther* 1977; **22:** 329–35.
4. Shader RI, *et al.* Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. *Clin Pharmacol Ther* 1978; **24:** 308–15.
5. Greenblatt DJ, *et al.* Diazepam absorption: effect of antacids and food. *Clin Pharmacol Ther* 1978; **24:** 600–9.
6. Shader RI, *et al.* Steady-state plasma desmethyldiazepam during long-term clorazepate use: effect of antacids. *Clin Pharmacol Ther* 1982; **31:** 180–3.
7. Klotz U, Reimann I. Delayed clearance of diazepam due to cimetidine. *N Engl J Med* 1980; **302:** 1012–14.
8. Gough PA, *et al.* Influence of cimetidine on oral diazepam elimination with measurement of subsequent cognitive change. *Br J Clin Pharmacol* 1982; **14:** 739–42.
9. Greenblatt DJ, *et al.* Clinical importance of the interaction of diazepam and cimetidine. *N Engl J Med* 1984; **310:** 1639–43.
10. Locniskar A, *et al.* Interaction of diazepam with famotidine and cimetidine, two H -receptor antagonists. *J Clin Pharmacol* 1986; **26:** 299–303.
11. Abernethy DR, *et al.* Interaction of cimetidine with the triazolobenzodiazepines alprazolam and triazolam. *Psychopharmacology (Berl)* 1983; **80:** 275–8.
12. Pourbaix S, *et al.* Pharmacokinetic consequences of long term coadministration of cimetidine and triazolobenzodiazepines, alprazolam and triazolam, in healthy subjects. *Int J Clin Pharmacol Ther Toxicol* 1985; **23:** 447–51.
13. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
14. Desmond PV, *et al.* Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. *Ann Intern Med* 1980; **93:** 266–8.
15. Grigoleit H-G, *et al.* Pharmacokinetic aspects of the interaction between clobazam and cimetidine. *Eur J Clin Pharmacol* 1983; **25:** 139–42.
16. Pullar T, *et al.* The effect of cimetidine on the single dose pharmacokinetics of oral clobazam and N-desmethylclobazam. *Br J Clin Pharmacol* 1987; **23:** 317–21.
17. Greenblatt DJ, *et al.* Interaction of cimetidine with oxazepam, lorazepam, and flurazepam. *J Clin Pharmacol* 1984; **24:** 187–93.
18. Sanders LD, *et al.* Interaction of H2-receptor antagonists and benzodiazepine sedation: a double-blind placebo-controlled investigation of the effects of cimetidine and ranitidine on recovery after intravenous midazolam. *Anaesthesia* 1993; **48:** 286–92.
19. Ochs HR, *et al.* Cimetidine impairs nitrazepam clearance. *Clin Pharmacol Ther* 1983; **34:** 227–30.
20. Greenblatt DJ, *et al.* Noninteraction of temazepam and cimetidine. *J Pharm Sci* 1984; **73:** 399–401.
21. Klotz U, *et al.* Effect of ranitidine on the steady state pharmacokinetics of diazepam. *Eur J Clin Pharmacol* 1983; **24:** 357–60.
22. Abernethy DR, *et al.* Ranitidine does not impair oxidative or conjugative metabolism: noninteraction with antipyrine, diazepam, and lorazepam. *Clin Pharmacol Ther* 1984; **35:** 188–92.
23. Fee JPH, *et al.* Diazepam disposition following cimetidine or ranitidine. *Br J Clin Pharmacol* 1984; **17:** 617P–18P.
24. Klotz U, *et al.* Nocturnal doses of ranitidine and nizatidine do not affect the disposition of diazepam. *J Clin Pharmacol* 1987; **27:** 210–12.
25. Fee JPH, *et al.* Cimetidine and ranitidine increase midazolam bioavailability. *Clin Pharmacol Ther* 1987; **41:** 80–4.
26. Wilson CM, *et al.* Effect of pretreatment with ranitidine on the hypnotic action of single doses of midazolam, temazepam and zopiclone. *Br J Anaesth* 1986; **58:** 483–6.
27. Vanderveen RP, *et al.* Effect of ranitidine on the disposition of orally and intravenously administered triazolam. *Clin Pharm* 1991; **10:** 539–43.
28. Gamble JAS, *et al.* Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br J Anaesth* 1976; **48:** 1181–5.
29. Bateman DN. The action of cisapride on gastric emptying and the pharmacokinetics of oral diazepam. *Eur J Clin Pharmacol* 1986; **30:** 205–8.
30. Gugler R, Jensen JC. Omeprazole inhibits elimination of diazepam. *Lancet* 1984; **i:** 969.
31. Andersson T, *et al.* Effect of omeprazole and cimetidine on plasma diazepam levels. *Eur J Clin Pharmacol* 1990; **39:** 51–4.
32. Andersson T, *et al.* Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. *Clin Pharmacol Ther* 1990; **47:** 79–85.
33. Caraco Y, *et al.* Interethnic difference in omeprazole's inhibition of diazepam metabolism. *Clin Pharmacol Ther* 1995; **58:** 62–72.
34. Lefebvre RA, *et al.* Influence of lansoprazole treatment on diazepam plasma concentrations. *Clin Pharmacol Ther* 1992; **52:** 458–63.
35. Gugler R, *et al.* Lack of pharmacokinetic interaction of pantoprazole with diazepam in man. *Br J Clin Pharmacol* 1996; **42:** 249–52.

General anaesthetics. A synergistic interaction has been found for the hypnotic effects of midazolam and *thiopental*.[1] Although midazolam failed to produce anaesthesia at the doses used, the drug caused a twofold increase in the anaesthetic potency of thiopental. Similar synergistic interactions have been seen between midazolam and both *methohexital*[2] and *propofol*.[3,4] The interaction between midazolam and propofol could not be explained solely by alteration in free-plasma concentration of either drug,[5] although a later study[6] does suggest that propofol reduces the clearance of midazolam via its inhibitory effects on the metabolism of midazolam by the cytochrome P450 isoenzyme CYP3A4. It has been reported that midazolam can produce a marked reduction in the concentration of *halothane* required for anaesthesia.[7]

1. Short TG, *et al.* Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth* 1991; **66:** 13–19.
2. Tverskoy M, *et al.* Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth* 1989; **63:** 109–12.
3. McClune S, *et al.* Synergistic interaction between midazolam and propofol. *Br J Anaesth* 1992; **69:** 240–5.
4. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; **67:** 539–45.
5. Teh J, *et al.* Pharmacokinetic interactions between midazolam and propofol: an infusion study. *Br J Anaesth* 1994; **72:** 62–5.
6. Hamaoka N, *et al.* Propofol decreases the clearance of midazolam by inhibiting CYP3A4: an in vivo and in vitro study. *Clin Pharmacol Ther* 1999; **66:** 110–7.
7. Inagaki Y, *et al.* Anesthetic interaction between midazolam and halothane in humans. *Anesth Analg* 1993; **76:** 613–7.

Grapefruit juice. Grapefruit juice has been reported to be able to increase the bioavailability of oral midazolam[1] or triazolam[2] and to raise peak plasma concentrations. However, these results have been contradicted by another study,[3] which found no evidence for an interaction.

1. Kupferschmidt HHT, *et al.* Interaction between grapefruit juice and midazolam in humans. *Clin Pharmacol Ther* 1995; **58:** 20–8.
2. Hukkinen SK, *et al.* Plasma concentrations of triazolam are increased by concomitant ingestion of grapefruit juice. *Clin Pharmacol Ther* 1995; **58:** 127–31.
3. Vanakoski J, *et al.* Grapefruit juice does not enhance the effects of midazolam and triazolam in man. *Eur J Clin Pharmacol* 1996; **50:** 501–8.

Kava. A patient whose medication included alprazolam, cimetidine, and terazosin became lethargic and disoriented after starting to take kava.[1] An interaction between kava and the benzodiazepine was suspected.

1. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med* 1996; **125:** 940–1.

Levodopa. For reference to the effects of benzodiazepines on levodopa, see Anxiolytics, p.808.

Neuromuscular blockers. For reference to the effect of diazepam on neuromuscular blockade, see p.1904.

Oral contraceptives. Some studies with alprazolam,[1] chlordiazepoxide,[2] and diazepam[3] have supported suggestions that oral contraceptives may inhibit the biotransformation of benzodiazepines metabolised by oxidation, although no significant pharmacokinetic alterations have been observed with clotiazepam,[4] or triazolam.[1] The biotransformation of benzodiazepines metabolised by conjugation, such as lorazepam, oxazepam, or temazepam, may be enhanced[1,2] or unchanged.[5] No consistent correlation has been observed between the above pharmacokinetic changes and clinical effects. It has been observed[6] that psychomotor impairment due to oral diazepam was greater during the menstrual pause than during the 21-daily oral contraceptive cycle. This may have been due to an effect of oral contraceptives on diazepam absorption. Another study[7] noted that women taking oral contraceptives appeared to be more sensitive to psychomotor impairment after single oral doses of alprazolam, lorazepam, or triazolam, than controls. The effects of temazepam were minimal in both groups. Alterations in sedative or amnesic effect could not be established with any certainty.

1. Stoehr GP, *et al.* Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. *Clin Pharmacol Ther* 1984; **36:** 683–90.
2. Patwardhan RV, *et al.* Differential effects of oral contraceptive steroids on the metabolism of benzodiazepines. *Hepatology* 1983; **3:** 248–53.
3. Abernethy DR, *et al.* Impairment of diazepam metabolism by low-dose estrogen-containing oral-contraceptive steroids. *N Engl J Med* 1982; **306:** 791–2.
4. Ochs HR, *et al.* Disposition of clotiazepam: influence of age, sex, oral contraceptives, cimetidine, isoniazid and ethanol. *Eur J Clin Pharmacol* 1984; **26:** 55–9.
5. Abernethy DR, *et al.* Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. *Clin Pharmacol Ther* 1983; **33:** 628–32.
6. Ellinwood EH, *et al.* Effects of oral contraceptives on diazepam-induced psychomotor impairment. *Clin Pharmacol Ther* 1984; **35:** 360–6.
7. Kroboth PD, *et al.* Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction. *Clin Pharmacol Ther* 1985; **38:** 525–32.

Penicillamine. Phlebitis associated with intravenous diazepam resolved with local heat but recurred on two separate occasions after oral penicillamine.[1]

1. Brandstetter RD, *et al.* Exacerbation of intravenous diazepam-induced phlebitis by oral penicillamine. *BMJ* 1981; **283:** 525.

Probenecid. Probenecid increased the half-life of intravenous lorazepam in 9 healthy subjects.[1] Probenecid was considered to impair glucuronide formation selectively and thus the clearance of drugs like lorazepam. Probenecid has also shortened the time to induce anaesthesia with midazolam in 46 patients.[2] The effect was considered to be due to competition for plasma protein binding sites. Probenecid has also been reported[3] to reduce the clearance of nitrazepam but not of temazepam.

1. Abernethy DR, *et al.* Probenecid inhibition of acetaminophen and lorazepam glucuronidation. *Clin Pharmacol Ther* 1984; **35:** 224.

2. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.
3. Brockmeyer NH, *et al.* Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. *Int J Clin Pharmacol Ther Toxicol* 1990; **28:** 387–93.

Smooth muscle relaxants. Intracavernosal *papaverine* produced prolonged erection in 2 patients who had been given intravenous diazepam as an anxiolytic before the papaverine.[1]

1. Vale JA, *et al.* Papaverine, benzodiazepines, and prolonged erections. *Lancet* 1991; **337:** 1552.

Tobacco smoking. The Boston Collaborative Drug Surveillance Program reported drowsiness as an adverse effect of diazepam or chlordiazepoxide less frequently in smokers than non smokers.[1] Pharmacokinetic studies have, however, been divided between those indicating that smoking induces the hepatic metabolism of benzodiazepines and those showing no effect on benzodiazepine pharmacokinetics.[2] Hence, diminished end-organ responsiveness may in part account for the observed clinical effects. Taking large amounts of xanthine-containing beverages as well may decrease any enzyme-inducing effects of smoking.[3]

1. Boston Collaborative Drug Surveillance Program, Boston University Medical Center. Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. *N Engl J Med* 1973; **288:** 277–80.
2. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.
3. Downing RW, Rickels K. Coffee consumption, cigarette smoking and reporting of drowsiness in anxious patients treated with benzodiazepines or placebo. *Acta Psychiatr Scand* 1981; **64:** 398–408.

Xanthines. There are reports of *aminophylline* given intravenously reversing the sedation from intravenous diazepam,[1-3] although not always completely[2] nor as effectively as flumazenil.[4] Blockade of adenosine receptors by aminophylline has been postulated as the mechanism of this interaction.[3,5]

Xanthine-containing beverages may be expected to decrease the incidence of benzodiazepine-induced drowsiness because of their CNS-stimulating effects and their ability to induce hepatic drug-metabolising enzymes. However, decreased drowsiness has only sometimes been seen and the actions of xanthines may themselves be decreased by heavy tobacco smoking.[6,7]

1. Arvidsson SB, *et al.* Aminophylline antagonises diazepam sedation. *Lancet* 1982; **ii:** 1467.
2. Kleindienst G, Usinger P. Diazepam sedation is not antagonised completely by aminophylline. *Lancet* 1984; **i:** 113.
3. Niemand D, *et al.* Aminophylline inhibition of diazepam sedation: is adenosine blockade of GABA-receptors the mechanism? *Lancet* 1984: **i:** 463–4.
4. Sibai AN, *et al.* Comparison of flumazenil with aminophylline to antagonise midazolam in elderly patients. *Br J Anaesth* 1991; **66:** 591–5.
5. Henauer SA, *et al.* Theophylline antagonises diazepam-induced psychomotor impairment. *Eur J Clin Pharmacol* 1983; **25:** 743–7.
6. Downing RW, Rickels K. Coffee consumption, cigarette smoking and reporting of drowsiness in anxious patients treated with benzodiazepines or placebo. *Acta Psychiatr Scand* 1981; **64:** 398–408.
7. Ghoneim MM, *et al.* Pharmacokinetic and pharmacodynamic interactions between caffeine and diazepam. *J Clin Psychopharmacol* 1986; **6:** 75–80.

Pharmacokinetics

Diazepam is readily and completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 30 to 90 minutes of oral doses. Diazepam is rapidly absorbed when given as a rectal solution; peak plasma concentrations are achieved after about 10 to 30 minutes. Absorption may be erratic after intramuscular injection and lower peak plasma concentrations may be obtained compared with those after oral doses. Diazepam is highly lipid soluble and crosses the blood-brain barrier; it acts promptly on the brain, and its initial effects decrease rapidly as it is redistributed into fat depots and tissues.

Diazepam has a biphasic half-life with an initial rapid distribution phase and a prolonged terminal elimination phase of 1 or 2 days; its action is further prolonged by the even longer half-life of 2 to 5 days of its principal active metabolite, desmethyldiazepam (nordazepam). Diazepam and desmethyldiazepam accumulate on repeated dosage and the relative proportion of desmethyldiazepam in the body increases with long-term use. No simple correlation has been found between plasma concentrations of diazepam or its metabolites and their therapeutic effect.

Diazepam is extensively metabolised in the liver, notably via the cytochrome P450 isoenzyme CYP2C19; in addition to desmethyldiazepam, its active metabolites include oxazepam, and temazepam. It is excreted in the urine, mainly in the form of free or conjugated metabolites. Diazepam is 98 to 99% bound to plasma proteins.

The plasma elimination half-life of diazepam and/or its metabolites is prolonged in neonates, in the elderly, and in patients with liver disease. In addition to crossing the blood-brain barrier, diazepam and its metabolites also cross the placental barrier and are distributed into breast milk.

◊ Reviews.

1. Bailey L, *et al.* Clinical pharmacokinetics of benzodiazepines. *J Clin Pharmacol* 1994; **34:** 804–11.

Absorption and plasma concentrations. ***CHRONIC ORAL ADMINISTRATION.*** In 36 patients who had received diazepam 2 to 30 mg daily for periods from one month to 10 years, plasma-diazepam concentrations were directly related to dose and inversely related to age.[1] There was a close association between the plasma concentrations of diazepam and its metabolite desmethyldiazepam and both concentrations were independent of the duration of therapy. Plasma-diazepam concentration ranges were 0.02 to 1.01 micrograms/mL, and plasma-desmethyldiazepam concentration ranges were 0.055 to 1.765 micrograms/mL. A similar study[2] reached the same general conclusions.

1. Rutherford DM, *et al.* Plasma concentrations of diazepam and desmethyldiazepam during chronic diazepam therapy. *Br J Clin Pharmacol* 1978; **6:** 69–73.
2. Greenblatt DJ, *et al.* Plasma diazepam and desmethyldiazepam concentrations during long-term diazepam therapy. *Br J Clin Pharmacol* 1981; **1:** 35–40.

RECTAL. In 6 *adults* given diazepam 10 mg by mouth or as a solution (*Valium injection*) by rectum, mean bioavailability was 76 and 81%, respectively compared with the same dose by intravenous injection.[1] Bioavailability was lower with suppositories than with the solution given rectally. Studies support the use of rectal solution rather than suppositories in children.[2,3]

1. Dhillon S, *et al.* Bioavailability of diazepam after intravenous, oral and rectal administration in adult epileptic patients. *Br J Clin Pharmacol* 1982; **13:** 427–32.
2. Dhillon S, *et al.* Rectal absorption of diazepam in epileptic children. *Arch Dis Child* 1982; **57:** 264–7.
3. Sonander H, *et al.* Effects of the rectal administration of diazepam. *Br J Anaesth* 1985; **57:** 578–80.

Distribution into breast milk. Concentrations of diazepam and desmethyldiazepam transferred from mother to infant via breast milk have been measured.[1,2]

See also under Precautions, above.

1. Erkkola R, Kanto J. Diazepam and breast-feeding. *Lancet* 1972; **i:** 1235–6.
2. Brandt R. Passage of diazepam and desmethyldiazepam into breast milk. *Arzneimittelforschung* 1976; **26:** 454–7.

The elderly. For mention of pharmacokinetics in the elderly, see under Precautions, above.

Hepatic impairment. For reference to the altered pharmacokinetics of diazepam in patients with hepatic impairment see Administration in Hepatic Impairment, below.

Metabolism. Most benzodiazepines are highly lipophilic compounds requiring biotransformation before excretion from the body, and many form active metabolites that affect the duration of action. The benzodiazepines may be classified as long-, intermediate-, or short-acting compounds.[1]

- **Long-acting** benzodiazepines are either N_1-desalkyl derivatives (*delorazepam* and *nordazepam*) or are oxidised in the liver to N_1-desalkyl derivatives (benzodiazepines so oxidised include *chlordiazepoxide*, *clobazam*, *clorazepate*, *cloxazolam*, *diazepam*, *flurazepam*, *halazepam*, *ketazolam*, *medazepam*, *oxazolam*, *pinazepam*, *prazepam*, and *quazepam*). Clorazepate and prazepam may be considered as prodrugs since the metabolite is the expected active principle. Both parent drug and metabolites contribute to the activity of the other long-acting drugs. Further biotransformation of N_1-desalkylated metabolites proceeds much more slowly than for the parent drug, and they therefore accumulate in the body after a few days of treatment. The rate-limiting step of their metabolism (with the exception of the 1,5-derivatives) is C3-hydroxylation to the pharmacologically active oxazepam or its 2′-halogenated analogues.
- **Intermediate-acting** benzodiazepines are 7-nitrobenzodiazepines such as *clonazepam*, *flunitrazepam*, and *nitrazepam* which are metabolised by nitroreduction with no important known active metabolites. The metabolites of long- and intermediate-acting benzodiazepines require conjugation before excretion in the urine.
- **Short-acting** benzodiazepines include the C3-hydroxylated benzodiazepines such as *lorazepam*, *lormetazepam*, *oxazepam*, and *temazepam* which undergo rapid conjugation with glucuronic acid to water-soluble inactive metabolites that are excreted in the urine, and drugs such as *alprazolam*, *brotizolam*, *estazolam*, *etizolam*, *midazolam*, *tofisopam*, and *triazolam* which require oxidation involving aliphatic hydroxylation before subsequent conjugation. Although these hydroxylated metabolites may retain pharmacological activity, they are unlikely to contribute significantly to clinical activity because of their negligible plasma concentrations and rapid inactivation by glucuronidation.

Drug-metabolising capacity is influenced by many factors including genetics, age, sex, endocrine and nutritional status, smoking, disease, and concurrent drug therapy. This results in wide interindividual variation in both parent drug concentrations and metabolite-to-parent drug ratios.

1. Caccia S, Garattini S. Formation of active metabolites of psychotropic drugs: an updated review of their significance. *Clin Pharmacokinet* 1990; **18:** 434–59.

Pregnancy. The passage of diazepam across the placenta depends in part on the relative degrees of protein binding in mother and fetus. This in turn is influenced by factors such as stage of pregnancy and plasma concentrations of free fatty acids in mother and fetus.[1-6] Adverse effects may persist in the neonate for several days after birth because of immature drug-metabolising enzymes. Competition between diazepam and bilirubin for protein binding sites could result in hyperbilirubinaemia in the neonate.[7]

For further adverse effects associated with the use of benzodiazepines during pregnancy, see under Precautions, above.

1. Lee JN, *et al.* Serum protein binding of diazepam in maternal and foetal serum during pregnancy. *Br J Clin Pharmacol* 1982; **14:** 551–4.
2. Kuhnz W, Nau H. Differences in in vitro binding of diazepam and N-desmethyldiazepam to maternal and fetal plasma proteins at birth: relation to free fatty acid concentration and other parameters. *Clin Pharmacol Ther* 1983; **34:** 220–6.
3. Kanto J, *et al.* Accumulation of diazepam and N-demethyldiazepam in the fetal blood during the labour. *Ann Clin Res* 1973; **5:** 375–9.
4. Nau H, *et al.* Decreased serum protein binding of diazepam and its major metabolite in the neonate during the first postnatal week related to increased free fatty acid levels. *Br J Clin Pharmacol* 1984; **17:** 92–8.
5. Ridd MJ, *et al.* The disposition and placental transfer of diazepam in cesarean section. *Clin Pharmacol Ther* 1989; **45:** 506–12.
6. Idänpään-Heikkilä J, *et al.* Placental transfer and fetal metabolism of diazepam-C in early human pregnancy. *Clin Pharmacol Ther* 1971; **12:** 293.
7. Notarianni LJ. Plasma protein binding of drugs in pregnancy and in neonates. *Clin Pharmacokinet* 1990; **18:** 20–36.

Uses and Administration

Diazepam is a long-acting benzodiazepine with anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnestic properties. Its actions are mediated by enhancement of the activity of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the brain. Diazepam is used in the short-term treatment of severe anxiety disorders (p.952), as a hypnotic in the short-term management of insomnia (p.957), as a sedative (p.956) and premedicant (p.1780), as an anticonvulsant (particularly in the management of status epilepticus and febrile convulsions), in the control of muscle spasm, and in the management of withdrawal symptoms (see also the references below).

Diazepam is **administered** orally, rectally, and parenterally with the risk of dependence very much influencing the dose and duration of treatment. Doses should be the lowest that can control symptoms and courses of treatment should be short, not normally exceeding 4 weeks, with diazepam being withdrawn gradually (see above). Elderly and debilitated patients should be given not more than one-half the usual adult dose. Dosage reduction may also be required in patients with hepatic or renal impairment.

Oral use is appropriate for many indications and modified-release formulations are available in some countries. *Rectal* use may be by suppository or rectal solution or gel. Diazepam is also given by deep intramuscular or slow intravenous injection, although absorption after *intramuscular injection* may be erratic and provides lower blood concentrations than those after oral doses. *Intravenous injection* should be carried out slowly into a large vein of the antecubital fossa at a recommended rate of no more than 1 mL of a 0.5% solution (5 mg) per minute. It is advisable to keep the patient in the supine position and under medical supervision for at least an hour after the dose. Diazepam may be given by continuous *intravenous infusion*; because of the risk of precipitation of diazepam, solutions should be freshly prepared following the manufacturer's directions regarding diluent and concentration of diazepam. Diazepam is substantially adsorbed onto

some plastics (see Sorption, above). Facilities for resuscitation should always be available when diazepam is given intravenously.

Diazepam may be given for **severe anxiety** in *oral* doses of 2 mg three times daily to a maximum of 30 mg daily. A wider dose range of 4 to 40 mg daily in divided doses is used in the USA with children over 6 months of age receiving up to 10 mg daily. Diazepam may be given as a *rectal solution* in a dose of 500 micrograms/kg repeated after 12 hours if necessary or as *suppositories* in a dose of 10 to 30 mg. Diazepam may sometimes have to be given by intramuscular or intravenous *injection* when a dose of up to 10 mg may be used, repeated if necessary after 4 hours.

The benzodiazepines have a limited role in **insomnia** and diazepam is used for the short-term management of insomnia associated with anxiety. The *BNF* recommends an *oral* dose of 5 to 15 mg at bedtime, although doses up to 30 mg are licensed. Doses of 1 to 5 mg at bedtime have been used in children and adolescents aged from 12 to 18 years to control **night terrors** and **sleepwalking**.

Diazepam may be given for **premedication** before general anaesthesia or to provide sedative cover for minor surgical or investigative procedures. In adults, *oral* doses are in the range of 5 to 20 mg and when given by intravenous *injection* the dose is usually 100 to 200 micrograms/kg. Diazepam may also be given for **sedation** during minor surgical and medical procedures; in adults doses of 10 to 20 mg, given by intravenous injection over 2 to 4 minutes, are recommended. Diazepam 500 micrograms/kg may also be given as a rectal solution. For premedication and sedation in children and adolescents aged from 1 month to 18 years, the *BNFC* suggests that an oral dose of 200 to 300 micrograms/kg may be given 45 to 60 minutes beforehand; the maximum dose is 10 mg for those aged up to 12 years and 20 mg for adolescents aged up to 18 years. Diazepam 100 to 200 micrograms/kg may be given by intravenous injection over 2 to 4 minutes, immediately before the procedure, to those aged 1 month and older; the maximum dose is 5 mg for children aged up to 12 years and 20 mg for adolescents aged up to 18 years. When given as a rectal solution, the *BNFC* suggests the following doses based on age: 1 to 3 years, 5 mg; 3 to 12 years, 5 to 10 mg; 12 to 18 years, 10 mg. Some regard the perioperative use of diazepam in children undesirable since its effect and onset of action are unreliable and paradoxical effects may occur.

Diazepam is used in a variety of **seizures**. It is given *orally* as an adjunct in some types of epilepsy; for this purpose, 2 to 60 mg may be given daily in divided doses. A *rectal gel* formulation is also available for adjunctive use in the management of episodes of increased seizure activity in adults and children aged 2 years and over with refractory epilepsy; doses range from 200 to 500 micrograms/kg, depending on age, repeated after 4 to 12 hours if necessary. For febrile convulsions, status epilepticus, and convulsions due to poisoning, giving a *rectal solution* may be appropriate; suppositories are not suitable because absorption is too slow. Recommended doses for the rectal solution differ but a typical dose is 500 micrograms/kg for adults and children over 10 kg, repeated every 12 hours if necessary; if convulsions are not controlled by the first dose the use of other anticonvulsive measures is recommended. Rectal solutions are not licensed for such use in children under 1 year of age in the UK, but the *BNFC* suggests giving the following doses, repeated after 10 minutes if necessary, based on age: neonates, 1.25 to 2.5 mg; 1 month to 2 years, 5 mg. For older children it recommends: 2 to 12 years, 5 to 10 mg; 12 to 18 years, 10 mg. Alternatively, diazepam may be given *intravenously* to adults in a dose of 10 to 20 mg given at a rate of 5 mg/minute and repeated if necessary after 30 to 60 minutes. Other schedules involve giving smaller amounts more frequently or giving diazepam *intramuscularly*, though again absorption may be too slow. Once the seizures have been controlled, a slow intravenous infusion providing up to 3 mg/kg over 24 hours has been used to protect against recurrence. Doses by intravenous injection in children are within the range of 200 to 300 micrograms/kg; alternatively 1 mg may be given for each year of age. The *BNFC* has suggested that neonates and children aged from 1 month to 12 years may be given doses of 300 to 400 micrograms/kg by intravenous injection over 3 to 5 minutes, repeated after 10 minutes if necessary.

Diazepam may be given *orally* in daily divided doses of 2 to 15 mg to alleviate **muscle spasm**. The dose may be increased in severe spastic disorders, such as cerebral palsy, to up to 60 mg daily in adults. The *BNFC* suggests initial oral doses in children and adolescents, based on age and given twice daily, as follows: 1 to 12 months, 250 micrograms/kg; 1 to 5 years, 2.5 mg; 5 to 12 years, 5 mg; 12 to 18 years, 10 mg (maximum of 40 mg daily). If given by intramuscular or slow intravenous *injection* the dose is 10 mg repeated if necessary after 4 hours. Larger doses are used in tetanus in adults and children aged 1 month and over with 100 to 300 micrograms/kg being given every 1 to 4 hours by intravenous injection. Alternatively 3 to 10 mg/kg may be given over 24 hours by continuous intravenous infusion or by nasoduodenal tube using a suitable liquid oral dose form. Diazepam may also be given by the rectal route as a *rectal solution* in a dose of 500 micrograms/kg for adults and children over 10 kg in weight, repeated every 12 hours if necessary.

Symptoms of the **alcohol withdrawal syndrome** may be controlled by diazepam given *orally* in a dose of 5 to 20 mg, repeated if required after 2 to 4 hours; another approach is to give 10 mg three or four times on the first day reducing to 5 mg three or four times daily as required. Diazepam may need to be given by *injection* if the symptoms are severe and if delirium tremens has developed; 10 to 20 mg by intramuscular or intravenous injection may be adequate, although some patients may require higher doses.

◊ Reviews.

1. Ashton H. Guidelines for the rational use of benzodiazepines: when and what to use. *Drugs* 1994; **48:** 25–40.

Administration in hepatic impairment. Oxidative metabolism of diazepam is apparently reduced in patients with hepatic impairment, resulting in a prolonged half-life and reduced clearance.[1-3] A reduction in dosage was generally required in these studies, but no specific advice is given in licensed information for the UK or USA.

1. Branch RA, *et al.* Intravenous administration of diazepam in patients with chronic liver disease. *Gut* 1976; **17:** 975–83.
2. Klotz U, *et al.* Disposition of diazepam and its major metabolite desmethyldiazepam in patients with liver disease. *Clin Pharmacol Ther* 1977; **21:** 430–6.
3. Ochs HR, *et al.* Repeated diazepam dosing in cirrhotic patients: cumulation and sedation. *Clin Pharmacol Ther* 1983; **33:** 471–6.

Administration in renal impairment. Diazepam and its metabolites are excreted in urine, and licensed drug information suggests that dosage reduction may be required in patients with renal impairment, but gives no specific advice on how to do this.

Cardiac arrhythmias. Although not considered to be an antiarrhythmic, diazepam has been tried with good effect in treating the cardiotoxicity of chloroquine poisoning (see p.601). However, diazepam has been reported to possess both antiarrhythmic and pro-arrhythmic properties, possibly depending on the dose.[1]

1. Kumagai K, *et al.* Antiarrhythmic and proarrhythmic properties of diazepam demonstrated by electrophysiological study in humans. *Clin Cardiol* 1991; **14:** 397–401.

Chloroquine poisoning. For reference to the possible use of diazepam to decrease the cardiotoxic effects of chloroquine, see p.601.

Conversion and dissociative disorders. Conversion and dissociative disorders (formerly known as hysteria) are characterised by physical symptoms that occur in the absence of organic disease. Medication has no part to play in the treatment of these disorders unless they are secondary to conditions such as depression or anxiety disorders requiring treatment in their own right.

There have been suggestions that sedatives such as diazepam or midazolam may be used to confirm the diagnosis of hysterical paralysis.[1,2] The test tends to exacerbate organic disease while psychiatric dysfunction may improve.

1. Ellis SJ. Diazepam as a truth drug. *Lancet* 1990; **336:** 752–3.
2. Keating JJ, *et al.* Hysterical paralysis. *Lancet* 1990; **336:** 1506–7.

Disturbed behaviour. For a discussion of the management of behaviour disturbances associated with various psychotic disorders, and the value of benzodiazepines, see p.954. Benzodiazepines may sometimes be useful in palliative care for the relief of terminal restlessness. Midazolam is often used although other benzodiazepines such as diazepam have also been tried.[1] A suggested dose for diazepam is 5 to 10 mg given slowly as a rectal solution and repeated every 8 to 12 hours. In practice, however, haloperidol may be preferred; a review suggested that benzodiazepines used alone might exacerbate the problem. If agitation was severe haloperidol or risperidone could be combined with lorazepam, reserving subcutaneous midazolam for refractory cases.[2]

1. Burke AL. Palliative care: an update on "terminal restlessness." *Med J Aust* 1997; **166:** 39–42.
2. Jakobsson M, Strang P. Midazolam (Dormicum) vid terminal oro och agitation: sistahandsalternativ i palliativ vård. *Lakartidningen* 1999; **96:** 2079–81.

Dyspnoea. Despite the hazards of use in patients with any form of respiratory depression or pulmonary insufficiency (see Respiratory System Disorders under Precautions, above) benzodiazepines such as diazepam have been tried in the treatment of dyspnoea (p.104), in the belief that reduction of an elevated respiratory drive may alleviate respiratory distress. However, benefits have not been confirmed. Benzodiazepines may be of use in patients with advanced cancer who have rapid shallow respiration. A daily dose of 5 to 10 mg has been suggested for diazepam.

Eclampsia and pre-eclampsia. Diazepam has been used for the initial control of impending or actual eclampsia (p.470), but magnesium sulfate is now generally the preferred treatment.

Epilepsy and other convulsive disorders. Some benzodiazepines such as diazepam are used for the control of status epilepticus (p.469), including status epilepticus in patients with porphyria (p.471—but see also Porphyria under Precautions, above), and for febrile convulsions (p.470); diazepam has also been used in eclampsia (see above) and for neonatal seizures (p.471). Benzodiazepines such as clobazam and clonazepam may be used in the management of epilepsy (p.465), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects. Diazepam has been used as an adjunct in the management of some types of epilepsy including myoclonus.

References.

1. Rosman NP, *et al.* A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. *N Engl J Med* 1993; **329:** 79–84.
2. Somerville ER, Antony JH. Position statement on the use of rectal diazepam in epilepsy. *Med J Aust* 1995; **163:** 268–9.
3. Uhari M, *et al.* Effect of acetaminophen and low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr* 1995; **126:** 991–5.
4. Akinbi MS, Welty TE. Benzodiazepines in the home treatment of acute seizures. *Ann Pharmacother* 1999; **33:** 99–102.
5. Rey E, *et al.* Pharmacokinetic optimisation of benzodiazepine therapy for acute seizures: focus on delivery routes. *Clin Pharmacokinet* 1999; **36:** 409–24.
6. Ogutu BR, *et al.* Pharmacokinetics and anticonvulsant effects of diazepam in children with severe falciparum malaria and convulsions. *Br J Clin Pharmacol* 2002; **53:** 49–57.

Extrapyramidal disorders. For reference to the use of benzodiazepines in the treatment of antipsychotic-induced extrapyramidal disorders, see Chlorpromazine, p.971.

Irritable bowel syndrome. Although some benzodiazepines have been used in the management of irritable bowel syndrome (p.1699) there is no evidence to support their use in this condition. The related compound dextofisopam is under investigation.

Mania. Benzodiazepines have been used as short-term adjuncts in the initial control of manic episodes in patients with bipolar disorder (p.372) until lithium has achieved its full effect.

Muscle spasm. Diazepam and other benzodiazepines may be used for the relief of muscle spasm (p.1887) of various aetiologies including that secondary to muscle or joint inflammation or trauma, such as in acute **low back pain** (p.7), or resulting from **spasticity** (p.1887), **dystonias** (p.809), **stiff-man syndrome** (see below), **cerebral palsy**, **poisoning**, or **tetanus** (p.1901). High doses are often required and treatment may be limited by adverse effects or by risk of dependence.

STIFF-MAN SYNDROME. Stiff-man syndrome is a rare condition characterised by painful intermittent spasms and rigidity of the axial and limb muscles. Its exact cause is unknown but there is some evidence to implicate autoantibodies against one of the enzymes involved in the synthesis of the neurotransmitter gamma-aminobutyric acid. It is frequently associated with auto-immune diseases and type 1 diabetes mellitus. Patients typically respond to benzodiazepines and this may be of use in the differential diagnosis of the syndrome. Diazepam has been the mainstay of treatment but clonazepam may also be of use, especially in familial startle disease, a rare congenital form of stiff-man syndrome. Although rigidity and spasms in stiff-man syndrome are not completely resolved by diazepam the degree of improvement can be sufficient to restore the functional level to near normal. However, large doses are often required and sedation might be a limiting factor in some patients. Other drugs that have been used when

diazepam is ineffective or poorly tolerated include baclofen or sodium valproate but benefit may be less evident. There have been isolated anecdotal reports of improvement with vigabatrin, tiagabine, and gabapentin. Antiepileptics or baclofen may sometimes be combined with benzodiazepines. Cortico-steroids may be of benefit, although any response may take several weeks, and the chronic nature of the disorder and the high incidence of type 1 diabetes mellitus may make their use problematic. Other attempts at immunomodulation such as plasmapheresis have yielded variable results; there is some evidence of the efficacy of immunoglobulins.

References.

1. Toro C, *et al.* Stiff-man syndrome. *Semin Neurol* 1994; **14:** 154–8.
2. Gerhardt CL. Stiff-man syndrome revisited. *South Med J* 1995; **88:** 805–808.
3. Stayer C, Meinck H-M. Stiff-man syndrome: an overview. *Neurologia* 1998; **13:** 83–8.
4. Levy LM, *et al.* The stiff-person syndrome - an autoimmune disorder affecting neurotransmission of γ-aminobutyric acid. *Ann Intern Med* 1999; **131:** 522–30.
5. Meinck H-M. Stiff man syndrome. *CNS Drugs* 2001; **15:** 515–26.
6. Dalakas MC, *et al.* High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; **345:** 1870–6.
7. Vasconcelos OM, Dalakas MC. Stiff-person syndrome. *Curr Treat Options Neurol* 2003; **5:** 79–90.

Nausea and vomiting. Benzodiazepines, particularly lorazepam, are used as adjuncts in the management of nausea and vomiting induced by cancer chemotherapy (p.1700), particularly anticipatory emesis.

Premenstrual syndrome. For mention of the limited role of benzodiazepines in the management of premenstrual syndrome, see p.2099.

Schizophrenia. Benzodiazepines may be useful adjuncts to antipsychotics in the initial management of schizophrenia (p.955).

Sleep-associated movement disorders. Sleep-associated movement disorders (p.958) rarely require treatment other than the symptomatic treatment of sleep-related medical problems. A number of such conditions, including restless legs syndrome, sleepwalking, and night terrors, have been reported to respond to benzodiazepines. Although the muscle relaxant and anxiolytic action of a benzodiazepine can be helpful in bruxism (teeth grinding) it has been recommended that they should only be prescribed on a short-term basis during the acute phase.

References.

1. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med* 1996; **100:** 333–7.

Substance dependence. The benzodiazepines are used in the management of symptoms of *alcohol* withdrawal (p.1626), of *opioid* withdrawal (p.101), and of *cocaine* withdrawal (p.1860).

Vertigo. Although intravenous diazepam has been used to abort acute attacks of vertigo of peripheral origin (p.565), it can prolong compensation and recovery from vestibular lesions.[1]

1. Rascol O, *et al.* Antivertigo medications and drug-induced vertigo: a pharmacological review. *Drugs* 1995; **50:** 777–91.

Preparations

BP 2008: Diazepam Injection; Diazepam Oral Solution; Diazepam Rectal Solution; Diazepam Tablets;
USP 31: Diazepam Capsules; Diazepam Extended-release Capsules; Diazepam Injection; Diazepam Tablets.

Proprietary Preparations (details are given in Part 3)

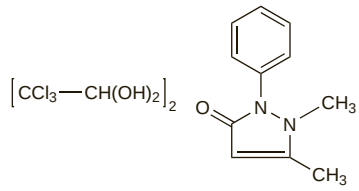
Arg.: Cuadel; Daiv; Dezepan; Diactal; Dipezona; Fabotranil; Glutasedan†; Lembrol; Plidan; Plidex T; Rupediz†; Saromet; Timab; Valium; ***Austral.:*** Antenex; Ducene; Valium; Valpam; ***Austria:*** Gewacalm; Psychopax; Stesolid; Umbrium; Valium; ***Belg.:*** Valium; ***Braz.:*** Ansilive; Calmociteno; Compaz; Diazefast; Diazepan†; Dienpax; Kiatrium; Letansil; Menostress; Noan; Pazolini; Relapax; Somaplus; Uni Diazepax; Valium; Valix†; Vetansil; ***Canad.:*** Diastat; Diazemuls; Novo-Dipam; Valium; ***Chile:*** Cardiosedantol; Elongal†; Pacinax; ***Cz.:*** Apaurin; Seduxen†; Stesolid; ***Denm.:*** Apozepam; Hexalid; Stesolid; Valaxona; Valium; ***Fin.:*** Diapam; Medipam; Stesolid; ***Fr.:*** Novazam†; Valium; ***Ger.:*** Diazep; Faustan; Lamra; Stesolid; Tranquase†; Valiquid; Valium; Valocordin-Diazepam; ***Gr.:*** Apollonset; Atarviton; Stedon; Stesolid; ***Hong Kong:*** Diazemuls; Kratium; Stesolid; Valpam; ***Hung.:*** Seduxen; Stesolid; ***India:*** Anxol; Calmpose; Elcion; Paxum; Placidox; Rec-DZ; Valium; Zepose; ***Indon.:*** Mentalium; Stesolid; Trazep; Valdimex; Valisanbe; Valium; ***Irl.:*** Anxicalm; Diazemuls; Stesolid; Valium; ***Israel:*** Assival; Diaz; Stesolid; ***Ital.:*** Aliseum; Ansiolin; Diazemuls; Micronoan; Noan; Tranquirit; Valium; Vatran; ***Malaysia:*** Diapine; Diapo; Valium; ***Mex.:*** Alboral; Arzepam; AT-V†; Benzyme; Diacepam†; Diapanil†; Diatex†; Freudal†; Ifa-Fonal; Laxyl; Onapan; Ortopsique; Prizem†; Relazepam; Tandial†; Valium; Zepan; Zeprat†; ***Neth.:*** Diazemuls; Stesolid; Valium; ***Norw.:*** Stesolid; Valium; Vival; ***NZ:*** D-Pam; Diazemuls; Propam; Stesolid; ***Philipp.:*** Nixtensyn; Trankil; Valium; ***Pol.:*** Relanium; Relsed; ***Port.:*** Bialzepam; Metamidol; Stesolid; Unisedil; Valium; ***Rus.:*** Apaurin (Апаурин); Relanium (Реланиум); Relium (Релиум); Seduxen (Седуксен); ***S.Afr.:*** Benzopin; Betapam; Calmpose; Doval; Pax; Tranject; Valium; ***Singapore:*** Diapine; Diapo; Stesolid; ***Spain:*** Aneurol; Aspaserine B6 Tranq†; Complutine; Gobanal; Pacium; Sico Relax†; Stesolid; Valium; Vincosedan; ***Swed.:*** Apozepam†; Stesolid; ***Switz.:*** Paceum; Psychopax; Stesolid; Valium; ***Thai.:*** Azepam; Diano; Diapam; Diapine; Dizan; Dizepam†; Sipam; Stesolid†; V Day Zepam†; Valenium†; Valium; Zopam; ***Turk.:*** Diapam; Diazem; Lizan; Nervium; ***UK:*** Dialar; Diazemuls; Rimapam; Stesolid; Tensium; Valclair; ***USA:*** Diastat; Valium; ***Venez.:*** Talema; Telsomet†; Valium†.

Multi-ingredient: ***Arg.:*** Arnol; Dafne; Dislembral†; Faradil; Pasminox Somatico; Plidex†; Tratobes; ***Austria:*** Betamed; Harmomed; ***Braz.:*** Dialudon; Dobesix†; Moderine; ***Chile:*** Calmosedan; Diapam; Mesolona†; Multisedil; Promidan; Sedantol; Sedilit; ***Cz.:*** Seduxen RG†; ***Fin.:*** Gastrodyn comp; Relapamil; Vertipam; ***Gr.:*** Distedon; ***India:*** Depsonil-DZ; Dericip Plus; ***Indon.:*** Analsik; Cetalgin; Danalgin; Hedix; Neurodial; Neuroval; Opineuron; Proneuron; ***Ital.:*** Gamibetal Plus; Spasen Somatico; Spasmeridan; Spasmomen Somatico; Valpinax; Valtrax; ***Mex.:*** Adepsique; Esbelcaps; Numencial; Qual; Redotex; ***Port.:*** Gamibetal Compositum†; ***Rus.:*** Reladorm (Реладорм); ***Spain:*** Ansium; Tepazepan; Tropargal; ***Turk.:*** Spazmo-Valibrin; ***USA:*** Emergent-Ez; ***Venez.:*** Tepazepam†.

Dichloralphenazone *(BAN)*

Dicloralfenazona; Dikloraalifenatsoni; Dikloralfenazon.

$C_{15}H_{18}Cl_6N_2O_5$ = 519.0.
CAS — 480-30-8.
ATC — N05CC04.
ATC Vet — QN05CC04.



Pharmacopoeias. In *US.*
USP 31 (Dichloralphenazone). A white microcrystalline powder with a slight odour characteristic of cloral hydrate. Freely soluble in water, in alcohol, and in chloroform; soluble in dilute acids. It is decomposed by dilute alkalis liberating chloroform.

Profile

Dichloralphenazone dissociates when given, to form cloral hydrate and phenazone. It has the general properties of cloral hydrate (p.979), although it is less likely to cause gastric irritation after oral doses. Phenazone-induced skin eruptions may, however, occur (see p.116). Dichloralphenazone is used in some countries in combination preparations mainly for the treatment of tension and vascular headaches.

Porphyria. Dichloralphenazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

USP 31: Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules.

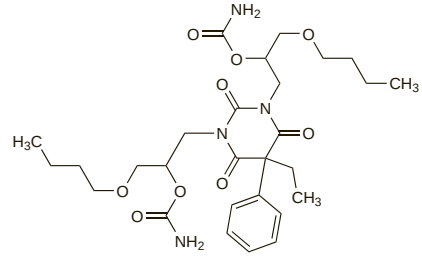
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***USA:*** Duradrin†; Midrin; Migratine†.

Difebarbamate *(rINN)*

Difébarbamate; Difebarbamato; Difebarbamatum. 1,3-Bis(3-butoxy-2-hydroxypropyl)-5-ethyl-5-phenylbarbituric acid dicarbamate ester.

Дифебарбамат

$C_{28}H_{42}N_4O_9$ = 578.7.
CAS — 15687-09-9.



Profile

Difebarbamate is a barbiturate with general properties similar to those of amobarbital (p.961). Tetrabamate, a complex of difebarbamate, febarbamate, and phenobarbital, has been used in the management of anxiety disorders and alcohol withdrawal syndrome but was also associated with the development of hepatitis. Furthermore barbiturates are not considered appropriate in the management of these conditions.

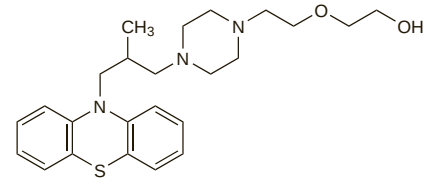
Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Hung.:*** Atrium†.

Dixyrazine

Diksyratsiini; Dixirazina; Dixyrazin; Dixyrazinum; UCB-3412. 2-(2-{4-[2-Methyl-3-(phenothiazin-10-yl)propyl]piperazin-1-yl}ethoxy)ethanol.

$C_{24}H_{33}N_3O_2S$ = 427.6.
CAS — 2470-73-7.
ATC — N05AB01.
ATC Vet — QN05AB01.



Profile

Dixyrazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has a piperazine side-chain. It is given for its antipsychotic, antiemetic, and sedative properties in oral doses ranging from 20 to 75 mg daily. Dixyrazine has also been given by injection.

◊ References.

1. Larsson S, *et al.* Premedication with intramuscular dixyrazine (Esucos): a controlled double-blind comparison with morphine-scopolamine and placebo. *Acta Anaesthesiol Scand* 1988; **32:** 131–4.
2. Karlsson E, *et al.* The effects of prophylactic dixyrazine on postoperative vomiting after two different anaesthetic methods for squint surgery in children. *Acta Anaesthesiol Scand* 1993; **37:** 45–8.
3. Oikkonen M, *et al.* Dixyrazine premedication for cataract surgery: a comparison with diazepam. *Acta Anaesthesiol Scand* 1994; **38:** 214–17.
4. Feet PO, Götestam KG. Increased antipanic efficacy in combined treatment with clomipramine and dixyrazine. *Acta Psychiatr Scand* 1994; **89:** 230–4.
5. Kokinsky E, *et al.* Postoperative nausea and vomiting in children using patient-controlled analgesia: the effect of prophylactic intravenous dixyrazine. *Acta Anaesthesiol Scand* 1999; **43:** 191–5.
6. Glaser C, *et al.* Dixyrazine for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 2004; **48:** 1287–91.

Porphyria. Dixyrazine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Preparations

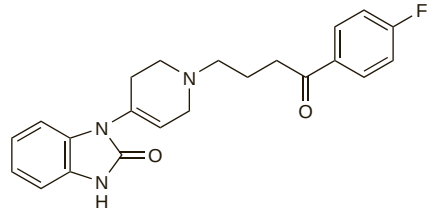
Proprietary Preparations (details are given in Part 3)
Austria: Esucos; ***Fin.:*** Esucos; ***Ital.:*** Esucos; ***Norw.:*** Esucos; ***Swed.:*** Esucos.

Droperidol *(BAN, USAN, rINN)*

Dropéridol; Droperidoli; Droperidolis; Droperidolum; McN-JR-4749; R-4749. 1-{1-[3-(4-Fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl}-benzimidazolin-2-one.

Дроперидол

$C_{22}H_{22}FN_3O_2$ = 379.4.
CAS — 548-73-2.
ATC — N01AX01; N05AD08.
ATC Vet — QN01AX01; QN05AD08.



Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*
Ph. Eur. 6.2 (Droperidol). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane and in dimethylformamide. Protect from light.
USP 31 (Droperidol). A white to light tan amorphous or microcrystalline powder. Practically insoluble in water; soluble 1 in 140 of alcohol, 1 in 4 of chloroform, and 1 in 500 of ether. Store under nitrogen in airtight containers at a temperature of 8° to 15°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. There is an increased risk of cardiotoxicity and prolongation of the QT interval (see p.970) with droperidol. Droperidol should not be used in patients with known or suspected QT prolongation; it should also be used with extreme caution in patients at risk of arrhythmias, including those