boy[1] 100 minutes after anorectal induction with 27.6 mg/kg methohexital.

1. Kaiser H, Al-Rafai S. Wie sicher ist die rektale Narkoseeinleitung mit Methohexital in der Kinderanaesthesie? *Anaesthesist* 1985; **34:** 359–60.

Interactions

As for Thiopental Sodium, p.1795.

Antidepressants. A 42-year-old woman[1] had a generalised tonic-clonic seizure immediately after being anaesthetised with methohexital for the last in a series of 6 electroconvulsive therapies. She had been receiving *paroxetine* throughout the series. A previous course, without concurrent paroxetine, had been uneventful.

1. Folkerts H. Spontaneous seizure after concurrent use of methohexital anesthesia for electroconvulsive therapy and paroxetine: a case report. *J Nerv Ment Dis* 1995; **183:** 115–16.

Pharmacokinetics

Methohexital is less lipid soluble than thiopental but concentrations sufficient to produce anaesthesia are attained in the brain within 30 seconds of an intravenous dose. Methohexital is also absorbed when given rectally, producing an effect within about 5 to 11 minutes. Recovery from anaesthesia occurs quickly as a result of rapid metabolism and redistribution into other body tissues. Methohexital does not appear to concentrate in fatty tissues to the same extent as other barbiturate anaesthetics. Protein binding has been reported to be about 73%. Methohexital is rapidly metabolised in the liver through demethylation and oxidation. The terminal half-life ranges from 1.5 to 6 hours. Methohexital diffuses across the placenta and has been detected in breast milk.

◊ References.

1. Swerdlow BN, Holley FO. Intravenous anaesthetic agents: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet* 1987; **12:** 79–110.
2. Le Normand Y, *et al.* Pharmacokinetics and haemodynamic effects of prolonged methohexitone infusion. *Br J Clin Pharmacol* 1988; **26:** 589–94.
3. Redke F, *et al.* Pharmacokinetics and clinical experience of 20-h infusions of methohexitone in intensive care patients with postoperative pyrexia. *Br J Anaesth* 1991; **66:** 53–9.
4. van Hoogdalem EJ, *et al.* Pharmacokinetics of rectal drug administration, part I: general considerations and clinical applications of centrally acting drugs. *Clin Pharmacokinet* 1991; **21:** 11–26.

Uses and Administration

Methohexital is a short-acting barbiturate anaesthetic that has actions similar to those of thiopental (p.1796) but it is about 2 to 3 times more potent. It is given as the sodium salt and has similar uses to thiopental in anaesthesia. Induction of anaesthesia is less smooth than with thiopental and there may be excitatory phenomena. It has a shorter duration of action than thiopental and recovery after an induction dose occurs within 5 to 7 minutes although drowsiness may persist for some time.

As with other barbiturate anaesthetics the dose of methohexital required varies greatly according to the state of the patient and the nature of other drugs also being used (see under Precautions of Thiopental, p.1795, and Interactions of Thiopental, p.1795, for further details). Methohexital sodium is usually given intravenously as a 1% solution. Higher concentrations may markedly increase the incidence of adverse effects. A typical dose for induction of anaesthesia is 50 to 120 mg given at a rate of about 10 mg (1 mL of a 1% solution) every 5 seconds. For the maintenance of general anaesthesia methohexital sodium may be given by intravenous injection in doses of 20 to 40 mg every 4 to 7 minutes as required or it may be given as a 0.2% solution by continuous intravenous infusion at a rate of 3 mL/minute.

For dosage in children, see below.

Administration in children. Although intravenous use is considered preferable in adults, in the USA methohexital sodium has been licensed for use in children only by the intramuscular and rectal routes: usual doses for the induction of anaesthesia are 6.6 to 10 mg/kg intramuscularly, as a 5% solution, or 25 mg/kg rectally, as a 1% solution. In some countries methohexital sodium has also been given intravenously to children: doses in the range of 1 to 2 mg/kg have been used.

Administration in the elderly. It is usually recommended that the dosage of barbiturate anaesthetics is reduced in the elderly. A study[1] in elderly patients has shown that although reducing the rate of intravenous dosage reduces the speed of induction, the dosage required is also reduced. Giving methohexital sodium 0.5% at a rate of 25 mg/minute induced anaesthesia in a mean of 83.8 seconds and required a mean dose of 0.56 mg/kg. Corresponding values for a rate of 100 mg/minute were 43.6 seconds and 1 mg/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; **70:** 423–7.

Dental sedation. Some anaesthetics are used as sedatives in dental procedures (see p.956). Methohexital has been tried for patient-controlled sedation in oral surgery under local anaesthesia.[1] In a group of 42 patients, results with 2.5 mg of methohexital compared favourably with those obtained in patients receiving 5 mg of propofol on demand, although patients in the methohexital group experienced a greater degree of postoperative drowsiness.

1. Hamid SK, *et al.* Comparison of patient-controlled sedation with either methohexitone or propofol. *Br J Anaesth* 1996; **77:** 727–30.

Preparations

USP 31: Methohexital Sodium for Injection.

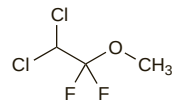
Proprietary Preparations (details are given in Part 3)
Austral.: Brietal; ***Austria:*** Brietal; ***Ger.:*** Brevimytal; ***Israel:*** Brietal†; ***Neth.:*** Brietal; ***Pol.:*** Brietal; ***Rus.:*** Brietal (Бриетал); ***USA:*** Brevital.

Methoxyflurane *(BAN, USAN, rINN)*

Méthoxyflurane; Methoxyfluranum; Metoksifluraani; Metoxifluran; Metoxiflurano; NSC-110432. 2,2-Dichloro-1,1-difluoro-1-methoxyethane; 2,2-Dichloro-1,1-difluoroethyl methyl ether.

Метоксифлуран

$C_3H_4Cl_2F_2O$ = 165.0.
CAS — 76-38-0.
ATC — N01AB03.
ATC Vet — QN01AB03.



Pharmacopoeias. In *US.*

USP 31 (Methoxyflurane). A clear, practically colourless, mobile liquid having a characteristic odour. It may contain a suitable stabiliser. B.p. about 105°. Soluble 1 in 500 of water; miscible with alcohol, with acetone, with chloroform, with ether, and with fixed oils. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Adverse Effects

As with other halogenated anaesthetics respiratory depression, hypotension, and malignant hyperthermia have been reported. Methoxyflurane sensitises the myocardium to sympathomimetics to a lesser extent than halothane; arrhythmias appear to be rare.

Methoxyflurane impairs renal function in a dose-related manner due to the effect of the released fluoride on the distal tubule and may cause polyuric or oliguric renal failure, oxaluria being a prominent feature. Nephrotoxicity is greater with methoxyflurane than with other halogenated anaesthetics because of slower metabolism over several days resulting in prolonged production of fluoride ions, and metabolism to other potentially nephrotoxic substances.

There have also been occasional reports of hepatic dysfunction, jaundice, and fatal hepatic necrosis. Headache has been reported by some patients. Cardiac arrest, gastrointestinal adverse effects, delirium, and prolonged postoperative somnolence have been observed.

See also Adverse Effects of General Anaesthetics, p.1779.

Precautions

The use of methoxyflurane is limited because of its potential to cause renal toxicity. It should not be used to achieve deep anaesthesia or for surgical procedures expected to last longer than 4 hours. Methoxyflurane is contra-indicated in the presence of renal impairment. Renal function and urine output should be monitored during anaesthesia. As with other halogenated anaesthetics it is advisable not to give methoxyflurane to patients who have shown signs of liver damage or fever after previous anaesthesia involving halogenated anaesthetics. Patients with known, or suspected, susceptibility to malignant hyperthermia should not be anaesthetised with methoxyflurane. Allowance may need to be made for any increase in CSF pressure or in cerebral blood flow.

There is significant absorption of methoxyflurane by the rubber and soda lime in anaesthetic circuits. PVC plastics are partially soluble in methoxyflurane.

See also Precautions for General Anaesthetics, p.1779.

Abuse. A 27-year-old nurse suffered from progressive renal disease and painful diffuse and multifocal periostitis, which had developed as a probable consequence of intermittent self-exposure to methoxyflurane possibly over a 9-year period.[1] There has also been a report[2] of hepatitis in a 39-year-old physician who repeatedly self-administered subanaesthetic concentrations of methoxyflurane for insomnia. Inhalation of about 2 mL of methoxyflurane had occurred once or twice almost every day for 6 weeks. A 125-mL bottle of methoxyflurane had been consumed in about 1 month.

1. Klemmer PJ, Hadler NM. Subacute fluorosis: a consequence of abuse of an organofluoride anesthetic. *Ann Intern Med* 1978; **89:** 607–11.
2. Okuno T, *et al.* Hepatitis due to repeated inhalation of methoxyflurane in subanaesthetic concentrations. *Can Anaesth Soc J* 1985; **32:** 53–5.

Porphyria. Methoxyflurane is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

Care is advised if adrenaline or other sympathomimetics are given to patients during methoxyflurane anaesthesia. The effects of competitive neuromuscular blockers are enhanced by methoxyflurane. The chronic use of hepatic enzyme-inducing drugs may enhance the metabolism of methoxyflurane thereby increasing the risk of nephrotoxicity. Use of nephrotoxic drugs with methoxyflurane should be avoided.

See also Interactions of General Anaesthetics, p.1779.

Pharmacokinetics

Methoxyflurane is absorbed on inhalation. The blood/gas partition coefficient is high. Methoxyflurane is metabolised to a greater extent than other inhalational anaesthetics. About 50 to 70% of absorbed methoxyflurane undergoes metabolism in the liver to free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid. Methoxyflurane is very soluble in adipose tissue and excretion may be slow. Peak plasma concentrations of fluoride occur 2 to 4 days after a dose. Methoxyflurane crosses the placenta.

Uses and Administration

Methoxyflurane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) of 0.16%, but because of its low vapour pressure, induction of general anaesthesia with methoxyflurane is slow. In recommended concentrations it is non-flammable and not explosive when mixed with oxygen. Methoxyflurane possesses good analgesic properties. It does not produce appreciable skeletal muscle relaxation at the concentrations used. Methoxyflurane does not relax the uterus and has little effect on uterine contractions during labour. It is used in subanaesthetic doses to provide analgesia for painful procedures and trauma. In anaesthetic doses, it has been used mainly for maintenance of general anaesthesia (p.1780), but safer anaesthetics are preferred because of its nephrotoxicity.

Concentrations of about 0.2 to 0.7% v/v are used to provide analgesia to conscious patients. The recommended maximum total dose for intermittent self-administration is 6 mL of liquid per day or 15 mL/week.

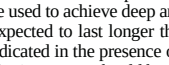
Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Penthrane†; Penthrox; ***NZ:*** Penthrox.

Nitrous Oxide

Azote, protoxyde d'; Azoto Protossido; Azotu(I) tlenek; Diazoto oksidas; Dikväveoxid; Dinitrogen Oxide; Dinitrogenii oxidum; Dinitrogén-oxid; Distickstoffmonoxid; Dityppioksidi; E942; Laughing Gas; Nitrogen Monoxide; Nitrogen Oxide; Nitrogenii Monoxidum; Nitrogenii Oxidum; Nitrogenium Oxydulatum; Oxid dusný; Óxido nitroso; Oxyde Nitreux; Oxydum Nitrosum; Protoxyde d'Azote; Stickoxydul.

N_2O = 44.01.
CAS — 10024-97-2.
ATC — N01AX13.
ATC Vet — QN01AX13.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of nitrous oxide:
Bulb; Buzz bomb; Cartridges; Fall down; Gas; Going to the dentist; Grocery store high; Hippy crack; Hysteria; Laughing gas; Nang; Nie; Nigh; Nitro; Nitrogen; Nitrous; Noss; Pan; Shoot the breeze; Tanks; Whippets; Wippets.

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

Ph. Eur. 6.2 (Nitrous Oxide). A colourless gas. One vol. measured at a pressure of 101 kPa dissolves, at 20°, in about 1.5 vol. of water. Store liquefied under pressure in suitable containers complying with the legal regulations.
The BP 2008 directs that Nitrous Oxide should be kept in approved metal cylinders which are painted blue and carry a label