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.

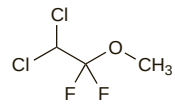
Proprietary Preparations (details are given in Part 3)
Austral.: Brietal; ***Austria:*** Brietal; ***Ger.:*** Brevimytal; ***Israel:*** Brietal†; ***Neth.:*** Brietal; ***Pol.:*** Brietal; ***Rus.:*** Brietal (Бриетал); ***USA:*** Brevital.

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.

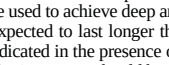
Preparations

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

stating 'Nitrous Oxide'. In addition, 'Nitrous Oxide' or the symbol 'N_2O' should be stencilled in paint on the shoulder of the cylinder.

USP 31 (Nitrous Oxide). A colourless gas, without appreciable odour or taste. One litre at 0° and at a pressure of 760 mmHg weighs about 1.97 g. One volume dissolves in about 1.4 volumes of water at 20° and at a pressure of 760 mmHg; freely soluble in alcohol; soluble in ether and in oils.

Flammability. Nitrous oxide supports combustion.

Storage and supply. Nitrous oxide is supplied compressed in metal cylinders. National standards are usually in operation for the labelling and marking of such cylinders.

Cylinders containing 50% nitrous oxide and 50% oxygen should be protected from the cold to prevent separation of the gases. Cylinders exposed to temperatures lower than −7° should be rolled at room temperature to ensure mixing or alternatively stored horizontally for 24 hours at a temperature of not less than 10°.

Adverse Effects

The main complications after use of nitrous oxide are those due to varying degrees of hypoxia. Prolonged use has been followed by megaloblastic anaemia and peripheral neuropathy. Depression of white cell formation may also occur. There is a risk of increased pressure and volume from the diffusion of nitrous oxide into air-containing cavities. Malignant hyperthermia has been reported rarely.

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

◊ Reviews.

1. Louis-Ferdinand RT. Myelotoxic, neurotoxic and reproductive adverse effects of nitrous oxide. *Adverse Drug React Toxicol Rev* 1994; **13:** 193–206.
2. Donaldson D, Meechan JG. The hazards of chronic exposure to nitrous oxide: an update. *Br Dent J* 1995; **178:** 95–100.
3. Weimann J. Toxicity of nitrous oxide. *Best Pract Res Clin Anaesthesiol* 2003; **17:** 47–61.

Effects on the blood. Nitrous oxide interacts with vitamin B_{12}. This blocks the transmethylation reaction for which vitamin B_{12} is a coenzyme and results in depletion of methionine and tetrahydrofolate. Metabolic consequences have been attributed to depletion of either or both. Interference by nitrous oxide with DNA synthesis prevents production of both leucocytes and red blood cells by the bone marrow. Megaloblastic changes in bone marrow and impaired granulocyte production are found in patients exposed to anaesthetic concentrations of nitrous oxide for 24 hours. In patients with normal bone marrow, stores of mature granulocytes will normally be adequate to prevent leucopenia during exposure for up to 3 days; in patients exposed to nitrous oxide for longer periods of time, leucopenia will develop and exposure for 4 days or longer can result in agranulocytosis. In general, healthy surgical patients can be given nitrous oxide for up to 24 hours without harm. In situations where nitrous oxide is used for more than 24 hours, folinic acid 30 mg twice daily has been given to protect the haematopoietic system. Repeat exposure to nitrous oxide at intervals of less than 3 days will have a cumulative effect on DNA synthesis and megaloblastic marrow changes have been reported following multiple short-term exposure.[1] Depletion of methionine has been implicated in the neurological deficit (see below) seen mainly after chronic use of nitrous oxide. It may also account for the fetotoxicity observed in *rats*, see Pregnancy, under Precautions, below.

1. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B . *Br J Anaesth* 1987; **59:** 3–13.

Effects on the nervous system. Neurological disorders (mainly myeloneuropathies and neuropathies) have occurred in chronic abusers of nitrous oxide.[1,2] Similar effects have been noted after repeated use of nitrous oxide in hospitalised patients. These neurological effects are considered to be due to nitrous oxide-induced methionine deficiency (see Effects on the Blood, above). Psychosis, responsive to treatment with vitamin B_{12}, has also been reported in a patient abusing nitrous oxide.[3]

In patients with undiagnosed subclinical deficiency of vitamin B_{12} (a coenzyme involved in methionine synthesis) neurological manifestations, including those consistent with subacute combined degeneration of the spinal cord, have occurred after a single exposure to nitrous oxide for anaesthesia.[4,5] Acute paralysis, due to degeneration of the spinal cord, has also been reported in a malnourished patient who had been abusing nitrous oxide for 10 days for the self-treatment of a painful sprained ankle.[6]

1. Miller MA, *et al.* Nitrous oxide "whippit" abuse presenting as clinical B12 deficiency and ataxia. *Am J Emerg Med* 2004; **22:** 124.
2. Doran M, *et al.* Toxicity after intermittent inhalation of nitrous oxide for analgesia. *BMJ* 2004; **328:** 1364–5.
3. Sethi NK, *et al.* Nitrous oxide "whippit" abuse presenting with cobalamin responsive psychosis. *J Med Toxicol* 2006; **2:** 71–4.
4. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B -deficient subjects? *JAMA* 1986: **255:** 1605–6.
5. Nestor PJ, Stark RJ. Vitamin B myeloneuropathy precipitated by nitrous oxide anaesthesia. *Med J Aust* 1996; **165:** 174.
6. Cartner M, *et al.* Paralysis caused by "nagging". *Med J Aust* 2007; **187:** 366–7.

Malignant hyperthermia. An 11-year-old girl whose father had died from malignant hyperthermia after anaesthesia developed hyperthermia after anaesthesia with nitrous oxide and oxygen.[1]

1. Ellis FR, *et al.* Malignant hyperpyrexia induced by nitrous oxide and treated with dexamethasone. *BMJ* 1974; **4:** 270–1.

Precautions

Hypoxic anaesthesia is dangerous and nitrous oxide should always be given with at least 20 to 30% oxygen. Nitrous oxide diffuses into gas-filled body cavities and care is essential when using it in patients at risk from such diffusion such as those with abdominal distension, occlusion of the middle ear, pneumothorax, or similar cavities in the pericardium or peritoneum. Care is also required in patients during or after air encephalography. Oxygen should be given during emergence from prolonged anaesthesia with nitrous oxide to prevent diffusion hypoxia where the alveolar oxygen concentration is diminished. See also Precautions for General Anaesthetics, p.1779. In addition to the above precautions, mixtures of equal parts of nitrous oxide and oxygen should not be used for analgesia in patients with head injuries with impairment of consciousness, maxillofacial injuries, decompression sickness, or those heavily sedated.

Nitrous oxide has been subject to abuse.

Abuse. 'Recreational' use or abuse of nitrous oxide has been referred to as "nagging" or "nanging". For some of the resulting adverse effects of nitrous oxide abuse, see Effects on the Nervous System, above.

Driving. A slight but quantified impairment in driving ability was found up to 30 minutes after 15 minutes' inhalation of nitrous oxide/oxygen mixtures.[1]

1. Moyes DG, *et al.* Driving after anaesthetics. *BMJ* 1979; **1:** 1425.

Epidural anaesthesia. Nitrous oxide diffuses into gas-filled body cavities and can increase the size of any air bubbles injected into the epidural space to determine placement of the needle in epidural anaesthesia.[1] This could result in uneven spread of the local anaesthetic and produce inadequate analgesia. The volume of air injected should be limited or another technique used to determine placement of the needle if nitrous oxide is to be given subsequently.

1. Stevens R, *et al.* Fate of extradural air bubbles during inhalation of nitrous oxide. *Br J Anaesth* 1994; **72:** 482P–483P.

Hazard to user. A scavenging system and effective ventilation may be necessary to control the nitrous oxide pollution that can occur when this gas is used for analgesia or anaesthesia. Risk areas include, in addition to operating theatres, delivery rooms and dental surgeries.[1-3] Occupational exposure can lead to serious toxicity with bone-marrow and neurological impairment.[2,3] Reduced fertility has been reported in female dental workers exposed to high concentrations of nitrous oxide;[4] such women also appear to have a higher rate of spontaneous abortion.[5] It has been suggested that nitrous oxide can also affect male fertility;[6] in one study a dose-related increase in the incidence of spontaneous abortion was found in the wives of men with occupational exposure to nitrous oxide.[7]

1. Munley AJ, *et al.* Exposure of midwives to nitrous oxide in four hospitals. *BMJ* 1986; **293:** 1063–4. Correction. *ibid.*; 1280.
2. Sweeney B, *et al.* Toxicity of bone marrow in dentists exposed to nitrous oxide. *BMJ* 1985; **291:** 567–9.
3. Brodsky JB, *et al.* Exposure to nitrous oxide and neurologic disease among dental professionals. *Anesth Analg* 1981; **60:** 297–301.
4. Rowland AS, *et al.* Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* 1992; **327:** 993–7.
5. Rowland AS, *et al.* Nitrous oxide and fertility. *N Engl J Med* 1993; **328:** 284.
6. Brodsky JB. Nitrous oxide and fertility. *N Engl J Med* 1993; **328:** 284–5.
7. Cohen EN, *et al.* Occupational disease in dentistry and chronic exposure to trace anesthetic gases. *J Am Dent Assoc* 1980; **101:** 21–31.

Pregnancy. Nitrous oxide is fetotoxic in *rats*.[1] However, retrospective reviews,[2] and individual case reports[3] have not shown nitrous oxide anaesthesia to be fetotoxic in humans. See also under Hazard to User, above.

1. Lane GA, *et al.* Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. *Science* 1980; **210:** 899–901.
2. Aldridge LM, Tunstall ME. Nitrous oxide and the fetus: a review and the results of a retrospective study of 175 cases of anaesthesia for insertion of Shirodkar suture. *Br J Anaesth* 1986; **58:** 1348–56.
3. Park GR, *et al.* Normal pregnancy following nitrous oxide exposure in the first trimester. *Br J Anaesth* 1986; **58:** 576–7.

Vitamin B_{12} deficiency. For reports of neurological dysfunction associated with the use of nitrous oxide in patients with undiagnosed subclinical vitamin B_{12} deficiency, see Effects on the Nervous System, above.

Interactions

Use of nitrous oxide with an inhalational anaesthetic accelerates the uptake of the latter from the lungs. This phenomenon is known as the *second gas effect*. It is due to the disproportionate absorption of nitrous oxide into the blood resulting in an increased alveolar concentration of the second gas.

The use of high doses of opioids such as fentanyl with nitrous oxide may result in a drop in heart rate and cardiac output.

See also Interactions for General Anaesthetics, p.1779.

Methotrexate. Combined use of nitrous oxide and methotrexate may increase some of the adverse effects of methotrexate therapy, see p.748.

Pharmacokinetics

Nitrous oxide is rapidly absorbed on inhalation. The blood/gas partition coefficient is low and most of the inhaled nitrous oxide is rapidly eliminated unchanged through the lungs though small amounts diffuse through the skin.

Uses and Administration

Nitrous oxide is an anaesthetic given by inhalation. It is a weak anaesthetic with a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) of 110%. It has strong analgesic properties, but produces little muscle relaxation. Nitrous oxide must be given with oxygen, otherwise hypoxia will occur.

Nitrous oxide with oxygen has been used in the induction and maintenance of general anaesthesia (p.1780). However, it is now mainly used as an adjuvant to other inhalational or intravenous anaesthetics, permitting them to be used at significantly lower concentrations. It is also used, with oxygen, in subanaesthetic concentrations for analgesia and sedation in emergency care and obstetric and other painful procedures, including dental procedures (see p.956).

For maintenance of anaesthesia a mixture containing 50 to 66% nitrous oxide with oxygen is commonly used. Recovery is usually rapid from nitrous oxide anaesthesia.

Nitrous oxide 25 to 50% v/v with oxygen is used for analgesia; cylinders containing premixed nitrous oxide 50% v/v and oxygen 50% v/v are available in some countries.

Alcohol withdrawal syndrome. The symptoms of acute alcohol withdrawal (p.1626) are usually managed with benzodiazepines but nitrous oxide has been reported[1] to reduce symptoms when tried in alcohol withdrawal. In mild to moderate cases a single inhalation of up to 20 minutes' duration of a nitrous oxide-oxygen mixture in analgesic doses has been used. However, a more recent controlled trial[2] did not find that treatment with nitrous oxide relieved the symptoms of alcohol withdrawal or reduce cravings.

1. Gillman MA, Lichtigfeld FJ. Analgesic nitrous oxide for alcohol withdrawal: a critical appraisal after 10 years' use. *Postgrad Med J* 1990; **66:** 543–6.
2. Alho H, *et al.* Long-term effects of and physiological responses to nitrous oxide gas treatment during alcohol withdrawal: a double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 2002; **26:** 1816–22.

Pain. A mixture of nitrous oxide 50% v/v and oxygen 50% v/v can provide good relief of pain (see Choice of Analgesic, p.2) without loss of consciousness and is suitable for self-administration. It has been widely used for analgesia and sedation during dental procedures. It is also used for short procedures such as dressing changes,[1,2] venepuncture and biopsy,[3] for pain relief during childbirth,[4] in the management of postoperative pain,[1] as an aid to postoperative physiotherapy, and for acute pain in emergency situations such as in ambulances and in the hospital setting.[3,5,6] Continuous inhalation of nitrous oxide-oxygen has been tried for periods longer than 24 hours in the management of pain in terminal cancer.[7] However, such a practice is not usually otherwise recommended[1] as it may result in megaloblastic bone-marrow changes.

1. Hull CJ. Control of pain in the perioperative period. *Br Med Bull* 1988; **44:** 341–56.
2. Gaukroger PB. Pediatric analgesia: which drug, which dose? *Drugs* 1991; **41:** 52–9.

3. Boulland P, *et al.* Mélange équimolaire oxygène-protoxyde d'azote (MEOPA): rappels théoriques et modalités pratiques d'utilisation. *Ann Fr Anesth Reanim* 2005; **24:** 1305–12.
4. Brownridge P. Treatment options for the relief of pain during childbirth. *Drugs* 1991; **41:** 69–80.
5. O'Sullivan Í, Benger J. Nitrous oxide in emergency medicine. *Emerg Med J* 2003; **20:** 214–17.
6. Faddy SC, Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting? *Emerg Med J* 2005; **22:** 901–8.
7. Fosburg MT, Crone RK. Nitrous oxide analgesia for refractory pain in the terminally ill. *JAMA* 1983; **250:** 511–13.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Pulmomix Forte†.

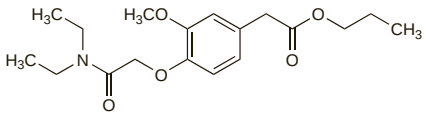
Multi-ingredient: ***Fr.:*** Kalinox; Medimix; ***S.Afr.:*** Entonox; ***UK:*** Entonox; Equanox.

Propanidid *(BAN, USAN, rINN)*

Bayer-1420; FBA-1420; Propanidide; Propanididum; TH-2180; WH-5668. Propyl 4-diethylcarbamoylmethoxy-3-methoxyphenylacetate.

Пропанидид

$C_{18}H_{27}NO_5$ = 337.4.
CAS — 1421-14-3.
ATC — N01AX04.
ATC Vet — QN01AX04.



Profile

Propanidid has been used as an intravenous anaesthetic for rapid induction and for maintenance of general anaesthesia of short duration.

Commercial preparations of propanidid were provided as a liquid in polyethoxylated castor oil. Anaphylactoid reactions associated with the vehicle led to the general withdrawal of propanidid from use.

Porphyria. Propanidid is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Preparations

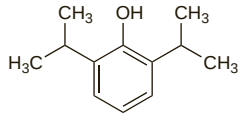
Proprietary Preparations (details are given in Part 3)
Arg.: Progray; ***Mex.:*** Panitol.

Propofol *(BAN, USAN, rINN)*

Disoprofol; ICI-35868; Propofoli; Propofolis; Propofolum. 2,6-Diisopropylphenol; 2,6-Bis(1-methylethyl)phenol.

Пропофол

$C_{12}H_{18}O$ = 178.3.
CAS — 2078-54-8.
ATC — N01AX10.
ATC Vet — QN01AX10.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Propofol). A colourless or very light yellow, clear liquid. Very slightly soluble in water; miscible with hexane and with methyl alcohol. Store under an inert gas. Protect from light.
USP 31 (Propofol). A clear, colourless to slightly yellowish liquid. Very slightly soluble in water; very soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in cyclohexane and in isopropyl alcohol. Store under an inert gas in airtight containers. Protect from light.

Adverse Effects

Early studies with propofol used a preparation formulated with polyethoxylated castor oil. Because of anaphylactoid reactions the preparation was reformulated with a vehicle of soya oil and purified egg phosphatide. Adverse effects with this preparation include pain on injection especially if the injection is into a small vein. Local pain may be reduced by injection into a large vein or by injection of intravenous lidocaine. Apnoea may be frequent; apnoea lasting longer than 60 seconds has been reported to occur in 12% of patients. There are isolated reports of pulmonary oedema. Cardiovascular effects include a reduction in blood pressure and bradycardia. There have been reports of convulsions (sometimes delayed in onset) and involuntary movements. Fever and pancreatitis have occurred very rarely. Discoloration of urine has been reported following prolonged use. Anaphylactoid reactions have been reported. Nausea, vomiting, and headache may occur during recovery.

Children given propofol for prolonged sedation have suffered severe reactions and there have been fatalities, see below.

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

Incidence of adverse effects. In May 1989 the UK CSM commented on the 268 reports of adverse reactions to propofol that it had received since propofol was introduced to the UK market, during which period about 2 million patients had been anaesthetised with the drug.[1] These included reports of:

- seizures (37 cases, 13 in known epileptics)
- involuntary movements (16 cases)
- opisthotonus (10 cases)
- anaphylactic reactions (32 cases)
- cardiac arrest (13 cases)
- delayed recovery (8 cases)

In 1992 the CSM pointed to the risk of **delayed convulsions** with propofol and its particular importance for day-case surgery.[2] While the incidence of convulsions was low (170 reports), 31% of the reports described the convulsions as delayed.

In June 1992 the CSM commented on the dangers of propofol for the **sedation of children** in intensive care,[3] a use for which it is contra-indicated in the UK. (This prohibition does not apply to its use for the sedation of ventilated adults—but see below—or to propofol's use as an *anaesthetic* in children. Sedation in children undergoing surgical and diagnostic procedures is not contra-indicated but is an unlicensed use, and is not recommended.[4])

The CSM reported that there had been 66 reports worldwide of serious adverse effects in children sedated with propofol, and some fatalities had ensued. The children had suffered neurological, cardiac, and renal effects, hyperlipidaemia, hepatomegaly, and metabolic acidosis. Five deaths had been reported to the CSM. These 5 children[5] were aged 4 weeks to 6 years and doses of propofol ranged from 4 to 10.7 mg/kg per hour. They developed metabolic acidosis, bradyarrhythmia, and progressive myocardial failure resistant to treatment. The latter has been reported by others to be significantly associated with the use of long-term, **high-dose** propofol infusions.[6]

Similar adverse effects resulting in fatalities have also been reported in **adult** patients with head injuries who received high doses of propofol infusion (greater than 5 mg/kg per hour) for long-term sedation.[7] The CSM subsequently reminded prescribers that the recommended dose range for sedation (up to 4 mg/kg per hour) should not be exceeded.[8] There has also been a report of death in a patient with a closed head injury who received propofol infusion at an average dose of 4.1 mg/kg per hour.[9]

The Australian Adverse Drug Reactions Advisory Committee[10] stated in December 2004 that it had received a report of lactic acidosis and another of torsade de pointes in adult patients receiving lower doses of propofol infusion, 30 and 100 mg/hour, respectively, for about 24 hours.

1. CSM. Propofol—convulsions, anaphylaxis and delayed recovery from anaesthesia. *Current Problems 26* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024442&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
2. CSM. Propofol and delayed convulsions. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
3. CSM. Serious adverse effects and fatalities in children associated with the use of propofol (Diprivan) for sedation. *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
4. CSM/MCA. Clarification: propofol (Diprivan) infusion contraindication. *Current Problems* 2002; **28:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
5. Parke TJ, *et al.* Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ* 1992; **305:** 613–16.
6. Bray RJ. Propofol infusion syndrome in children. *Paediatr Anaesth* 1998; **8:** 491–9.
7. Cremer OL, *et al.* Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; **357:** 117–18.
8. CSM/MCA. Long term, high dose propofol (Diprivan) infusion. *Current Problems* 2001; **27:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
9. Ernest D, French C. Propofol infusion syndrome: report of an adult fatality. *Anaesth Intensive Care* 2003; **31:** 316–19.
10. Adverse Drug Reactions Advisory Committee (ADRAC). Propofol: danger of prolonged and high infusion rates in ICU. *Aust Adverse Drug React Bull* 2004; **23:** 23–4. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0412.htm (accessed 14/12/04)

Effects on the cardiovascular system. The main effect of propofol on the cardiovascular system is a fall in both systolic and diastolic blood pressure of 20 to 30%. The compensatory tachycardia seen after a fall in arterial pressure with other intravenous anaesthetics is not usually seen with propofol. Propofol can also decrease systemic vascular resistance, cardiac output, myocardial blood flow, and myocardial oxygen consumption. Bradycardia can occur even in those premedicated with antimuscarinics, and can occasionally be profound and lead to asystole.[1] Despite these cardiodepressant effects propofol in doses of 1.5 to 2.5 mg/kg does not generally cause unacceptable haemodynamic changes in patients with a healthy cardiovascular system although concern has been expressed about its safety in cardiac surgical patients.[2]

Patients (especially children) given propofol for continuous sedation in intensive care units have suffered adverse cardiac reactions with bradyarrhythmia, progressive myocardial failure, and death—see above.

1. Tramèr MR, *et al.* Propofol and bradycardia: causation, frequency and severity. *Br J Anaesth* 1997; **78:** 642–51.
2. Ginsberg R, Lippmann M. Haemodynamic effects of propofol. *Br J Anaesth* 1994; **72:** 370–1.

Effects on lipids. Prolonged infusion of propofol may be associated with increases in serum triglycerides. In one patient this was believed to have been the cause of necrotising pancreatitis.[1]

1. Metkus AP, *et al.* A firefighter with pancreatitis. *Lancet* 1996; **348:** 1702.

Effects on mental function. There have been anecdotal reports[1] of disinhibited behaviour or sexually orientated hallucinations associated with the use of propofol, but a study using subanaesthetic doses found no evidence that propofol produced euphoria or other mood changes.[2]

1. Canaday BR. Amorous, disinhibited behaviour associated with propofol. *Clin Pharm* 1993; **12:** 449–51.
2. Whitehead C, *et al.* The subjective effects of low-dose propofol. *Br J Anaesth* 1994; **72** (suppl 1): 89.

Effects on the nervous system. See under Precautions, below.

Effects on respiration. See under Precautions, below.

Hypersensitivity. Anaphylactic reactions associated with polyethoxylated castor oil used in propofol preparations had prompted a change to the use of soya oil and egg phosphatide in the formulation. A group of workers have reported a patient who experienced anaphylactic shock when given the reformulated emulsion.[1] A possible case of anaphylaxis to this formulation has also been reported in a child with allergies to egg and peanut oil.[2]

1. Laxenaire MC, *et al.* Anaphylactic shock due to propofol. *Lancet* 1988; **ii:** 739–40.
2. Hofer KN, *et al.* Possible anaphylaxis after propofol in a child with food allergy. *Ann Pharmacother* 2003; **37:** 398–401.

Infection. Between June 1990 and February 1993 62 cases of postsurgical infections identified in 7 hospitals in the USA were attributed to improper handling of propofol.[1] The infusion was not prepared aseptically and the syringes used in the infusion pumps were reused for several patients. Propofol is formulated as a soybean fat emulsion and the injection contains no antimicrobial preservative although, in the USA, the formulation now contains the microbial-retarding agent, disodium edetate (see under Administration, below). However, either formulation still has the potential to support microbial growth. UK and US licensed product information now warns of the importance of aseptic technique in the preparation and use of propofol. Microbial multiplication did not appear to be clinically significant when propofol infusions were prepared and given using conventional aseptic techniques.[2]

1. Bennett SN, *et al.* Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *N Engl J Med* 1995; **333:** 147–54.
2. Farrington M, *et al.* Do infusions of midazolam and propofol pose an infection risk to critically ill patients? *Br J Anaesth* 1994; **72:** 415–17.

Malignant hyperthermia. From an *in-vitro* study it was concluded that propofol does not trigger malignant hyperthermia.[1] There is a report of the safe use of propofol in 19 patients considered susceptible to malignant hyperthermia.[2]

1. Denborough M, Hopkinson KC. Propofol and malignant hyperpyrexia. *Lancet* 1988; **i:** 191.
2. Harrison GG. Propofol in malignant hyperthermia. *Lancet* 1991; **337:** 503.

Pain on injection. Product information suggests the use of lidocaine or alfentanil to reduce the pain associated with injection of conventional formulations of propofol (see Administration, below); alternatively, the larger veins in the forearm and antecubital fossa can be used. Studies indicate that metoclopramide[1] might also be effective. The pain is thought to be caused by the proportion of the propofol dose that is present in the aqueous rather than the oily phase of the emulsion. It has been suggested[2] that the analgesic effect of lidocaine, and possibly metoclopramide, is due to a pH-lowering effect, causing more propofol to be present in the oily phase, but a study show-