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†.

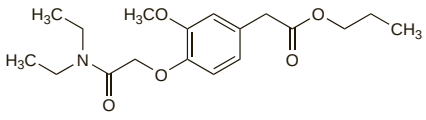
Multi-ingredient: ***Fr.:*** Kalinox; Medimix; ***S.Afr.:*** Entonox; ***UK:*** Entonox; Equanox.

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

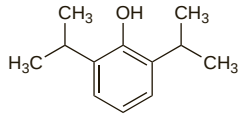
Proprietary Preparations (details are given in Part 3)
Arg.: Progray; ***Mex.:*** Panitol.

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-

ing that lidocaine given by iontophoresis also reduces pain[3] suggests this is not the only mechanism. In another attempt to reduce pain by decreasing the amount of aqueous propofol, a formulation containing a mixture of medium-chain and long-chain triglycerides (*Propofol-Lipuro*), assumed to improve distribution into the lipid phase, has been introduced in a number of countries. However, studies in adults[4] and children[5] suggest that the reduction in pain with the newer formulation is not as great as that achieved by mixing lidocaine with the conventional long-chain formulation.

1. Ganta R, Fee JPH. Pain on injection of propofol: comparison of lignocaine with metoclopramide. *Br J Anaesth* 1992; **69:** 316–17.
2. Eriksson M, *et al.* Effect of lignocaine and pH on propofol-induced pain. *Br J Anaesth* 1997; **78:** 502–6.
3. Sadler PJ, *et al.* Iontophoretically applied lidocaine reduces pain on propofol injection. *Br J Anaesth* 1999; **82:** 432–4.
4. Adam S, *et al.* Propofol-induced injection pain: comparison of a modified propofol emulsion to standard propofol with premixed lidocaine. *Anesth Analg* 2004; **99:** 1076–9.
5. Nyman Y, *et al.* Propofol injection pain in children: a prospective randomized double-blind trial of a new propofol formulation versus propofol with added lidocaine. *Br J Anaesth* 2005; **95:** 222–5.

Urine discoloration. A case report of dark green urine in a 16-year-old during a prolonged infusion of propofol.[1]

1. Bodenham A, *et al.* Propofol infusion and green urine. *Lancet* 1987; **ii:** 740.

Precautions

Propofol should not be given to patients known to be allergic to it. Propofol should be used with caution in patients with hypovolaemia, epilepsy, or lipid metabolism disorders, and in the elderly. Since there have been reports of delayed convulsions associated with the use of propofol it is recommended that special care should be taken when propofol is used for day-case surgery. When used in patients with increased intracranial pressure it should be given slowly to avoid a substantial decrease in mean arterial pressure and a resultant decrease in cerebral perfusion pressure. It is also recommended that propofol should not be used with ECT. Premedication with an antimuscarinic may be advisable since propofol does not cause vagal inhibition.

Propofol is used to provide continuous sedation for ventilated adult patients under intensive care. Account should be taken of increasing the patient's lipid load. If the duration of sedation is in excess of 3 days, lipid concentrations should be monitored. Children aged 16 years or less should not be sedated in this manner with propofol (see Incidence of Adverse Effects, above). Propofol is not recommended for use in obstetrics including caesarean section. See also Precautions for General Anaesthetics, p.1779.

For the need for aseptic handling of propofol see Administration, below.

Abuse. References to the abuse of propofol.

1. Kranioti EF, *et al.* Lethal self administration of propofol (Diprivan): a case report and review of the literature. *Forensic Sci Int* 2007; **167:** 56–8.
2. Wischmeyer PE, *et al.* A survey of propofol abuse in academic anesthesia programs. *Anesth Analg* 2007; **105:** 1066–71.

CNS effects. Epileptic activity was seen[1] on the EEGs of 3 patients given propofol and it was suggested that it might be useful in ECT, but others[2,3] found that the duration of seizures was less with propofol anaesthesia than with methohexital anaesthesia. It has been suggested that propofol should not be used with ECT[4] and this is the advice in UK licensed product information.

Some consider that abnormal movements induced by propofol are not associated with cortical seizure activity.[5,6] These appear to be more frequent with low doses of propofol[6] and can be abolished in children by increasing the induction dose of propofol from 3 to 5 mg/kg.

1. Hodkinson BP, *et al.* Propofol and the electroencephalogram. *Lancet* 1987; **ii:** 1518.
2. Simpson KH, *et al.* Seizure duration after methohexitone or propofol for induction of anaesthesia for electroconvulsive therapy (ECT). *Br J Anaesth* 1987; **59:** 1323P–1324P.
3. Rampton AJ, *et al.* Propofol and electroconvulsive therapy. *Lancet* 1988; **i:** 296–7.
4. Anonymous. Addendum: propofol better avoided with ECT at present. *Drug Ther Bull* 1990; **28:** 72.
5. Borgeat A, *et al.* Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation. *Br J Anaesth* 1993; **70:** 459–61.
6. Borgeat A, *et al.* Propofol and epilepsy: time to clarify. *Anesth Analg* 1994; **78:** 198–9.

Impaired respiration. The manufacturer has stated[1] that some patients who have received propofol for sedation in regional anaesthesia have experienced bradypnoea or hypoxaemia, or both. A reduction in oxygen saturation has also been noted in other patients sedated for endoscopy.[2] UK product information therefore recommends that oxygen saturation should be monitored and that oxygen supplementation should be readily available.

1. Arnold BDC. Sedation with propofol during regional anaesthesia. *Br J Anaesth* 1993; **70:** 112.
2. Patterson KW, *et al.* Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam. *Br J Anaesth* 1991; **67:** 108–11.

Interactions

The use of propofol with other CNS depressants, including those used in premedication, may increase the sedative, anaesthetic, and cardiorespiratory depressant effects of propofol. It is recommended that propofol is given after opioids so that the dose of propofol can be carefully titrated against the response. The dosage of propofol should be reduced if used with nitrous oxide or halogenated anaesthetics. Although propofol does not potentiate the effects of neuromuscular blockers, bradycardia and asystole have occurred after use of propofol with atracurium or suxamethonium (but see under Adverse Effects, above for the effects of propofol itself on the cardiovascular system).

See also Interactions of General Anaesthetics, p.1779.

Benzodiazepines. Propofol and *midazolam* have been reported to act synergistically.[1-3]

1. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; **67:** 539–45.
2. McClune S, *et al.* Synergistic interaction between midazolam and propofol. *Br J Anaesth* 1992; **69:** 240–5.
3. Teh J, *et al.* Pharmacokinetic interactions between midazolam and propofol: an infusion study. *Br J Anaesth* 1994; **72:** 62–5.

Clonidine. Premedication with clonidine has been reported[1] to reduce intraoperative requirements of propofol.

1. Guglielminotti J, *et al.* Effects of premedication on dose requirements for propofol: comparison of clonidine and hydroxyzine. *Br J Anaesth* 1998; **80:** 733–6.

Gastrointestinal drugs. The dose of propofol required for induction is reduced in patients given *metoclopramide*.[1]

1. Page VJ, Chhipa JH. Metoclopramide reduces the induction dose of propofol. *Acta Anaesthesiol Scand* 1997; **41:** 256–9.

General anaesthetics. Use with *halothane* or *isoflurane* has been reported to increase serum concentrations of propofol.[1] Synergy has been reported between propofol and *etomidate*.[2]

1. Grundmann U, *et al.* Propofol and volatile anaesthetics. *Br J Anaesth* 1994; **72** (suppl 1): 88.
2. Drummond GB, Cairns DT. Do propofol and etomidate interact kinetically during induction of anaesthesia? *Br J Anaesth* 1994; **73:** 272P.

Local anaesthetics. A reduction in the amount of propofol required to provide adequate hypnosis[1] or sedation[2] has been reported after *bupivacaine*[1] or *lidocaine*.[1,2] However, lidocaine is often added to propofol emulsions to reduce the pain of injection, see under Administration, below.

1. Ben-Shlomo I, *et al.* Hypnotic effect of iv propofol is enhanced by im administration of either lignocaine or bupivacaine. *Br J Anaesth* 1997; **78:** 375–7.
2. Mallick A, *et al.* Local anaesthesia to the airway reduces sedation requirements in patients undergoing artificial ventilation. *Br J Anaesth* 1996; **77:** 731–4.

Opioids. In a study mean blood concentrations of propofol were higher in patients pretreated with *fentanyl* compared with patients maintained only on nitrous oxide.[1] However, others[2] were unable to confirm this interaction.

1. Cockshott ID, *et al.* Pharmacokinetics of propofol in female patients. *Br J Anaesth* 1987; **59**: 1103–10.
2. Dixon J, *et al.* Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol. *Br J Anaesth* 1990; **64:** 142–7.

Pharmacokinetics

The pharmacokinetics of propofol are best described by a 3-compartment model. After a single bolus dose, two distribution phases are seen. The first phase has a half-life of 2 to 4 minutes. This is followed by a slow distribution phase with a half-life of 30 to 60 minutes. Significant metabolism of propofol occurs during the second phase. The termination of anaesthetic effect after a single intravenous bolus or maintenance infusion is due to extensive redistribution from the brain to other tissues and to metabolic clearance. Propofol is over 95% bound to plasma proteins. It undergoes extensive hepatic metabolism to conjugates which are eliminated in the urine. The terminal half-life ranges from 3 to 12 hours; with prolonged use, the terminal half-life may be longer. The pharmacokinetics of propofol do not appear to be altered by gender, chronic hepatic cirrhosis, or chronic renal impairment. Propofol crosses the placental barrier and is distributed into breast milk.

◊ References.

1. Saint-Maurice C, *et al.* Pharmacokinetics of propofol in young children after a single dose. *Br J Anaesth* 1989; **63:** 667–70.
2. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacokinet* 1989; **17:** 308–26.
3. Gin T, *et al.* Pharmacokinetics of propofol in women undergoing elective caesarean section. *Br J Anaesth* 1990; **64:** 148–53.
4. Servin F, *et al.* Pharmacokinetics of propofol infusions in patients with cirrhosis. *Br J Anaesth* 1990; **65:** 177–83.
5. Jones RDM, *et al.* Pharmacokinetics of propofol in children. *Br J Anaesth* 1990; **65:** 661–7.
6. Morgan DJ, *et al.* Pharmacokinetics of propofol when given by intravenous infusion. *Br J Clin Pharmacol* 1990; **30:** 144–8.
7. Gin T, *et al.* Disposition of propofol at caesarean section and in the postpartum period. *Br J Anaesth* 1991; **67:** 49–53.
8. Bailie GR, *et al.* Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. *Br J Anaesth* 1992; **68:** 486–91.
9. Altmayer P, *et al.* Propofol binding in human blood. *Br J Anaesth* 1994; **72** (suppl 1): 86.
10. Oei-Lim VLB, *et al.* Pharmacokinetics of propofol during conscious sedation using target-controlled infusion in anxious patients undergoing dental treatment. *Br J Anaesth* 1998; **80:** 324–31.
11. Dawidowicz AL, *et al.* Free and bound propofol concentrations in human cerebrospinal fluid. *Br J Clin Pharmacol* 2003; **56:** 545–50.
12. Hiraoka H, *et al.* Kidneys contribute to the extrahepatic clearance of propofol in humans, but not lungs and brain. *Br J Clin Pharmacol* 2005; **60:** 176–82.
13. Nitsun M, *et al.* Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; **79:** 549–57.

Uses and Administration

Propofol is a short-acting anaesthetic given intravenously for the induction and maintenance of general anaesthesia (p.1780). It is also used for sedation (p.956) in adult patients undergoing diagnostic procedures, in those undergoing surgery with local or regional anaesthesia, and in ventilated adult patients under intensive care. When used for anaesthesia, induction is rapid, as is recovery. Propofol has no analgesic activity and supplementary analgesia may be required.

Propofol is available as a 1 or 2% emulsion. The 1% emulsion may be given by intravenous injection or infusion, but the 2% emulsion is for infusion only. Infusions and injections should be prepared using aseptic techniques, see Administration, below.

Induction of **anaesthesia** is generally carried out by giving propofol by injection or infusion at a rate of 40 mg every 10 seconds; a rate of 20 mg every 10 seconds may be used in high-risk patients including elderly, neurosurgical, and debilitated patients. Most *adults* under 55 years of age can be anaesthetised by a dose of 1.5 to 2.5 mg/kg; high-risk patients usually require a dose of 1 to 1.5 mg/kg.

When used for maintenance propofol is infused at a rate of between 4 to 12 mg/kg per hour (or 3 to 6 mg/kg per hour for elderly and debilitated patients); alternatively intermittent bolus injections of 20 to 50 mg may be given; rapid bolus doses should be avoided in high-risk patients.

A novel delivery system is also available for the induction and maintenance of anaesthesia in adults. The Diprifusor target-controlled infusion system allows the speed of induction and depth of anaesthesia to be controlled by specifying target blood concentrations of propofol. Initial target concentrations for induction range from 4 to 8 micrograms/mL for patients under 55 years of age; lower initial target concentrations should be used in older and debilitated patients and should be increased gradually thereafter in steps of 0.5 to 1 microgram/mL at intervals of 1 minute to achieve a gradual induction of anaesthesia. Target concentrations for maintenance are 3 to 6 micrograms/mL.

In the UK, *children* aged 1 month and over may be given propofol for the induction and maintenance of anaesthesia. The dose should be adjusted for weight and age and administered slowly until the onset of anaesthesia. Most children aged over 8 years require an induction dose of 2.5 mg/kg; younger children may require a higher dose within the range of 2.5 to 4 mg/kg. Doses of 9 to 15 mg/kg per hour by intravenous infusion or intermittent bolus injections are suitable for

maintenance. The 2% emulsion formulation of propofol should only be used in children aged over 3 years. In the USA, children aged 3 years and over may be given propofol for the induction of anaesthesia; those aged 2 months and over may receive propofol for maintenance of anaesthesia. Doses are similar to those used in the UK.

For **sedation** in diagnostic and surgical procedures in *adults* an initial infusion of 6 to 9 mg/kg per hour may be given for 3 to 5 minutes; alternatively 0.5 to 1 mg/kg may be injected slowly over 1 to 5 minutes. An infusion of 1.5 to 4.5 mg/kg per hour may be used for maintenance of sedation. High-risk patients usually require a 20% reduction in the maintenance dose.

For the sedation of ventilated adults propofol can be given by intravenous infusion in a dose of 0.3 to 4 mg/kg per hour. If the duration of sedation is in excess of 3 days, lipid concentrations should be monitored.

Propofol is contra-indicated for sedation in *children* aged 16 years or less.

◊ Reviews.

1. Langley MS, Heel RC. Propofol: a review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. *Drugs* 1988; **35:** 334–72.
2. Larijani GE, *et al.* Clinical pharmacology of propofol: an intravenous anesthetic agent. *DICP Ann Pharmacother* 1989; **23:** 743–9.
3. Bryson HM, *et al.* Propofol: an update of its use in anaesthesia and conscious sedation. *Drugs* 1995; **50:** 513–59.
4. Fulton B, Sorkin EM. Propofol: an overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. *Drugs* 1995; **50:** 636–57.

Administration. Propofol is formulated as an oil-in-water emulsion for injection. Strict aseptic techniques must be maintained when handling propofol as, in some countries (including the UK), the parenteral product contains no antimicrobial preservatives and the vehicle can support rapid growth of microorganisms. Aseptic techniques must also be applied to formulations, such as those available in the USA, that contain the microbial-retarding agent disodium edetate, as microbial growth is still possible. An emulsion containing 1% of propofol may be diluted with glucose 5% immediately before use but it should not be diluted to a concentration of less than 2 mg/mL. An emulsion containing 2 % of propofol should not be diluted. The use of a 5-micron filter needle to withdraw propofol emulsion from an ampoule does not cause significant loss of drug.[1] A reduction in concentration of propofol can occur when the diluted emulsion is run through polyvinyl chloride intravenous tubing.[1] Propofol 1 or 2% may be given into a running intravenous infusion through a Y-site close to the injection site and under these circumstances it is compatible with glucose 5%, sodium chloride 0.9%, and glucose with sodium chloride intravenous solutions.

Because injection of propofol can be painful, it may be mixed with alfentanil or lidocaine before use. UK licensed product information advises mixing lidocaine 0.5 or 1% injection (without preservatives) in a ratio of 1:20 with propofol injection 1% immediately before use; similarly, alfentanil injection 500 micrograms/mL may be mixed in a ratio of 1:20 to 1:50 with propofol 1%. It advises against mixing the 2% emulsion of propofol with other drugs.

1. Bailey LC, *et al.* Effect of syringe filter and I.V. administration set on delivery of propofol emulsion. *Am J Hosp Pharm* 1991; **48:** 2627–30.

Nausea and vomiting. It is commonly believed that propofol is associated with less postoperative nausea and vomiting than some other anaesthetics.[1,2] However, a review[3] concluded that any reduction in nausea and vomiting when using propofol anaesthesia may be short term and clinically relevant only for maintenance anaesthesia in procedures with an inherent risk of nausea and vomiting.

There are also reports[4-8] indicating that propofol may have some intrinsic antiemetic action when used in sub-hypnotic doses although a study[9] of the effect of sedative and non-sedative (subhypnotic) doses against apomorphine-induced vomiting has suggested that any antiemetic effect is probably due to sedation.

1. McCollum JSC, *et al.* The antiemetic action of propofol. *Anaesthesia* 1988; **43:** 239–40.
2. Woodward WM, *et al.* Comparison of post-operative nausea and vomiting after thiopentone/isoflurane or propofol infusion for 'bat-ear' correction in children. *Br J Anaesth* 1994; **72** (suppl 1): 92.
3. Tramèr M, *et al.* Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. *Br J Anaesth* 1997: **78:** 247–55.
4. Borgeat A, *et al.* Adjuvant propofol for refractory cisplatin-associated nausea and vomiting. *Lancet* 1992; **340:** 679–80.
5. Törn K, *et al.* Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. *Br J Anaesth* 1994; **73:** 411–12.
6. Borgeat A, *et al.* Adjuvant propofol enables better control of nausea and emesis secondary to chemotherapy for breast cancer. *Can J Anaesth* 1994; **41:** 1117–19.
7. Ewalenko P, *et al.* Antiemetic effect of subhypnotic doses of propofol after thyroidectomy. *Br J Anaesth* 1996; **77:** 463–7.
8. Gan TJ, *et al.* Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. *Anesthesiology* 1997; **87:**779–84.
9. Thörn S-E, *et al.* Propofol effects upon apomorphine induced vomiting. *Br J Anaesth* 1994; **72** (suppl 1): 90.

Pruritus. Propofol is one of many drugs that have been tried in the management of pruritus (p.1582). Sub-hypnotic doses of propofol appear to have an antipruritic action. It has produced conflicting results in the treatment and prophylaxis of pruritus associated with epidural and intrathecal morphine[1-4] although it appears to be able to relieve cholestasis-associated pruritus.[5] It has been suggested that propofol might act by suppression of the spinal transmission of pruritic signals.

1. Borgeat A, *et al.* Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology* 1992; **76:** 510–12.
2. Törn K, *et al.* Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. *Br J Anaesth* 1994; **73:** 411–12.
3. Warwick JP, *et al.* The effect of subhypnotic doses of propofol on the incidence of pruritus after intrathecal morphine for caesarean section. *Anaesthesia* 1997; **52:** 270–5.
4. Beilin Y, *et al.* Subhypnotic doses of propofol do not relieve pruritus induced by intrathecal morphine after cesarean section. *Anesth Analg* 1998; **86:** 310–3.
5. Borgeat A, *et al.* Subhypnotic doses of propofol relieve pruritus associated with liver disease. *Gastroenterology* 1993; **104:** 244–7.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p.469). A short-acting barbiturate such as thiopental is usually used. Propofol is also used[1-4] although good controlled studies of its effectiveness are lacking; in addition, it has caused seizures when used in anaesthesia (see CNS Effects, under Precautions, above) and should be given with caution to patients with epilepsy. The risks of respiratory and cerebral depression, as well as of lipid overload with prolonged therapy, should also be borne in mind. It may induce involuntary movements and care is required to distinguish these from seizures. Nonetheless, it has a rapid onset of action and its effects are maintained while the infusion is maintained; recovery is rapid on stopping. A suggested regimen for management[2] is an initial intravenous bolus of 1 to 2 mg/kg followed by an infusion of 2 to 10 mg/kg per hour guided by EEG monitoring. The dose should be gradually reduced and the infusion tapered 12 hours after seizure activity is halted. Lower doses should be used in the elderly. A study[5] comparing propofol with high-dose barbiturates in patients with refractory status epilepticus concluded that recurrent seizures were common when propofol infusions were suddenly stopped but not when the infusions were gradually tapered.

1. Brown LA, Levin GM. Role of propofol in refractory status epilepticus. *Ann Pharmacother* 1998; **32:** 1053–9.
2. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998; **338:** 970–6.
3. Marik PE, Varon J. The management of status epilepticus. *Chest* 2004; **126:** 582–91.
4. van Gestel JPJ, *et al.*Propofol and thiopental for refractory status epilepticus in children. *Neurology* 2005; **65:** 591–2.
5. Stecker MM, *et al.* Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia* 1998; **39:** 18–26.

Tetanus. Sedation with propofol has been used in the treatment of tetanus (p.1901) to control spasms and rigidity.

Preparations

BP 2008: Propofol Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Diprivan; Fresofol; Gobbifol; Oleo-Lax; Recofol†; ***Austral.:*** Diprivan; Recofol; ***Austria:*** Diprivan; ***Belg.:*** Diprivan; ***Braz.:*** Bioprofol†; Diprivan; Porpovan; Profolen; Pronest†; Propoabbott; Propovan; Provive†; ***Canad.:*** Diprivan; ***Chile:*** Diprivan; ***Cz.:*** Diprivan; Recofol; ***Denm.:*** Diprivan; ***Fin.:*** Diprivan†; Recofol; ***Fr.:*** Diprivan; ***Ger.:*** Disoprivan; Recofol†; ***Gr.:*** Diprivan; Recofol; ***Hong Kong:*** Diprivan; ***Hung.:*** Diprivan; Recofol†; ***India:*** Diprivan; ***Indon.:*** Diprivan; Fresofol; Recofol; Safol; ***Irl.:*** Diprivan; ***Israel:*** Diprivan; Diprofol; Recofol; ***Ital.:*** Diprivan; ***Malaysia:*** Diprivan; Fresofol; ***Mex.:*** Cryotol; Diprivan; Fresofol; Indufol; Propocam†; Provive; Recofol; ***Neth.:*** Diprivan; Recofol; ***Norw.:*** Diprivan; Recofol†; ***NZ:*** Diprivan; Fresofol; Recofol†; ***Philipp.:*** Diprivan; Fresofol; ***Pol.:*** Abbofol; Diprivan; Plofed; ***Port.:*** Diprivan; Recofol†; ***Rus.:*** Diprivan (Дипривaн); Recofol (Рекофол); ***S.Afr.:*** Diprivan; Recofol; ***Singapore:*** Diprivan; Pofol†; Recofol; ***Spain:*** Diprivan; Ivofol; Recofol; ***Swed.:*** Diprivan; Propolipid; Recofol; ***Switz.:*** Ansiven†; Disoprivan; Recofol; ***Thai.:*** Diprivan†; Fresofol; Pofol; Recofol; ***Turk.:*** Diprivan; Pofol; Recofol; ***UK:*** Diprivan; Propoven; ***USA:*** Diprivan; ***Venez.:*** Anespro; Diprivan; Profol.

Sevoflurane *(BAN, USAN, rINN)*

BAX-3084; MR-654; Sevofluraani; Sevofluran; Sévoflurane; Sevoflurano; Sevofluranum. Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether; 1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)-propane.

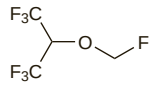
Севофлуран

$C_4H_3F_7O$ = 200.1.

CAS — 28523-86-6.

ATC — N01AB08.

ATC Vet — QN01AB08.



Pharmacopoeias. In *US.*

USP 31 (Sevoflurane). A clear, colourless, volatile, non-flammable liquid. Slightly soluble in water; miscible with alcohol, with chloroform, and with ether. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

As with other halogenated anaesthetics sevoflurane may cause cardiorespiratory depression, hypotension, and malignant hyperthermia. However, the effects of sevoflurane on heart rate have only been seen at higher concentrations and it appears to have little effect on heart rhythm in comparison to other halogenated anaesthetics. Sevoflurane appears to sensitise the myocardium to sympathomimetics to a lesser extent than halothane or enflurane. Other effects seen with sevoflurane include agitation, especially in children, laryngospasm, and increased cough and salivation. Acute renal failure has also been noted. Shivering, nausea, and vomiting have been reported in the postoperative period.

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

Effects on the cardiovascular system. The cardiovascular effects of sevoflurane are similar to those of isoflurane (see p.1786) but it does not produce coronary steal. Also sevoflurane produces less tachycardia than isoflurane suggesting that it may be preferable in those predisposed to myocardial ischaemia.

Effects on the kidneys. Investigations[1] of the nephrotoxic potential of sevoflurane have found no evidence of renal function impairment despite peak plasma-fluoride ion concentrations greater than 50 nanomol/mL (a level considered to be nephrotoxic) being recorded in some patients at the end of sevoflurane anaesthesia,[2] and clinical experience would tend to support this.[3] The lack of renal toxicity with sevoflurane may be due to low concentrations of intrarenally generated fluoride ions;[4] in comparison, methoxyflurane defluorination in the kidney is much greater and may contribute to its known nephrotoxicity.

Compound A, formed by the breakdown of sevoflurane by carbon dioxide absorbents (see under Precautions, below), is nephrotoxic in *rats.*[1] However, studies in humans undergoing sevoflurane anaesthesia have detected no renal impairment postoperatively even when compound A was detected in the anaesthetic circuits.

1. Malan TP. Sevoflurane and renal function. *Anesth Analg* 1995; **81:** S39–S45.
2. Kobayashi Y, *et al.* Serum and urinary inorganic fluoride concentrations after prolonged inhalation of sevoflurane in humans. *Anesth Analg* 1992; **74:** 753–7.
3. Gentz BA, Malan TP. Renal toxicity with sevoflurane: a storm in a teacup? *Drugs* 2001; **61:** 2155–62.
4. Kharasch ED, *et al.* Human kidney methoxyflurane and sevoflurane metabolism: intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. *Anesthesiology* 1995; **82:** 689–99.

Effects on the liver. There have been signs of hepatotoxicity in *animal* studies but in studies in humans, markers for hepatocellular dysfunction were no greater after sevoflurane anaesthesia than those after isoflurane.[1] UK licensed product information also states that there have only been rare postmarketing reports of hepatic failure and necrosis for which causality has not been established. The metabolism of sevoflurane differs from other halogenated anaesthetics in such a way that metabolites implicated in liver toxicity are not formed (see Pharmacokinetics, below).

1. Darling JR, *et al.* Comparison of the effects of sevoflurane with those of isoflurane on hepatic glutathione-S-transferase concentrations after body surface surgery. *Br J Anaesth* 1994; **73:** 268P.

Effects on the nervous system. Clonic and tonic seizure-like movements of the extremities have been reported[1] in a child during induction of anaesthesia using sevoflurane. It was considered that this might have been a result of seizure activity in the CNS or due to myoclonus of the extremities.

1. Adachi M, *et al.* Seizure-like movements during induction of anaesthesia with sevoflurane. *Br J Anaesth* 1992; **68:** 214–15.

Precautions

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with sevoflurane. Although the effects of sevoflurane on cerebral pressure are minimal in normal patients, safety in those