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.

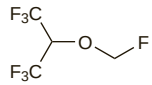
Севофлуран

$C_4H_3F_7O$ = 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

with raised intracranial pressure has not been established and therefore sevoflurane should be used with caution. As emergence and recovery are particularly rapid with sevoflurane patients may require early postoperative pain relief.

See also Precautions for General Anaesthetics, p.1779.

Carbon dioxide absorbents. The breakdown of sevoflurane by carbon dioxide absorbents (such as soda lime) results in the formation of pentafluoroisopropenyl fluoromethyl ether (PIFE; compound A), and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether (PMFE; Compound B). Compound A has been shown to be nephrotoxic in *rats* (see under Effects on the Kidneys, above). Even during short exposure times, as required for induction of anaesthesia, use of moist soda lime is important to minimise sevoflurane degradation, which is aggravated by a high potassium hydroxide content of the soda lime.[1]

Licensed product information states that increased amounts of compound A may be formed if barium hydroxide lime is used as a carbon dioxide absorbent rather than soda lime.

The use of desiccated carbon dioxide absorbents with sevoflurane has also been associated with rare cases of extreme heat and smoke or fire developing in the anaesthetic apparatus.[2]

1. Funk W, *et al*. Dry soda lime markedly degrades sevoflurane during simulated inhalation induction. *Br J Anaesth* 1999; **82:** 193–8.
2. Abbott Laboratories, Canada. Important safety information regarding the use of Sevorane AF (sevoflurane) in conjunction with anesthesia machines. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/sevorane_hpc-cps-eng.pdf (accessed 08/08/08)

Interactions

Care is advised if adrenaline or other sympathomimetics are given during sevoflurane anaesthesia. The effects of competitive neuromuscular blockers such as atracurium are enhanced by sevoflurane (see p.1904). The metabolism, and hence toxicity, of sevoflurane may be increased by drugs or compounds that induce cytochrome P450 isoenzyme CYP2E1 including isoniazid and alcohol.

See also Interactions of General Anaesthetics, p.1779.

◊ References.

1. Dale O. Drug interactions in anaesthesia: focus on desflurane and sevoflurane. *Baillieres Clin Anaesthesiol* 1995; **9:** 105–17.

Pharmacokinetics

Sevoflurane is absorbed on inhalation. The blood/gas partition coefficient is low. Up to 5% of the absorbed dose of sevoflurane is metabolised in the liver by the cytochrome P450 isoenzyme CYP2E1 and defluorinated to its major metabolites hexafluoroisopropanol (HFIP), inorganic fluoride, and carbon dioxide. HFIP is rapidly conjugated with glucuronic acid and eliminated in the urine. Sevoflurane crosses the placenta.

◊ References.

1. Behne M, *et al*. Clinical pharmacokinetics of sevoflurane. *Clin Pharmacokinet* 1999; **36:** 13–26.

Uses and Administration

Sevoflurane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) ranging from 1.4% in the elderly to 3.3% in neonates. It is used for the induction and maintenance of general anaesthesia (p.1780). It is non-flammable. Sevoflurane has a nonpungent odour and does not cause respiratory irritation. It also has muscle relaxant properties which may be sufficient for some surgical procedures to be performed without a neuromuscular blocker. However, it possesses no analgesic properties.

Sevoflurane is given using a calibrated vaporiser. For induction, sevoflurane is given in concentrations of up to 5% v/v in adults, with oxygen or a mixture of oxygen and nitrous oxide. Concentrations of up to 7% v/v may be used in children. A short-acting barbiturate or other intravenous induction agent may be given before inhaling sevoflurane. Induction with sevoflurane is rapid (surgical anaesthesia in less than 2 minutes) and smooth because of its nonpungent odour. Maintenance of anaesthesia is achieved with a concentration of 0.5 to 3% v/v with or without nitrous oxide.

◊ Reviews.

1. Patel SS, Goa KL. Sevoflurane: a review of its pharmacodynamic and pharmacokinetic properties and its clinical use in general anaesthesia. *Drugs* 1996; **51:** 658–700.
2. Smith I, *et al*. Sevoflurane—a long-awaited volatile anaesthetic. *Br J Anaesth* 1996; **76:** 435–45.
3. Grounds RM, Newman PJ. Sevoflurane. *Br J Hosp Med* 1997; **57:** 43–6.
4. Goa KL, *et al*. Sevoflurane in paediatric anaesthesia: a review. *Paediatr Drugs* 1999; **1:** 127–53.
5. Ghatge S, *et al*. Sevoflurane: an ideal agent for adult day-case anesthesia? *Acta Anaesthesiol Scand* 2003; **47:** 917–31.
6. Sakai EM, *et al*. Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; **25:** 1773–88.

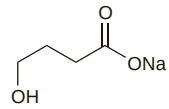
Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Eraldin; Sevorane; ***Austral.:*** Sevorane; ***Austria:*** Sevorane; ***Belg.:*** Sevoranet†; ***Braz.:*** Sevocris; Sevorane; ***Canad.:*** Sevorane; ***Chile:*** Sevorane; ***Cz.:*** Sevorane; ***Denm.:*** Sevorane; ***Fin.:*** Sevorane; ***Fr.:*** Sevorane; ***Ger.:*** Sevorane; ***Gr.:*** Sevorane; ***Hong Kong:*** Sevorane; ***Hung.:*** Sevorane; ***Indon.:*** Sevorane; ***Irl.:*** Sevorane; ***Israel:*** Sevorane; ***Ital.:*** Sevorane; ***Malaysia:*** Sevorane; ***Mex.:*** Sevorane; ***Neth.:*** Sevorane; ***Norw.:*** Sevorane; ***NZ:*** Sevorane; ***Philipp.:*** Sevorane; ***Pol.:*** Sevorane; ***Port.:*** Sevorane; ***Rus.:*** Sevoran (Севоран); ***S.Afr.:*** Ultane; ***Singapore:*** Sevorane; ***Spain:*** Sevorane; ***Swed.:*** Sevorane; ***Switz.:*** Sevorane; ***Thai.:*** Sevorane; ***Turk.:*** Sevorane; ***USA:*** Sojourn; Ultane; ***Venez.:*** Sevorane.

Sodium Oxybate *(USAN)*

NSC-84223; Oxibato sódico; Sodium Gamma-hydroxybutyrate; Wy-3478. Sodium 4-hydroxybutyrate.

$C_4H_7NaO_3$ = 126.1.
CAS — 502-85-2.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of sodium oxybate or gamma-hydroxybutyrate:
Blue nitro; Blue verve; Caps; Cherry Meth; Date rape drug; Drogue Du Cambriolage Sexuel Parfait; Easy lay; Everclear; EZLay; Fantasy; G; Gamma Oh; Gamma-OH; GBH; Georgia home boy; GHB; Goop; Great hormones at bedtime; Grievous bodily harm; G-riffic; Jib; Liquid E; Liquid ecstacy; Liquid ecstasy; Liquid G; Liquid X; Organic quaalude; Salty water; Scoop; Sleep; Sleep-500; Soap; Somatomax; Somatomax PM; Vita-G; Water.

Pharmacopoeias. In *Chin.*

Adverse Effects

When used in general anaesthesia adverse effects with sodium oxybate include abnormal muscle movements during the induction period and nausea and vomiting. Occasional emergence delirium has been reported. Bradycardia frequently occurs. Respiration may be slowed and hypokalaemia has been reported.

The most common adverse reactions seen in patients taking sodium oxybate orally for the management of narcolepsy are dizziness, headache, and, particularly in women, nausea. Other common reactions include anorexia, vomiting, diarrhoea, peripheral oedema, abnormal dreams and nightmares, sleepwalking, confusion, depression, anxiety, insomnia, paraesthesia, somnolence, tremor, amnesia, blurred vision, sweating, muscle cramps, nocturnal enuresis, urinary incontinence, asthenia, and fatigue. Blood pressure may also be increased. Psychosis, convulsions, hallucinations, agitation, hypersensitivity, and faecal incontinence are less common; rarely, respiratory depression has been reported.

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

Effects on electrolyte balance. A report of severe metabolic disorders occurring during therapy with sodium oxybate and tetracosactide in 4 patients with severe head injuries.[1] The disorders consisted of hypernatraemia, hypokalaemia, and metabolic acidosis.

1. Béal JL, *et al*. Troubles métaboliques induits par l'association gamma-hydroxy butyrate de sodium et tétracosactide chez le traumatisé crânien. *Therapie* 1983; **38:** 569–71.

Precautions

In general anaesthesia, sodium oxybate should not be given to patients with severe hypertension, bradycardia, conditions associated with defects of cardiac conduction, epilepsy, eclampsia, renal impairment, or alcohol abuse.

Treatment with oral sodium oxybate is contra-indicated in patients with succinic semialdehyde dehydrogenase deficiency, an enzyme involved in its metabolism to succinic acid. Its use is also contra-indicated in patients with epilepsy as safety and efficacy have not been established; convulsions have been reported with sodium oxybate use.

Patients with a history of depression or suicide attempt should be carefully monitored for depressive symptoms while taking sodium oxybate. The high sodium content of sodium oxybate (0.75 g of sodium in a 4.5 g daily dose) should be considered in patients with heart failure, hypertension, or impaired renal function.

Rebound symptoms with an increased frequency of cataplexy may be seen when sodium oxybate is stopped. There has also been rare reports of withdrawal symptoms such as insomnia, headache, dizziness, anxiety, hallucinations, and psychotic disorders following the illicit use of sodium oxybate (see Abuse, below).

See also Precautions for General Anaesthetics, p.1779.

Abuse. Reports[1] of acute poisoning with sodium oxybate following illicit use led the FDA to issue warnings[2] about its potential for abuse. It is usually supplied illicitly as the sodium salt under a variety of names (see above) and has been promoted for body building, weight loss, as a psychedelic substance, and as a sleep aid. Adverse effects include vomiting, drowsiness, amnesia, hypotonia, vertigo, respiratory depression, and involuntary movements. Seizure-like activity, bradycardia, hypotension, and respiratory arrest have also been reported. Resolution of symptoms occurs spontaneously over 2 to 96 hours. However, some patients have required hospitalisation and respiratory support and deaths have been reported in several countries.[3-5] Severity of symptoms depends on the dose of sodium oxybate and the presence of other drugs such as alcohol, benzodiazepines, cannabis, or amfetamines. Prolonged use of large doses may lead to a withdrawal syndrome on discontinuation.[6-8]

There is also a report of CNS depression after ingestion of a chemical derivative, gamma-butyrolactone (GBL).[9] Another derivative, 1,4-butanediol is abused similarly.[7] Withdrawal symptoms have also been associated with discontinuation of these 2 substances in abusers.[8]

1. CDC. Multistate outbreak of poisonings associated with illicit use of gamma hydroxy butyrate. *JAMA* 1991; **265:** 447–8.
2. FDA. Warning about GHB. *JAMA* 1991; **265:** 1802.
3. Anonymous. GBH death indicates increasing problem. *Pharm J* 1996; **256:** 441.
4. CDC. Gamma hydroxy butyrate use—New York and Texas, 1995–1996. *JAMA* 1997; **277:** 1511.
5. Caldicott DGE, *et al*. Fatalities associated with the use of γ-hydroxybutyrate and its analogues in Australasia. *Med J Aust* 2004; **181:** 310–13.
6. Galloway GP, *et al*. Physical dependence on sodium oxybate. *Lancet* 1994; **343:** 57.
7. Rodgers J, *et al*. Liquid ecstasy: a new kid on the dance floor. *Br J Psychiatry* 2004; **184:** 104–6.
8. Wojtowicz JM, *et al*. Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *CJEM* 2008; **10:** 69–74.
9. LoVecchio F, *et al*. Butyrolactone-induced central nervous system depression after ingestion of RenewTrient, a "dietary supplement". *N Engl J Med* 1998; **339:** 847–8.

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

Interactions

In anaesthesia, sodium oxybate enhances the effects of opioid analgesics, barbiturates, and competitive neuromuscular blockers. The CNS depressant effects of sodium oxybate may be potentiated by alcohol, sedative-hypnotics, and other CNS depressants. The risk of respiratory depression may also be increased by benzodiazepines.

See also Interactions of General Anaesthetics, p.1779.

Pharmacokinetics

After oral doses sodium oxybate is rapidly but incompletely absorbed from the gastrointestinal tract; absolute bioavailability is about 25%. Peak concentrations are reached within 0.5 to 2 hours. Absorption may be delayed and decreased following a high fat meal. Protein binding is less than 1%. Sodium oxybate is metabolised in the liver via GHB dehydrogenase to succinic semialdehyde, which is then converted to succinic acid via another enzyme, succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle and is metabolised to carbon dioxide, which is expired, and water. Less than 5% of unchanged drug appears in the urine; faecal excretion is also negligible.

◊ References.

1. Palatini P, *et al*. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol* 1993; **45:** 353–6.
2. Scharf MB, *et al*. Pharmacokinetics of gammahydroxybutyrate (GHB) in narcoleptic patients. *Sleep* 1998; **21:** 507–14.

Uses and Administration

Sodium oxybate has hypnotic properties and, in its endogenous form, gamma-hydroxybutyrate (a catabolite of gamma-aminobutyric acid), increases dopamine concentrations in the brain. It is given intravenously usually with an opioid analgesic and a neuroleptic to produce general anaesthesia (p.1780). Skeletal muscle relaxants may also be necessary. Sodium oxybate given orally is used in the treatment of cataplexy in patients with narcolepsy; in the USA it is also indicated for the excessive daytime sleepiness associated with narcolepsy.

In general anaesthesia a solution of sodium oxybate equivalent to 20% of the acid is given slowly by intravenous injection, usually in a dose of 60 mg/kg; further smaller doses may be required in long procedures. In children 100 mg/kg may be used.