For the management of narcolepsy in adults, sodium oxybate is given in initial oral doses of 4.5 g daily, as two equally-divided doses. The first dose should be taken at bedtime while in bed and at least 2 to 3 hours after food; the second dose should be taken 2.5 to 4 hours later also while sitting in bed. Both doses should be prepared before going to bed: each dose should be diluted with 60 mL of water. The initial dose may be increased in steps of 1.5 g (0.75 g per dose) every 1 to 2 weeks to a maximum dose of 9 g daily. If therapy has been stopped for more than 14 consecutive days, titration should be restarted at the lowest dose. Reduced doses are recommended in patients with hepatic impairment (see below).

Administration in hepatic impairment. The recommended initial oral dose of sodium oxybate (see above) should be halved in patients with hepatic impairment. Subsequent increases should be monitored against effect.

Alcohol withdrawal syndrome. Gamma-hydroxybutyric acid has been reported[1] to be effective in reducing symptoms of alcohol withdrawal (p.1626) and to be of use as an aid in the maintenance of abstinence.[2,3] However, following reports of CNS toxicity associated with abuse of gamma-hydroxybutyric acid its role in the treatment of substance abuse disorders appears questionable.[4]

1. Gallimberti L, *et al.* Gamma-hydroxybutyric acid for treatment of alcohol withdrawal syndrome. *Lancet* 1989; **ii:** 787–9.
2. Gallimberti L, *et al.* Gamma-hydroxybutyric acid in the treatment of alcohol dependence: a double blind study. *Alcohol Clin Exp Res* 1992; **16:** 673–6.
3. Addolorato G, *et al.* Maintaining abstinence from alcohol with γ-hydroxybutyric acid. *Lancet* 1998; **351:** 38.
4. Quinn DI, *et al.* Pharmacokinetic and pharmacodynamic principles of illicit drug use and treatment of illicit drug users. *Clin Pharmacokinet* 1997; **33:** 344–400.

Narcoleptic syndrome. Sodium oxybate[1-7] given at night is used to improve cataplexy and excessive daytime sleepiness in patients with narcoleptic syndrome (p.2148).

For a reference to the pharmacokinetics of sodium oxybate in narcoleptic patients, see above.

1. Scharf MB, *et al.* The effects and effectiveness of γ-hydroxybutyrate in patients with narcolepsy. *J Clin Psychiatry* 1985; **46:** 222–5.
2. Mamelak M, *et al.* Treatment of narcolepsy with γ-hydroxybutyrate: a review of clinical and sleep laboratory findings. *Sleep* 1986; **9:** 285–9.
3. Scrima L, *et al.* Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy-cataplexy: double-blind subjective measures. *Biol Psychiatry* 1989; **26:** 331–43.
4. US Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep* 2002; **25:** 42–9.
5. US Xyrem Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep* 2003; **26:** 31–5.
6. Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep Med* 2005; **6:** 415–21.
7. Lemon MD, *et al.* Sodium oxybate for cataplexy. *Ann Pharmacother* 2006; **40:** 433–40.

Preparations

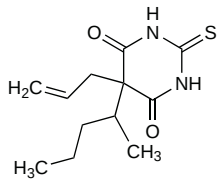
Proprietary Preparations (details are given in Part 3)
Austria: Alcover; ***Cz.:*** Xyrem; ***Fr.:*** Gamma-OH; ***Ger.:*** Somsanit; ***Hung.:*** Alcover†; ***Ital.:*** Alcover; ***Neth.:*** Xyrem; ***Port.:*** Xyrem; ***UK:*** Xyrem; ***USA:*** Xyrem.

Thiamylal Sodium

Tiamilal sódico. Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate.

$C_{12}H_{17}N_2NaO_2S$ = 276.3.

CAS — 77-27-0 (thiamylal); 337-47-3 (thiamylal sodium).



(thiamylal)

Pharmacopoeias. In *Jpn.*

Profile

Thiamylal sodium is a short-acting intravenous barbiturate anaesthetic. It is possibly slightly more potent than thiopental sodium (p.1796) and has similar actions and uses. It has been used for the production of complete anaesthesia of short duration, for the induction of general anaesthesia, or for inducing a hypnotic state.

Thiopental Sodium *(BANM, rINN)*

Natrium Isopentylaethylthiobarbituricum (cum Natrio Carbonico); Penthiobarbital Sodique; Sodyum Tiopental; Sodyum Tiopenton; Soluble Thiopentone; Thiomebumalnatrium cum Natrii Carbonate; Thiopental et carbonate sodiques; Thiopental Sodique; Thiopental Sodium and Sodium Carbonate; Thiopental sodná sůl a uhličitan sodný; Thiopentalum Natricum; Thiopentalum natricum et natrii carbonas; Thiopentobarbitalum Solubile; Thiopentone Sodium; Tiopentaalinatrium; Tiopentaalinatrium ja natriumkarbonaatti; Tiopental sódico; Tiopentalio natrio druska ir natrio karbonatas; Tiopentalnatrium; Tiopentál-nátrium és nátrium-karbonát; Tiopentalnatrium och natriumkarbonat. Sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate.

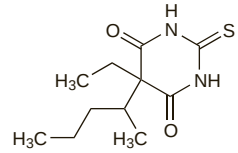
Тиопентал Натрий

$C_{11}H_{17}N_2NaO_2S$ = 264.3.

CAS — 76-75-5 (thiopental); 71-73-8 (thiopental sodium).

ATC — N01AF03; N05CA19.

ATC Vet — QN01AF03; QN05CA19.



(thiopental)

NOTE. The name thiobarbital has been applied to thiopental and has also been used to describe a barbiturate of different composition.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.* Some include thiopental sodium with, some without, anhydrous sodium carbonate; some only include a sterile mixture for injection.

Ph. Eur. 6.2 (Thiopental Sodium and Sodium Carbonate; Thiopental Sodium BP 2008). A yellowish-white hygroscopic powder. It contains 84 to 87% thiopental and 10.2 to 11.2% sodium. Freely soluble in water; partly soluble in dehydrated alcohol. Store in airtight containers. Protect from light.

USP 31 (Thiopental Sodium). A white to off-white crystalline powder, or yellowish-white to pale greenish-yellow hygroscopic powder. May have a disagreeable odour. Its solutions are alkaline to litmus, decompose on standing, and on boiling, precipitation occurs. Soluble in water and in alcohol; insoluble in ether, in petroleum spirit, and in benzene. Store in airtight containers.

Incompatibility. Solutions of thiopental sodium are incompatible with acidic and oxidising substances including some antibacterials, neuromuscular blockers and analgesics. Compounds commonly listed as incompatible include amikacin sulfate, benzylpenicillin salts, cefapirin sodium, codeine phosphate, ephedrine sulfate, fentanyl citrate, glycopyrronium bromide, morphine sulfate, pentazocine lactate, prochlorperazine edisilate, suxamethonium salts, and tubocurarine chloride. Solutions decompose on standing and precipitation occurs on boiling.

Stability. Loss of thiopental in PVC and cellulose propionate delivery systems has been reported,[1,2] but in another study,[3] no loss of potency was noted. Adsorption has been reported[4] not to occur in polyolefin infusion bags.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.
3. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
4. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.

Adverse Effects and Treatment

As for Phenobarbital, p.492.

Excitatory phenomena such as coughing, hiccuping, sneezing, and muscle twitching or jerking may occur with any of the barbiturate anaesthetics, particularly during induction, but they occur more frequently with methohexital than with thiopental. Cough, sneezing, and laryngeal spasm or bronchospasm may also occur during induction. The intravenous injection of concentrated solutions of thiopental sodium such as 5% may result in thrombophlebitis. Extravasation of barbiturate anaesthetics may cause tissue necrosis. Intra-arterial injection causes severe arterial spasm with burning pain and may cause prolonged blanching of the forearm and hand and gangrene of digits. Hypersensitivity reactions have been reported. Barbiturate anaesthetics can cause respiratory depression. They depress cardiac output and often cause an initial fall in blood pressure, and overdosage may result in circulatory failure. Arrhythmias may occur. Postoperative vomiting is infrequent but shivering may occur and there may be persistent drowsiness, confusion, and amnesia. Headache has also been reported.

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

Hypersensitivity. Anaphylactic reactions to thiopental have been reported[1,2] although such reactions are rare. There has also been a report of haemolytic anaemia and renal failure in association with the development of an anti-thiopental antibody in a patient who had undergone general anaesthesia induced by thiopental.[3]

1. Westacott P, *et al.* Anaphylactic reaction to thiopentone: a case report. *Can Anaesth Soc J* 1984; **31:** 434–8.
2. Moneret-Vautrin DA, *et al.* Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; **64:** 743–5.
3. Habibi B, *et al.* Thiopental-related immune hemolytic anemia and renal failure: specific involvement of red-cell antigen I. *N Engl J Med* 1985; **312:** 353–5. Correction. *ibid.*; 1136.

Intra-arterial injection. Accidental intra-arterial injection of thiopental sodium produces severe arterial spasm with intense burning pain. Anaesthesia, paresis, paralysis, and gangrene may occur. Therapy has concentrated on dilution of injected thiopental, prevention and treatment of arterial spasm, prophylaxis of thrombosis, thrombectomy and other measures to sustain good blood flow. There has been a report[1] of the successful use of urokinase intra-arterially in the management of one patient accidentally given thiopental intra-arterially.

1. Vangerven M, *et al.* A new therapeutic approach to accidental intra-arterial injection of thiopentone. *Br J Anaesth* 1989; **62:** 98–100.

Precautions

Barbiturate anaesthetics are contra-indicated when there is dyspnoea or respiratory obstruction such as in acute severe asthma or when maintenance of an airway cannot be guaranteed.

Barbiturate anaesthetics should be used with caution in shock and dehydration, hypovolaemia, severe anaemia, hyperkalaemia, toxaemia, myasthenia gravis, myxoedema and other metabolic disorders, or in severe renal disease. Caution is also required in patients with cardiovascular disease, muscular dystrophies, adrenocortical insufficiency, or with increased intracranial pressure. Reduced doses are required in the elderly and in severe hepatic disease.

See also Precautions for General Anaesthetics, p.1779.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers received thiopental, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

In two groups of 8 women undergoing induction with thiopental, the milk-to-plasma ratio was less than 1 in both groups and it was considered that the effects of thiopental on breast-fed infants would be negligible.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Andersen LW, *et al.* Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. *Acta Anaesthesiol Scand* 1987; **31:** 30–2.

Porphyria. Barbiturates including thiopental sodium have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients.

Interactions

Difficulty may be experienced in producing anaesthesia with the usual dose of barbiturate anaesthetics in patients accustomed to taking alcohol or other CNS depressants; additional anaesthetics may be necessary. Patients being treated with phenothiazine antipsychotics may experience increased hypotension. Some phenothiazines, especially promethazine, may also increase the incidence of excitatory phenomena produced by barbiturate anaesthetics; cyclizine may possibly have a similar effect. Opioid analgesics can potentiate the respiratory depressant effect of barbiturate anaesthetics and the dose of the anaesthetic may need to be reduced. Use with nitrous oxide greatly reduces the dose of barbiturate anaesthetics required for