anaesthesia. Reduced doses of thiopental may be required in patients receiving sulfafurazole.

See also Interactions of General Anaesthetics, p.1779.

Antidepressants. Potentiation of barbiturate anaesthesia may be expected in patients receiving *tricyclic antidepressants* or *MAOIs* (see Anaesthesia under Precautions of Amitriptyline, p.378 and for Phenelzine, p.417, respectively).

Antipsychotics. For mention of the effect of *droperidol* on thiopental see Gastrointestinal Drugs, below.

Aspirin. Pretreatment with aspirin, a highly protein-bound drug, has been shown to potentiate thiopental anaesthesia.[1]

1. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.

Gastrointestinal drugs. *Metoclopramide* profoundly reduced the dose of thiopental required to produce hypnosis in female patients; *droperidol* had a similar effect.[1]

1. Mehta D, *et al.* Metoclopramide decreases thiopental hypnotic requirement. *Anesth Analg* 1993; **77:** 784–7.

Probenecid. Pretreatment with probenecid, a highly protein-bound drug, has been shown to potentiate thiopental anaesthesia.[1]

1. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.

Pharmacokinetics

Thiopental is highly lipid soluble and when it is given intravenously as the sodium salt, concentrations sufficient to produce unconsciousness are achieved in the brain within 30 seconds. Onset of action occurs within 8 to 10 minutes when thiopental sodium is given rectally but absorption may be unpredictable if a suspension rather than a solution is used. Recovery from anaesthesia is also rapid due to redistribution to other tissues, particularly fat. About 80% of thiopental may be bound to plasma proteins, although reports show a wide range of figures. Thiopental is metabolised almost entirely in the liver, but as it is only released slowly from lipid stores this occurs at a very slow rate.

It is mostly metabolised to inactive metabolites but a small amount is desulfurated to pentobarbital. Repeated or continuous use can lead to accumulation of thiopental in fatty tissue and this can result in prolonged anaesthesia and respiratory and cardiovascular depression. Elimination of thiopental after bolus injection can be described by a triexponential curve. The terminal elimination half-life has been reported to be 10 to 12 hours in adults and about 6 hours in children. However, values of 26 to 28 hours have been reported in obese patients and pregnant patients at term. Thiopental readily diffuses across the placenta and is distributed into breast milk.

◊ References.

1. Gaspari F, *et al.* Elimination kinetics of thiopentone in mothers and their newborn infants. *Eur J Clin Pharmacol* 1985; **28:** 321–5.
2. Swerdlow BN, Holley FO. Intravenous anaesthetic agents: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet* 1987; **12:** 79–110.
3. Esener Z, *et al.* Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br J Anaesth* 1992; **69:** 586–8.
4. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; **75:** 344–51.

Uses and Administration

Thiopental is a short-acting barbiturate anaesthetic. It is given intravenously, usually for the induction of general anaesthesia (p.1780), but may be used as the sole anaesthetic to maintain anaesthesia for short procedures with minimal painful stimuli. It is also used in anaesthesia as a supplement to other anaesthetics and as a hypnotic in balanced anaesthesia. Thiopental sodium may also be used intravenously in the control of refractory tonic-clonic status epilepticus and in neurosurgical patients to reduce increased intracranial pressure. It has also been given rectally for basal anaesthesia or basal narcosis.

Thiopental does not usually produce excitation and induction of anaesthesia is usually smooth. It has poor muscle relaxant properties and a muscle relaxant must be given before intubation is attempted. Thiopental also has poor analgesic properties and small doses may even lower the pain threshold. Recovery from moderate doses usually occurs within 10 to 30 minutes, but the patient may remain sleepy or confused for several hours. Large doses, repeated smaller doses, or continuous use may markedly delay recovery.

In **anaesthesia**, the dosage of thiopental varies greatly according to the state of the patient and the nature of other drugs being used concurrently (see under Precautions above and Interactions above for further details). Thiopental is usually given intravenously as the sodium salt as a 2.5% solution but a 5% solution is occasionally used. UK licensed product information states that a typical dose for inducing anaesthesia is 100 to 150 mg injected over 10 to 15 seconds, repeated after 30 to 60 seconds according to response. It also recommends that the total dosage used should not exceed 500 mg; in pregnant patients the total maximum dose is 250 mg. In some other countries, it is recommended that induction begin with a test dose of 25 to 75 mg; thereafter, a dose of 50 to 75 mg may be given at intervals of 20 to 40 seconds according to response. Once anaesthesia has been established, additional doses of 25 to 50 mg may be given as necessary. When thiopental is used as the sole anaesthetic, anaesthesia can be maintained by repeat doses as needed or by continuous intravenous infusion of a 0.2 or 0.4% solution.

To **reduce elevations of intracranial pressure** in neurological patients, thiopental sodium is licensed for use as intermittent bolus injections of 1.5 to 3 mg/kg if adequate ventilation is provided (but see also Cerebrovascular Disorders, below). Higher doses have been tried.

For suggested doses in refractory tonic-clonic **status epilepticus** see Status Epilepticus, below.

For dosage in *children* and the *elderly*, also see below.

◊ References.

1. Russo H, Bressolle F. Pharmacodynamics and pharmacokinetics of thiopental. *Clin Pharmacokinet* 1998; **35:** 95–134.

Administration in children. For the *induction of anaesthesia* in children, UK licensed product information recommends that thiopental sodium is given by slow intravenous injection (over 10 to 15 seconds) in a dose of 2 to 7 mg/kg; the dose may be repeated after 1 minute.

In the treatment of prolonged *status epilepticus* (see below), the *BNFC* recommends an initial dose of up to 2 mg/kg in neonates or up to 4 mg/kg in children aged 1 month and over, given as a slow intravenous injection; for all patients, this should then be followed by a continuous intravenous infusion of up to 8 mg/kg per hour, adjusted according to response.

Intravenous injections are normally given as a 2.5% solution; the *BNFC* recommends that intravenous infusions are given as a 0.25% solution.

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 demonstrated that although reducing the rate of intravenous injection reduced the speed of induction, the dosage required was also reduced. Giving thiopental sodium 2.5% solution at a rate of 125 mg/minute induced anaesthesia in a mean of 90.8 seconds and required a mean dose of 2.8 mg/kg. Corresponding values for a rate of 500 mg/minute were 40.8 seconds and 5 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.

Anaesthesia. Some of the adverse effects of the neuromuscular blocker suxamethonium may be reduced when thiopental is used as part of the anaesthetic regimen. For a suggestion that thiopental may help to counteract the rise in intra-ocular pressure associated with the use of suxamethonium for intubation, see under Anaesthesia, p.1900.

Cerebrovascular disorders. Barbiturates are considered to be suitable anaesthetics for use in patients with or at risk of raised intracranial pressure. Barbiturate-induced coma (commonly with pentobarbital or thiopental) has been used, both therapeutically and prophylactically, to protect the brain from ischaemia resulting from neurological insults including head injury, stroke, Reye's syndrome, and hepatic encephalopathy.[1-3] Rationale includes the ability of barbiturates to reduce intracranial pressure and to reduce metabolic demands of cerebral tissues. Although thiopental protected patients against the neuropsychiatric complications of cardiopulmonary bypass,[4] the Brain Resuscitation Clinical Trial I Study Group[5] found no cerebral benefit from thiopental in comatose survivors of cardiac arrest. Nor did others[6] observe any benefit from thiopental-induced coma in infants with severe birth asphyxia. A review in 1989 considered that there was no convincing evidence of improvement in neurological outcome to justify the risks of the procedure in conditions causing global ischaemia, although use of barbiturates without necessarily inducing coma might have a limited role in reduction of raised intracranial pressure refractory to other therapy. Use of barbiturates in the setting of regional cerebral ischaemia, including use during cardiopulmonary bypass to prevent focal neurological complications, remained controversial.[1] A systematic review[7] came to similar conclusions, pointing out that although the barbiturates may reduce intracranial pressure their hypotensive effects are likely to offset any beneficial action on cerebral perfusion, perhaps accounting for the lack of evidence for any clinical benefit.

For a discussion of the treatment of raised intracranial pressure, including a mention of the use of barbiturates, see p.1181.

1. Rogers MC, Kirsch JR. Current concepts in brain resuscitation. *JAMA* 1989; **261:** 3143–7.
2. Lyons MK, Meyer FB. Cerebrospinal fluid physiology and the management of increased intracranial pressure. *Mayo Clin Proc* 1990; **65:** 684–707.
3. Woster PS, LeBlanc KL. Management of elevated intracranial pressure. *Clin Pharm* 1990; **9:** 762–72.
4. Nussmeier NA, *et al.* Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. *Anesthesiology* 1986; **64:** 165–70.
5. Abramson NS, *et al.* Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. *N Engl J Med* 1986; **314:** 397–403.
6. Eyre JA, Wilkinson AR. Thiopentone induced coma after severe birth asphyxia. *Arch Dis Child* 1986; **61:** 1084–9.
7. Roberts I. Barbiturates for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 16/06/05).

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.

Doses of thiopental sodium in the treatment of status epilepticus appear to vary widely and may be defined by local clinical protocols. Licensed product information and the *BNF* recommend a dose of 75 to 125 mg intravenously as a 2.5% solution. Other regimens advocate an initial loading dose followed by further intermittent doses or a continuous infusion. One high dose regimen suggests an intravenous loading dose of 5 mg/kg followed after 30 minutes by an infusion given at a rate of 1 to 3 mg/kg per hour and adjusted to maintain a maximum blood concentration of 60 to 100 micrograms/mL.[1] It has been recommended that dosage should be continued for at least 12 hours after seizure activity has ceased and then slowly stopped.[2] Recovery may be prolonged.[3]

For the dose of thiopental in children see Administration in Children, above.

1. O'Brien MD. Management of major status epilepticus in adults. *BMJ* 1990; **301:** 918.
2. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
3. Parviainen I, *et al.* High-dose thiopental in the treatment of refractory status epilepticus in intensive care unit. *Neurology* 2002; **59:** 1249–51.

Preparations

BP 2008: Thiopental Injection;
USP 31: Thiopental Sodium for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Bensulf; Hipnopento; Pentothal†; ***Austral.:*** Pentothal; ***Belg.:*** Pentothal; ***Braz.:*** Thionembutal; Thiopentax; ***Canad.:*** Pentothal; ***Chile:*** Pentothal†; ***Denm.:*** Pentothal; ***Fin.:*** Pentothal; ***Ger.:*** Trapanal; ***Gr.:*** Pentothal; ***Hong Kong:*** Pentothal; ***Hung.:*** Trapanal†; ***India:*** Anesthal; ***Indon.:*** Pentothal; ***Irl.:*** Intraval Sodium†; ***Israel:*** Pentothal; ***Ital.:*** Farmotal; Pentothal; ***Malaysia:*** Pentotex; ***Mex.:*** Pentarim; Pentothal; Sodipental; ***Neth.:*** Pentothal; ***Norw.:*** Pentothal; ***NZ:*** Intraval; ***Philipp.:*** Pentobrim; Pentothal; ***Singapore:*** Pentothal†; ***Spain:*** Pentothal; Tiobarbital; ***Swed.:*** Pentothal; ***Switz.:*** Pentothal; ***Thai.:*** Pentothal; ***Turk.:*** Pental; Pentothal; ***USA:*** Pentothal; ***Venez.:*** Pentothal†.

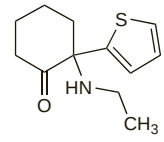
Tiletamine Hydrochloride *(BANM, USAN, rINNM)*

CI-634; CL-399; CN-54521-2; Hidrocloruro de tiletamina; Tilétamine, Chlorhydrate de; Tiletamini Hydrochloridum. 2-Ethylamino-2-(2-thienyl)cyclohexanone hydrochloride.

Тилетамина Гидрохлорид

$C_{12}H_{17}NOS,HCl = 259.8$.

CAS — 14176-49-9 (tiletamine); 14176-50-2 (tiletamine hydrochloride).



(tiletamine)

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Tiletamine Hydrochloride). A white to off-white crystalline powder. Freely soluble in water; slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol;

freely soluble in 0.1N hydrochloric acid. pH of a 10% solution in water is between 3.0 and 5.0. Store in airtight containers.

Profile

Tiletamine has similar properties to ketamine (p.1787). It is used as the hydrochloride with zolazepam (p.1037) for general anaesthesia in veterinary medicine.

Trichloroethylene *(rINN)*

Trichlorethylene; Trichlorethylenum; Trichloroethene; Trichloroéthylène; Trichloroethylenum; Trichloroetylen; Tricloroetileno.

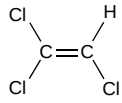
Трихлороэтилен

$CHCl:CCl_2$ = 131.4.

CAS — 79-01-6.

ATC — N01AB05.

ATC Vet — QN01AB05.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of trichloroethylene: Trichlo.

Stability. NOTE. Trichloroethylene used for anaesthetic purposes contains thymol 0.01% w/v as a stabiliser and is coloured blue for identification. It is non-flammable.

Adverse Effects and Precautions

Trichloroethylene increases the rate and decreases the depth of respiration and may be followed by apnoea. The sensitivity of the heart to beta-adrenergic activity may increase, possibly with ventricular arrhythmias.

Acute exposure to trichloroethylene may be followed by dizziness, lightheadedness, lethargy, nausea, and vomiting; hepatic and renal dysfunction may follow. Fatalities have occurred, although temporary unconsciousness is a more common manifestation.

Chronic poisoning may result in visual disturbances, intolerance to alcohol as manifested by transient redness of the face and neck (degreasers' or trichloroethylene flush), impairment of performance, hearing defects, neuralgia, and mild liver dysfunction. Prolonged contact with trichloroethylene can cause dermatitis, eczema, burns, and conjunctivitis.

Dependence has been reported in medical personnel and factory workers who regularly inhale trichloroethylene vapour.

If trichloroethylene is used as an anaesthetic it should not be used in closed-circuit apparatus since there is a reaction with soda lime to produce a toxic end product that may cause cranial nerve paralysis and possibly death.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

◊ Reviews of the toxicity of trichloroethylene.

1. Health and Safety Executive. Trichloroethylene. *Toxicity Review* 6. London: HMSO, 1982.
2. WHO. Trichloroethylene. *Environmental Health Criteria 50.* Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc50.htm (accessed 26/05/04)
3. Davidson IWF, Beliles RP. Consideration of the target organ toxicity of trichloroethylene in terms of metabolite toxicity and pharmacokinetics. *Drug Metab Rev* 1991; **23:** 493–599.

Abuse. Toxicity associated with inhalation of volatile substances including trichloroethylene has been reviewed.[1,2] Trichloroethylene can damage the kidney, liver, heart, and lung. However, in young healthy subjects, organ toxicity becomes apparent only with intensive and protracted abuse of volatile substances.

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.
2. Anonymous. Solvent abuse: little progress after 20 years. *BMJ* 1990; **300:** 135–6.

Carcinogenicity. The use of trichloroethylene in foods, drugs, and cosmetics was banned by the FDA after studies demonstrating that hepatocellular carcinomas could be induced in *mice* by chronic exposure to very high doses. However, similar effects have not been found in *rats* and larger species and several epidemiologic studies have failed to demonstrate an increased incidence of liver tumours, total mortality or mortality due to cancer in workers exposed to trichloroethylene. Suggestions that the carcinogenicity of trichloroethylene is due to one of its intermediate metabolites, cloral hydrate, have raised concern over the continuing use of cloral hydrate as a medicine. For further details, see p.979.

Effects on the liver. References[1,2] to hepatotoxicity after occupational exposure to trichloroethylene. See also Carcinogenicity, above.

1. McCunney RJ. Diverse manifestations of trichloroethylene. *Br J Ind Med* 1988; **45:** 122–6.
2. Schattner A, Malnick SDH. Anicteric hepatitis and uveitis in a worker exposed to trichloroethylene. *Postgrad Med J* 1990; **66:** 730–1.

Effects on the skin. A report[1] of scleroderma in 3 patients occupationally exposed to trichloroethylene and, in 2 cases, also to trichloroethane.

1. Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichlorethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; **67:** 263–4.

Interactions

The arrhythmogenic effects of trichloroethylene may be potentiated by sympathomimetics such as adrenaline. Alcohol consumption after chronic exposure to trichloroethylene may result in a reddening of the skin (see Adverse Effects and Precautions, above).

See also Interactions of General Anaesthetics, p.1779.

Pharmacokinetics

Trichloroethylene is rapidly absorbed by inhalation and ingestion. Percutaneous absorption can occur. Some of the inhaled trichloroethylene is slowly eliminated through the lungs; trichloroethylene is metabolised primarily in the liver, cloral hydrate (see p.979) being the first stable major metabolite formed; most is then metabolised to trichloroethanol and trichloroacetic acid which are excreted in the urine. The latter may be used as an indicator of industrial exposure. Trichloroethylene diffuses across the placenta.

Uses and Administration

Trichloroethylene is a volatile halogenated anaesthetic given by inhalation. It has been used in some countries for the maintenance of light anaesthesia (p.1780) but it has weak anaesthetic properties compared to other halogenated anaesthetics and poor muscle relaxant activity, and safer anaesthetics are generally preferred. It has also been used to supplement anaesthesia with nitrous oxide-oxygen or halothane. Trichloroethylene is a potent analgesic and has been used in subanaesthetic concentrations to provide analgesia for obstetrics, emergency management of trauma, and other acutely painful procedures.

Trichloroethylene is used in industry as a solvent for oils and fats, for degreasing metals, and for dry cleaning. It has also been used in type correction fluids but is no longer included in most brands.

Xenon

Ksenon; Xénon; Xenón; Xenonum.

Xe = 131.293.

ATC — N01AX15.

ATC Vet — QN01AX15.

Profile

Xenon is a non-explosive gas. Mixtures of 60 or 70% v/v xenon with oxygen have been tried as a general anaesthetic.

◊ References.

1. Lachmann B, *et al.* Safety and efficacy of xenon in routine use as an inhalational anaesthetic. *Lancet* 1990; **335:** 1413–15.
2. Yagi M, *et al.* Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide. *Br J Anaesth* 1995; **74:** 670–3.
3. Goto T, *et al.* Emergence times from xenon anaesthesia are independent of the duration of anaesthesia. *Br J Anaesth* 1997; **79:** 595–9.
4. Rossaint R, *et al.* Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. *Anesthesiology* 2003; **98:** 6–13.
5. Sanders RD, *et al.* Xenon: no stranger to anaesthesia. *Br J Anaesth* 2003; **91:** 709–17.
6. Bedi A, *et al.* Use of xenon as a sedative for patients receiving critical care. *Crit Care Med* 2003; **31:** 2470–7.
7. Preckel B, Schlack W. Xenon—cardiovascularly inert? *Br J Anaesth* 2004; **92:** 786–9.
8. Sanders RD, *et al.* Xenon: elemental anaesthesia in clinical practice. *Br Med Bull* 2005; **71:** 115–35.
9. Baskar N, Hunter JD. Xenon as an anaesthetic gas. *Br J Hosp Med* 2006; **67:** 658–61.

Preparations

Proprietary Preparations (details are given in Part 3)

Port.: Lenoxe.