Porphyria. Enflurane is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

Care is advised if adrenaline or other sympathomimetics are given to patients during enflurane anaesthesia. The effects of competitive neuromuscular blockers such as atracurium are enhanced by enflurane (see p.1904).

See also Interactions of General Anaesthetics, p.1779.

Antibacterials. For the effects of *isoniazid* on enflurane defluorination, see Effects on the Kidneys under Adverse Effects, above.

Antidepressants. It appeared likely that the enflurane-induced seizure activity seen in 2 patients could have been enhanced by *amitriptyline*.[1] It may be advisable to avoid the use of enflurane in patients requiring tricyclic antidepressants, especially when the patient has a history of seizures or when hyperventilation or high enflurane concentrations are a desired part of the anaesthetic technique.

1. Sprague DH, Wolf S. Enflurane seizures in patients taking amitriptyline. *Anesth Analg* 1982; **61:** 67–8.

Disulfiram. For the effect of disulfiram on the metabolism of enflurane, see Effects on the Kidneys under Adverse Effects, above.

Pharmacokinetics

Enflurane is absorbed on inhalation. The blood/gas partition coefficient is low. It is mostly excreted unchanged through the lungs. Up to 10% of inhaled administered enflurane is metabolised in the liver, mainly to inorganic fluoride.

◊ References.

1. Bengtson JP, *et al.* Uptake of enflurane and isoflurane during spontaneous and controlled ventilation. *Anaesth Intensive Care* 1992; **20:** 191–5.
2. Devchand D, *et al.* The uptake of enflurane during anaesthesia. *Anaesthesia* 1995; **50:** 491–5.

Uses and Administration

Enflurane is a volatile halogenated anaesthetic given by inhalation. It is an isomer of isoflurane. It has anaesthetic actions similar to those of halothane (p.1785). Enflurane has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) ranging from 1.7% in middle age to 2.5% in children. Enflurane is given using a calibrated vaporiser for induction and maintenance of general anaesthesia (p.1780); it is also used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures (below).

To avoid CNS excitement a short-acting barbiturate or other intravenous induction agent is recommended before the inhalation of enflurane. Anaesthesia may be induced using enflurane alone with oxygen or in nitrous oxide-oxygen mixtures. In general, enflurane concentrations of 2 to 4.5% v/v produce surgical anaesthesia in 7 to 10 minutes. Anaesthesia may be maintained with a concentration of 0.5 to 3% v/v of enflurane; a concentration of 3% v/v should not be exceeded during spontaneous respiration. Although enflurane is reported to possess muscle relaxant properties, neuromuscular blockers may nevertheless be required. Postoperative analgesia may be necessary.

Concentrations of 0.25 to 1% v/v of enflurane are used to provide analgesia for vaginal delivery during childbirth and of 0.5 to 1% v/v to supplement other general anaesthetics during caesarean section.

Pain. Enflurane is used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures although a study[1] was unable to confirm that it had an analgesic effect at subanaesthetic concentrations.

1. Tomi K, *et al.* Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; **70:** 684–6.

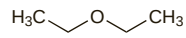
Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Enforan; Inhelthran†; ***Austral.:*** Ethrane†; ***Austria:*** Ethrane; ***Braz.:*** Enfluthane; Etrane; ***Denm.:*** Efrane†; ***Fin.:*** Efrane†; ***Ger.:*** Ethrane†; ***Indon.:*** Ethrane; ***Irl.:*** Ethrane; ***Israel:*** Alyrane; Ethrane; ***Ital.:*** Ethrane†; ***Mex.:*** Enfran; Ethrane; ***Neth.:*** Ethrane†; ***NZ:*** Ethrane†; ***Philipp.:*** Alyrane; Ethrane; ***Rus.:*** Ethrane (Этран)†; ***S.Afr.:*** Ethrane; ***Swed.:*** Efrane†; ***Switz.:*** Ethrane†; ***Turk.:*** Ethrane; ***UK:*** Alyrane†; ***USA:*** Ethrane; ***Venez.:*** Ethrane.

Anaesthetic Ether

Aether ad Narcosin; Aether anaestheticus; Aether pro Narcosi; Aether Purissimus; Altatáshoz való éter; Anestesiaeetteri, narkoosieetteri; Anestetinis eteris; Diethyl Ether; Éter anestésico; Eter do nakozy; Eter etylowy; Éter Puríssimo; Ether; Ether Anesthesicus; Éther anesthésique; Ether Anestheticus; Ether Ethylicus; Ether Ethylicus pro Narcosi; Ether k narkóze; Ethyl Ether; Narkoseter.

$(C_2H_5)_2O$ = 74.12.
CAS — 60-29-7.
ATC — N01AA01.
ATC Vet — QN01AA01.



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

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet*.

Ph. Eur. 6.2 (Ether, Anaesthetic). Diethyl ether to which an appropriate quantity of a non-volatile antoxidant may have been added. It contains not more than 2 g/litre of water. A clear, colourless, volatile, highly flammable, and very mobile liquid. Distillation range 34° to 35°.

Soluble 1 in 15 of water; miscible with alcohol and with fatty oils. Store at a temperature of 8° to 15° in airtight containers. Protect from light. Ether remaining in a partly used container may deteriorate rapidly. The label should state the name and concentration of any added non-volatile antoxidant.

USP 31 (Ether). It consists of 96 to 98% of $C_4H_{10}O$, the remainder consisting of alcohol and water. Ether for anaesthetic use contains not more than 0.2% of water. It is a colourless, mobile, highly flammable, highly volatile liquid, having a characteristic sweet, pungent odour. It is slowly oxidised by the action of air and light, with the formation of peroxides. Its vapour, when mixed with air and ignited, may explode. B.p. about 35°.

Soluble 1 in 12 of water; miscible with alcohol, with chloroform, with dichloromethane, with petroleum spirit, with benzene, and with fixed and volatile oils; soluble in hydrochloric acid. Store in partly-filled, airtight containers, remote from fire and at a temperature not exceeding 40°. Protect from light. Ether to be used for anaesthesia must be preserved in airtight containers of not more than 3 kg capacity and is not to be used for anaesthesia if it has been removed from the original container longer than 24 hours.

Labelling. The label should state that it is suitable for use as an anaesthetic.

Stability. Ether is very volatile and flammable and mixtures of its vapour with oxygen, nitrous oxide, or air at certain concentrations are explosive. It should not be used in the presence of an open flame or any electrical apparatus liable to produce a spark. Precautions should be taken against the production of static electrical discharge.

Storage. The Pharmaceutical Society of Great Britain's Department of Pharmaceutical Sciences found that free ether, even in low concentrations, caused softening of PVC bottles and was associated with loss by permeation.[1]

1. Anonymous. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Adverse Effects

Ether has an irritant action on the mucous membrane of the respiratory tract; it stimulates salivation and increases bronchial secretion. Laryngeal spasm may occur. Ether causes vasodilatation which may lead to a severe fall in blood pressure and it reduces blood flow to the kidneys; it also increases capillary bleeding. The bleeding time is unchanged but the prothrombin time may be prolonged. Ether may cause malignant hyperthermia in certain individuals. Alterations in kidney and liver function have been reported. Convulsions occasionally occur. Hyperglycaemia due to gluconeogenesis has been noted.

Recovery is slow from prolonged ether anaesthesia and postoperative vomiting is common. Acute overdosage of ether is characterised by respiratory failure and cardiac arrest.

Dependence on ether or ether vapour has been reported. Prolonged contact with ether spilt on any tissue produces necrosis.

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

Precautions

Ether anaesthesia is contra-indicated in patients with diabetes mellitus, impaired kidney function, raised CSF pressure, and severe liver disease. Its use is not advisable in hot and humid conditions in patients with fever, as convulsions are liable to occur, particularly in children and in patients who have been given atropine.

See also Precautions for General Anaesthetics, p.1779.

Interactions

Ether enhances the action of competitive neuromuscular blockers to a greater degree than most other anaesthetics. However, it does not potentiate the arrhythmogenic effect of sympathomimetics, including adrenaline, as much as other inhalational anaesthetics.

See also Interactions of General Anaesthetics, p.1779.

Uses and Administration

Ether is an anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) of 1.92%. Ether is still used in some countries for the induction and maintenance of general anaesthesia although it has been replaced in many other countries by the halogenated anaesthetics. It possesses a respiratory stimulant effect in all but the deepest planes of anaesthesia. Ether also possesses analgesic and muscle relaxant properties. Premedication with an antimuscarinic such as atropine is necessary to reduce salivary and bronchial secretions.

Solvent ether is described on p.2023.

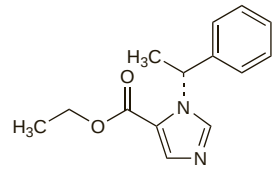
Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Hoffmans Druppels.

Etomidate *(BAN, USAN, rINN)*

Etomidaatti; Etomidát; Etomidat; Etomidatas; Étomidate; Etomidato; Etomidatum; R-16659; R-26490 (etomidate sulfate). *R*-(+)-Ethyl 1-(α-methylbenzyl)imidazole-5-carboxylate.

Этомидат
$C_{14}H_{16}N_2O_2$ = 244.3.
CAS — 33125-97-2.
ATC — N01AX07.
ATC Vet — QN01AX07.



NOTE. Do not confuse with edetate; see Inappropriate Administration under Sodium Edetate, p.1464.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Etomidate). A white or almost white powder. M.p. about 68°. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Adverse Effects and Precautions

Excitatory phenomena (especially involuntary myoclonic muscle movements, which are sometimes severe) are common after injection of etomidate, but may be reduced by giving an opioid analgesic or a short-acting benzodiazepine beforehand. Pain on injection may be reduced by giving etomidate into a large vein in the arm rather than into the hand, or, again, by premedication with an opioid analgesic. Convulsions may occur rarely, as may laryngospasm and cardiac arrhythmias. Hypersensitivity reactions including anaphylaxis have been reported. Etomidate is associated with less hypotension than other drugs commonly used for induction.

Because etomidate inhibits adrenocortical function during maintenance anaesthesia (see below) its use is limited to induction of anaesthesia. In addition it should not be used in patients whose adrenocortical function is already reduced or at risk of being reduced.

Etomidate should be used with care in the elderly, who may be more prone to cardiac depression; lower doses may be required. The dose of etomidate should also be reduced in patients with hepatic cirrhosis. Caution may be appropriate in patients with pre-existing epilepsy.

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

Effects on the endocrine system. Etomidate used for sedation in an intensive care unit was implicated in an increase in mortality.[1] The UK CSM agreed that etomidate could cause a significant fall in circulating plasma-cortisol concentrations, unresponsive to corticotropin stimulation.[2] As a result of this effect, use of etomidate is restricted to induction of anaesthesia. Licensed product information advises that the postoperative rise in serum-cortisol concentration, which has been observed after thiopental induction, is delayed for about 3 to 6 hours when etomidate is used for induction.

A study comparing the effects of etomidate with those of methohexital on the adrenocortical function of neonates borne by mothers who received these agents for induction of anaesthesia before caesarean section indicated that there was no evidence to preclude the use of etomidate in such patients. However, regardless of which anaesthetic agent was used, early feeding was recommended to avoid neonatal hypoglycaemia.[3]

1. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet* 1983; **i:** 1270.
2. Goldberg A. Etomidate. *Lancet* 1983; **ii:** 60.
3. Crozier TA, *et al.* Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate. *Br J Anaesth* 1993; **70:** 47–53.

Hypersensitivity. Reactions involving immediate widespread cutaneous flushing or urticaria attributed to etomidate have been described.[1] There have also been reports[2,3] of anaphylactic reactions after injection of etomidate.

1. Watkins J. Etomidate: an 'immunologically safe' anaesthetic agent. *Anaesthesia* 1983; **38** (suppl): 34–8.
2. Sold M, Rothhammer A. Lebensbedrohliche anaphylaktoide reaktion nach etomidat. *Anaesthesist* 1985; **34:** 208–10.
3. Krumholz W, *et al.* Ein fall von anaphylaktoider reaktion nach gabe von etomidat. *Anaesthesist* 1984; **33:** 161–2.

Porphyria. Etomidate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

A reduced dose of etomidate may be necessary in patients who have received antipsychotics, sedatives, or opioids. The hypnotic effect of etomidate has been potentiated by other sedative drugs.

See also Interactions of General Anaesthetics, p.1779.

Calcium-channel blockers. Prolonged anaesthesia and Cheyne-Stokes respiration following etomidate injection has been reported in 2 patients also given *verapamil*.[1]

1. Moore CA, *et al.* Potentiation of etomidate anesthesia by verapamil: a report of two cases. *Hosp Pharm* 1989; **24:** 24–5.

General anaesthetics. For a report of synergy between *propofol* and etomidate, see p.1792.

Pharmacokinetics

After injection, etomidate is rapidly redistributed from the CNS to other body tissues, and undergoes rapid metabolism in the liver and plasma. Pharmacokinetics are complex and have been described by both 2- and 3-compartment models. Etomidate is about 76% bound to plasma proteins. It is mainly excreted in the urine, but some is excreted in the bile. It may cross the placenta and is distributed into breast milk.

◊ References.

1. Levron JC, Assoune P. Pharmacocinétique de l'étomidate. *Ann Fr Anesth Reanim* 1990; **9:** 123–6.
2. Sfez M, *et al.* Comparaison de la pharmacocinétique de l'étomidate chez l'enfant et chez l'adulte. *Ann Fr Anesth Reanim* 1990; **9:** 127–31.
3. Esener Z, *et al.* Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br J Anaesth* 1992; **69:** 586–8.

Uses and Administration

Etomidate is an intravenous anaesthetic used for the induction of general anaesthesia (p.1780). Anaesthesia is rapidly induced and may last for 6 to 10 minutes with a single usual dose. Recovery is usually rapid without hangover effect. Etomidate has no analgesic activity.

For the induction of anaesthesia, etomidate is available as a conventional or an emulsion injection formulation. The usual dose is 300 micrograms/kg of etomidate given slowly, preferably into a large vein in the arm, although a lower dose of 150 micrograms/kg of the emulsion formulation may be sufficient. An initial dose of 150 to 200 micrograms/kg is recommended in the elderly, subsequently adjusted according to effects. Dosage should also be reduced in hepatic cirrhosis. Children may require up to 30% more than the usual adult dose of the emulsion formulation. Opioid analgesics or benzodiazepines as premedication reduce myoclonic muscle movements; opioids also reduce injection site pain. A neuromuscular blocker is necessary if intubation is required.

Administration in the elderly. A study[1] in elderly patients has demonstrated that although reducing the rate of intravenous injection of etomidate reduces the speed of induction, the dosage required is also reduced. Giving etomidate 0.2% solution at a rate of 10 mg/minute induced anaesthesia in a mean of 89.6 seconds and required a mean dose of 0.11 mg/kg. Corresponding values for a rate of 40 mg/minute were 47.7 seconds and 0.26 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. Etomidate might be useful for induction if rapid tracheal intubation is required with a competitive neuromuscular blocker as it has been shown to reduce the time to onset of block with vecuronium.[1,2]

1. Gill RS, Scott RPF. Etomidate shortens the onset time of neuromuscular block. *Br J Anaesth* 1992; **69:** 444–6.
2. Bergen JM, Smith DC. A review of etomidate for rapid sequence intubation in the emergency department. *J Emerg Med* 1997; **15:** 221–30.

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, but other anaesthetics including etomidate have also been tried[1] for intractable convulsive status epilepticus. However, like a number of other anaesthetics there have been reports of seizures associated with its use in anaesthesia,[2] especially in patients with epilepsy.

1. Yeoman P, *et al.* Etomidate infusions for the control of refractory status epilepticus. *Intensive Care Med* 1989; **15:** 255–9.
2. Nicoll K, Callender J. Etomidate-induced convulsion prior to electroconvulsive therapy. *Br J Psychiatry* 2000; **177:** 373.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Hypnomidate; ***Belg.:*** Hypnomidate; ***Braz.:*** Hypnomidate; ***Chile:*** Hypnomidate†; ***Cz.:*** Hypnomidate; ***Fr.:*** Hypnomidate; ***Ger.:*** Hypnomidate; ***Gr.:*** Hypnomidate; ***Mex.:*** Hypnomidate; ***Neth.:*** Hypnomidate; ***Pol.:*** Hypnomidate; ***Port.:*** Hypnomidato; ***S.Afr.:*** Hypnomidate; ***Spain:*** Hypnomidate; ***Turk.:*** Hypnomidate; ***UK:*** Hypnomidate; ***USA:*** Amidate.

Halothane *(BAN, rINN)*

Alotano; Halotaani; Halotán; Halotan; Halotanas; Halotano; Halothan; Halothanum; Phthorothanum. *(RS)*-2-Bromo-2-chloro-1,1,1-trifluoroethane.

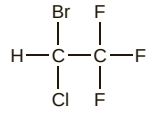
Галотан

$CHBrCl.CF_3$ = 197.4.

CAS — 151-67-7.

ATC — N01AB01.

ATC Vet — QN01AB01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Halothane). A clear, colourless, mobile, dense, non-flammable liquid. Distillation range 49° to 51°. Slightly soluble in water; miscible with dehydrated alcohol and with trichloroethylene. Halothane contains 0.01% w/w of thymol. Store at a temperature not greater than 25° in airtight containers. Protect from light.
USP 31 (Halothane). A colourless, mobile, non-flammable, heavy liquid having a characteristic odour resembling that of chloroform. It contains not less than 0.008% and not more than 0.012% of thymol, by weight, as a stabiliser. It should contain not more than 0.03% of water. Distillation range 49° to 51°.
Slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with fixed oils. Store in airtight containers at a temperature not greater than 40°. Protect from light. Dispense only in the original container.

Incompatibility. In the presence of moisture, halothane reacts with many metals. Rubber and some plastics deteriorate when in contact with halothane vapour or liquid.

Stability. Halothane contains 0.01% w/w of thymol as a stabiliser; some commercial preparations may also contain up to 0.00025% w/w of ammonia. Thymol does not volatilise with halothane and therefore accumulates in the vaporiser. It may give a yellow colour to any remaining liquid; halothane that has discoloured should be discarded.

Adverse Effects

As with other halogenated anaesthetics, halothane has a depressant action on the cardiovascular system and reduces blood pressure; signs of overdosage are bradycardia and profound hypotension. It is also a respiratory depressant and can cause cardiac arrhythmias; there have been instances of cardiac arrest. The sensitivity of the heart to sympathomimetic amines is increased.

Adverse effects on the liver have limited its use in recent years (see below); these effects range from liver dysfunction to fatal hepatitis and necrosis and are more frequent following repeated use.

Halothane can produce nausea, vomiting, and shivering. Malignant hyperthermia has been reported.

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

Effects on the cardiovascular system. The incidence of cardiac arrhythmias is higher with halothane than with enflurane or isoflurane; also the arrhythmogenic threshold with injected adrenaline is lower with halothane than isoflurane or enflurane.

Arrhythmias are considered to be very common in children anaesthetised with halothane and in the UK it is recommended that it should not be used for dental procedures outside hospital in those under 18 years old.

Effects on the kidneys. Renal failure has been reported after halothane anaesthesia,[1,2] sometimes with concurrent liver failure.[2]

1. Cotton JR, *et al.* Acute renal failure following halothane anesthesia. *Arch Pathol Lab Med* 1976; **100:** 628–9.
2. Gelman ML, Lichtenstein NS. Halothane-induced nephrotoxicity. *Urology* 1981; **17:** 323–7.

Effects on the liver. Liver damage has been recognised as an adverse effect of halothane for many years.[1-3] It may be severe, and associated with a high mortality.

Two types of hepatotoxicity are recognised; in **type I** there is a minor disturbance in liver function shown by increases in liver enzyme values; this may occur in up to 30% of patients given halothane,[4] or more if activity is measured by glutathione S-transferase rather than serum aminotransferase.[5] Subsequent re-exposure to halothane is not necessarily associated with liver damage.[2,6]

Type II hepatotoxicity, which is rarer, involves massive liver cell necrosis; reported incidences[2] range from 1 in 2500 to 1 in 36 000. Type II liver toxicity is characterised by several clinical features: non-specific gastrointestinal upset, delayed pyrexia, jaundice, eosinophilia, serum autoantibodies, rash, and arthralgia.[1,3] Biochemical tests of liver function show changes typical of hepatocellular damage; histological features are typified by centrilobular necrosis.[1] Several **risk factors** for development of serious toxicity have become apparent;[1-3] they include repeated exposure, previous adverse reactions to halothane (jaundice, pyrexia), female gender, obesity, middle age, genetic predisposition, enzyme induction, and a history of drug allergy.

The **causes** of halothane hepatotoxicity have been debated. Type I reactions may result from toxic products of halothane metabolism, possibly influenced by genetic factors or from an imbalance between hepatic oxygen supply and demand. Changes in cellular calcium homoeostasis may also be involved. Type II reactions are most likely immune-mediated.[1,2] It has been suggested[4] that metabolism of halothane produces a reactive metabolite which binds covalently to proteins in the endoplasmic reticulum of hepatocytes. In susceptible patients it is believed that these metabolite-modified proteins provoke an immune response which is responsible for the liver damage. Findings[7,8] have implicated the cytochrome P450 isoenzyme CYP2E1 as having a major role in the metabolism of halothane and patients with high levels of this isoenzyme may be predisposed to developing immune-medicated liver damage after halothane exposure.

The UK CSM,[9] after receiving 84 further reports of hepatotoxicity between 1978 and 1985, issued the following **guidelines** on **precautions** to be taken before using halothane:

- a careful anaesthetic history should be taken to determine previous exposure and previous reactions to halothane
- repeated exposure to halothane within a period of at least 3 months should be avoided unless there are overriding clinical circumstances. An opinion has been expressed that the 3-month interval between exposures would be unlikely to prevent hepatotoxicity[2]
- a history of unexplained jaundice or pyrexia in a patient following exposure to halothane is an absolute contra-indication to its future use in that patient

These guidelines were reiterated in 1997 after the CSM were notified of a further 15 cases of acute liver failure all requiring transplantation.[10]

The problem of patients sensitised to halothane who require **subsequent anaesthesia** with a volatile anaesthetic has been discussed.[4] Although the incidence of hepatotoxicity produced by *enflurane* appears to be less than with halothane it is of a similar nature and there have been reports of several patients who apparently had cross-sensitivity to both. Hepatotoxicity with *isoflurane* appears to be rare and it was suggested that for the majority of patients sensitised to halothane, isoflurane would be likely to be free from hepatotoxic effects. However, there has been a report[11] of a patient who had had two previous exposures to isoflurane and subsequently developed liver function abnormalities after receiving halothane. Hepatotoxicity with *desflurane* (see p.1781) might also be associated with sensitisation to halothane.

1. Ray DC, Drummond GB. Halothane hepatitis. *Br J Anaesth* 1991; **67:** 84–99.
2. Neuberger JM. Halothane and hepatitis: incidence, predisposing factors and exposure guidelines. *Drug Safety* 1990; **5:** 28–38.
3. Rosenak D, *et al.* Halothane and liver damage. *Postgrad Med J* 1989; **65:** 129–35.
4. Kenna JG, Neuberger JM. Immunopathogenesis and treatment of halothane hepatitis. *Clin Immunother* 1995; **3:** 108–24.