5. Allan LG, *et al.* Hepatic glutathione S-transferase release after halothane anaesthesia: open randomised comparison with isoflurane. *Lancet* 1987; **i:** 771–4.
6. Neuberger J, Williams R. Halothane anaesthesia and liver damage. *BMJ* 1984; **289:** 1136–9.
7. Kharasch ED, *et al.* Identification of the enzyme responsible for oxidative halothane metabolism: implications for prevention of halothane hepatitis. *Lancet* 1996; **347:** 1367–71.
8. Kenna JC, *et al.* Formation of the C[F] CO-protein antigens implicated in the pathogenesis of halothane hepatitis is catalyzed in human liver microsomes in vitro by CYP 2E1. *Br J Clin Pharmacol* 1997; **43:** 209.
9. CSM. Halothane hepatotoxicity. *Current Problems 18* 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024425&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
10. CSM/MCA. Safety issues in anaesthesia: reminder: hepatotoxicity with halothane. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)
11. Slayter KL, *et al.* Halothane hepatitis in a renal transplant patient previously exposed to isoflurane. *Ann Pharmacother* 1993; **27:** 101.

Precautions

The risk of halothane hepatitis led the UK CSM to issue guidelines on its use (see Effects on the Liver, under Adverse Effects, above). It is also recommended that patients be informed of any reactions and that this be done in addition to the updating of the patients' medical records.

It is recommended in the UK that halothane should not be used for dental procedures outside hospital in patients under 18 years old.

Halothane reduces uterine muscle tone during pregnancy and generally its use is not recommended in obstetrics because of the increased risk of postpartum haemorrhage.

Premedication with atropine has been recommended to reduce vagal tone and to prevent bradycardia and severe hypotension.

Allowance may need to be made for any increase in CSF pressure or in cerebral blood flow. Halothane should be used with caution in patients with phaeochromocytoma.

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with halothane.

See also Precautions for General Anaesthetics, p.1779.

Abuse. A brief review[1] of abuse of volatile anaesthetics found that of 14 patients who had ingested or sniffed halothane 10 had died. Another patient who had injected halothane intravenously also died. There has also been another report[2] of fatalities resulting from acute pulmonary oedema after intravenous injection of halothane.

1. Yamashita M, *et al.* Illicit use of modern volatile anaesthetics. *Can Anaesth Soc J* 1984; **31:** 76–9.
2. Berman P, Tattersal M. Self-poisoning with intravenous halothane. *Lancet* 1982; **i:** 340.

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

Trace amounts of halothane have been detected in the breast milk of an anaesthetist exposed to environmental halothane in the operating theatre.[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 25/05/04)
2. Coté CJ, *et al.* Trace concentrations of halothane in human breast milk. *Br J Anaesth* 1976; **48:** 541–3.

Porphyria. Halothane has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Adrenaline and most other sympathomimetics, and theophylline should be avoided during halothane anaesthesia since they can produce cardiac arrhythmias; the risk of arrhythmias is also increased if halothane is used in patients receiving dopaminergics. The effects of competitive neuromuscular blockers such as atracurium, and of ganglion blockers such as trimetaphan are enhanced by halothane and if required they should be given in reduced dosage. Morphine increases the depressant effects of halothane on respiration. Chlorpromazine also enhances the respiratory depressant effect of halothane. The effects of both ergometrine and oxytocin on the parturient uterus are diminished by halothane.

See also Interactions of General Anaesthetics, p.1779.

Antiepileptics. For a case of *phenytoin* intoxication associated with halothane anaesthesia, see p.497.

Benzodiazepines. *Midazolam* has been reported to potentiate the anaesthetic action of halothane.[1]

1. Inagaki Y, *et al.* Anesthetic interaction between midazolam and halothane in humans. *Anesth Analg* 1993; **76:** 613–17.

General anaesthetics. For a report that halothane increases serum concentrations of *propofol*, see p.1792.

Neuromuscular blockers. For the potentiation of the neuromuscular blockade of neuromuscular blockers such as *atracurium* by halothane, see p.1904. For increased toxicity during halothane anaesthesia, see *suxamethonium* p.1911.

Trichloroethane. A report[1] of 2 patients showing evidence of chronic cardiac toxicity after repeated exposure to trichloroethane. In both cases there was circumstantial evidence of a deterioration after routine anaesthetic use of halothane.

1. McLeod AA, *et al.* Chronic cardiac toxicity after inhalation of 1,1,1-trichloroethane. *BMJ* 1987; **294:** 727–9.

Xanthines. For references to increased cardiotoxicity when patients taking *theophylline* were anaesthetised with halothane, see p.1145.

Pharmacokinetics

Halothane is absorbed on inhalation. It has a relatively low solubility in blood and is more soluble in the neutral fats of adipose tissue than in the phospholipids of brain cells. Up to 80% of inhaled halothane is excreted unchanged through the lungs. Up to 20% is metabolised by the liver by oxidative and, under hypoxic conditions, reductive pathways. Urinary metabolites include trifluoroacetic acid and bromide and chloride salts (oxidative pathway) and fluoride salts (reductive pathway). Halothane diffuses across the placenta and has been detected in breast milk.

Uses and Administration

Halothane 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 0.64% in the elderly to 1.08% in infants. It is non-flammable and is not explosive when mixed with oxygen at normal atmospheric pressure. It is not irritant to the skin and mucous membranes and does not produce necrosis when spilt on tissues. It suppresses salivary, bronchial, and gastric secretions and dilates the bronchioles. However, its use has diminished due to the risk of hepatotoxicity; in the UK, it is only available on a named-patient basis and in other countries, such as the USA, it has been withdrawn from the market.

Halothane is used for the induction and maintenance of general anaesthesia (p.1780) and is given using a calibrated vaporiser to provide close control over the concentration of inhaled vapour.

Anaesthesia may be induced with 2 to 4% v/v of halothane in oxygen or mixtures of nitrous oxide and oxygen; induction may also be started at a concentration of 0.5% v/v and increased gradually to the required level. For induction in children a concentration of 1.5 to 2% v/v has been used. It takes up to about 5 minutes to attain surgical anaesthesia and halothane produces little or no excitement in the induction period. The more usual practice is to induce anaesthesia with an intravenous agent. Anaesthesia is maintained with concentrations of 0.5 to 2% v/v depending on the flow rate used; the lower concentration is usually suitable for the elderly.

Adequate muscle relaxation is only achieved with deep anaesthesia so a neuromuscular blocker is given to increase muscular relaxation if necessary.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ineltano; ***Austral.:*** Fluothane; ***Austria:*** Fluothane†; ***Braz.:*** Fluothane; ***Chile:*** Fluothane†; ***Cz.:*** Narcotan; ***Fr.:*** Fluothane†; ***Ger.:*** Fluothane†; ***Gr.:*** Fluothane†; ***Hung.:*** Narcotan; ***India:*** Fluothane; ***Indon.:*** Fluothane; ***Israel:*** Fluothane†; ***Malaysia:*** Fluothane†; ***NZ:*** Fluothane; ***Pol.:*** Narcotan; ***S.Afr.:*** Fluothane†; ***Spain:*** Fluothane; ***Swed.:*** Fluothane†; ***Turk.:*** Fluothane; ***USA:*** Fluothane†.

Isoflurane *(BAN, USAN, rINN)*

Compound 469; Isofluraani; Isofluran; Isoflurano; Isofluranum; Izoflurán; Izofluran; Izofluranas. 1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether; 2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane.

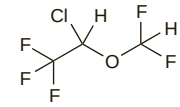
Изофлуран

$C_3H_2ClF_5O$ = 184.5.

CAS — 26675-46-7.

ATC — N01AB06.

ATC Vet — QN01AB06.



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

Ph. Eur. 6.2 (Isoflurane). A clear, colourless, mobile, heavy liquid. B.p. about 48°. It is non-flammable. Practically insoluble in water; miscible with dehydrated alcohol and with trichloroethylene. Store in airtight containers. Protect from light.

USP 31 (Isoflurane). A clear, colourless, volatile liquid having a slight odour. B.p. about 49°. Insoluble in water; miscible with common organic solvents and with fats and oils. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As with other halogenated anaesthetics, respiratory depression, hypotension, arrhythmias, and malignant hyperthermia have been reported; patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with isoflurane. Isoflurane differs from halothane and enflurane in that it produces less cardiac depression than either drug and heart rate may be increased. Also isoflurane sensitises the myocardium to sympathomimetics to a lesser extent than halothane and enflurane. The incidence of cardiac arrhythmias is lower with isoflurane than with halothane. Shivering, nausea, and vomiting have been reported in the postoperative period.

Induction with isoflurane is not as smooth as with halothane and this may be connected with its pungency; breath holding, coughing, and laryngospasm may occur. It has been reported to increase the cerebrospinal pressure and should be used with caution in patients with raised intracranial pressure. Isoflurane relaxes the uterine muscle; increased blood loss may occur after curettage or termination of pregnancy.

In order to minimise the risk of developing elevated carboxyhaemoglobin levels, carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as isoflurane (see below).

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

◊ A comparison[1] of isoflurane and halothane for outpatient dental anaesthesia in children considered that isoflurane would produce fewer arrhythmias than halothane, but that the ease of induction and the quality of anaesthesia was inferior to that with halothane. Others[2] also found a higher incidence of coughing, salivation, and laryngospasm with isoflurane than halothane, but felt that it could be used as an alternative.

Further information on the adverse effects profile of isoflurane can be obtained from the report of and commentaries on an extensive multicentre study of patients undergoing anaesthesia with this agent.[3,4]

1. Cattermole RW, *et al.* Isoflurane and halothane for outpatient dental anaesthesia in children. *Br J Anaesth* 1986; **58:** 385–9.
2. McAteer PM, *et al.* Comparison of isoflurane and halothane in outpatient paediatric dental anaesthesia. *Br J Anaesth* 1986; **58:** 390–3.
3. Forrest JB, *et al.* A multi-centre clinical evaluation of isoflurane. *Can Anaesth Soc J* 1982; **29** (suppl): S1–S69.
4. Levy WJ. Clinical anaesthesia with isoflurane: a review of the multicentre study. *Br J Anaesth* 1984; **56:** 101S–112S.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water

content. No cases of this complication had been reported to date in the UK.

1. Committee on Safety of Medicines/Medicines Control Agency. Safety issues in anaesthesia: volatile anesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Effects on the cardiovascular system. Isoflurane is considered to produce less cardiovascular depression than halothane. However, the results of a study[1] suggest that while this may be true for young patients, in elderly patients isoflurane appears to have a cardiac depressant effect similar to that of halothane.

1. McKinney MS, *et al.* Cardiovascular effects of isoflurane and halothane in young and elderly adult patients. *Br J Anaesth* 1993; **71:** 696–701.

CEREBRAL BLOOD FLOW. Autoregulation of cerebral blood flow appears to be impaired at higher concentrations of isoflurane. A study[1] in healthy subjects found that increasing isoflurane anaesthesia from a concentration of 1 to 2 MAC increased cerebral blood flow and reduced cerebral oxygen metabolism.

1. Olsen KS, *et al.* Effect of 1 or 2 MAC isoflurane with or without ketanserin on cerebral blood flow autoregulation in man. *Br J Anaesth* 1994; **72:** 66–71.

CORONARY CIRCULATION. Halothane, enflurane, and isoflurane decrease coronary perfusion pressure, coronary blood flow, ventricular function, and myocardial oxygen demand. Halothane and enflurane have a variable effect on coronary vascular resistance, but isoflurane dilates coronary vessels.[1] There has been concern over the potential of isoflurane to produce coronary steal and whether this effect is detrimental in patients with ischaemic heart disease.[2] However, despite conflicting results of individual studies[3-6] an early review[7] concluded that isoflurane could be used safely even in high-risk patients with coronary artery disease provided that blood pressure and heart rate were maintained close to baseline concentrations. A subsequent review[8] considered that more recent evidence supported the use of isoflurane as the anaesthetic agent of choice in patients with coronary heart disease.

1. Quail AW. Modern inhalational anaesthetic agents: a review of halothane, isoflurane and enflurane. *Med J Aust* 1989; **150:** 95–102.
2. Stoelting RK. Anesthesiology. *JAMA* 1991; **265:** 3103–5.
3. Buffington CW, *et al.* The prevalence of steal-prone coronary anatomy in patients with coronary artery disease: an analysis of the coronary artery surgery study registry. *Anesthesiology* 1988; **69:** 721–7.
4. Inoue K, *et al.* Does isoflurane lead to a higher incidence of myocardial infarction and perioperative death than enflurane in coronary artery surgery? A clinical study of 1178 patients. *Anesth Analg* 1990; **71:** 469–74.
5. Slogoff S, *et al.* Steal-prone coronary anatomy and myocardial ischemia associated with four primary anesthetic agents in humans. *Anesth Analg* 1991; **72:** 22–7.
6. Stühmeier KD, *et al.* Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery. *Br J Anaesth* 1992; **69:** 602–6.
7. Hogue CW, *et al.* Anesthetic-induced myocardial ischemia: the isoflurane-coronary steal controversy. *Coron Artery Dis* 1993; **4:** 413–19.
8. Agnew NM, *et al.* Isoflurane and coronary heart disease. *Anaesthesia* 2002; **57:** 338–47.

Effects on the kidneys. See under Metabolism in Pharmacokinetics, below.

Effects on the liver. Of 45 cases of isoflurane-associated hepatotoxicity reported to the FDA between 1981 and 1984 there was some other cause for the liver damage in 29. While isoflurane might have been one of the causes of the damage in the other 16 cases, there was not a reasonable likelihood of an association between isoflurane and postoperative liver impairment.[1] Subsequent rare cases of hepatotoxicity,[2-7] sometimes fatal,[2,5,7] have suggested that isoflurane may induce hepatitis, though much less frequently than halothane, and that there may be cross-sensitisation with other halogenated anaesthetics.

See also under the Adverse Effects of Halothane, p.1784.

1. Stoelting RK, *et al.* Hepatic dysfunction after isoflurane anesthesia. *Anesth Analg* 1987; **66:** 147–53.
2. Carrigan TW, Straughen WJ. A report of hepatic necrosis and death following isoflurane anesthesia. *Anesthesiology* 1987; **67:** 581–3.
3. Sinha A, *et al.* Isoflurane hepatotoxicity: a case report and review of the literature. *Am J Gastroenterol* 1996; **91:** 2406–9.
4. Hasan F. Isoflurane hepatotoxicity in a patient with a previous history of halothane-induced hepatitis. *Hepatogastroenterology* 1998; **45:** 518–22.
5. Turner GB, *et al.* Fatal hepatotoxicity after re-exposure to isoflurane: a case report and review of the literature. *Eur J Gastroenterol Hepatol* 2000; **12:** 955–9.
6. Malnick SDH, *et al.* Acute cholestatic hepatitis after exposure to isoflurane. *Ann Pharmacother* 2002; **36:** 261–3.
7. Ihtiyar E, *et al.* Fatal isoflurane hepatotoxicity without re-exposure. *Indian J Gastroenterol* 2006; **25:** 41–2.

Effects on the nervous system. Seizures associated with induction of anaesthesia with isoflurane have been reported in patients without known neurological abnormalities and not undergoing neurosurgery.[1,2] However, data from a retrospective analysis of patients undergoing intracranial surgery indicated that when convulsions occurred postoperatively in these conditions, it was the neurosurgical procedures rather than the anaesthetics that were responsible.[3]

See also under Status Epilepticus in Uses, below.

1. Poulton TJ, Ellingson RJ. Seizure associated with induction of anesthesia with isoflurane. *Anesthesiology* 1984; **61:** 471–6.
2. Hymes JA. Seizure activity during isoflurane anesthesia. *Anesth Analg* 1985; **64:** 367–8.
3. Christys AR, *et al.* Retrospective study of early postoperative convulsions after intracranial surgery with isoflurane or enflurane anaesthesia. *Br J Anaesth* 1989; **62:** 624–7.

Effects on the respiratory tract. A study[1] conducted mainly in adults found that humidification of anaesthetic mixtures containing isoflurane could reduce respiratory complications such as coughing, laryngospasm, and breath-holding that were usually associated with the use of isoflurane for induction. However, a similar study[2] in children failed to confirm these findings.

1. van Heerden PV, *et al.* Effect of humidification on inhalation induction with isoflurane. *Br J Anaesth* 1990; **64:** 235–7.
2. McAuliffe GL, *et al.* Effect of humidification on inhalation induction with isoflurane in children. *Br J Anaesth* 1994; **73:** 587–9.

Effects on the skin. There have been rare reports of contact dermatitis to isoflurane in anaesthetists.[1,2]

1. Caraffini S, *et al.* Isoflurane: an uncommon cause of occupational airborne contact dermatitis. *Contact Dermatitis* 1998; **38:** 286.
2. Muncaster A, *et al.* Allergic contact dermatitis to isoflurane. *Br J Dermatol* 1999; **141:** (suppl 55): 96–7.

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

Interactions

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

See also Interactions of General Anaesthetics, p.1779.

General anaesthetics. For a report that isoflurane increases serum concentrations of *propofol*, see p.1792.

Pharmacokinetics

Isoflurane is absorbed on inhalation. The blood/gas partition coefficient is lower than that of enflurane or halothane. It is mostly excreted unchanged through the lungs. About 0.2% of inhaled isoflurane is metabolised, mainly to inorganic fluoride.

Metabolism. In 26 patients sedated with isoflurane for 24 hours, plasma fluoride ion concentration increased from a mean of 4.03 nanomol/mL to 13.57 nanomol/mL in 12 hours after stopping sedation.[1] These fluoride concentrations were considered to be too low to cause clinical renal dysfunction. In 30 patients sedated with isoflurane for up to 127 hours (mean duration was 36 hours), mean plasma fluoride ion concentration increased[2] to 20.01 nanomol/mL during sedation and continued rising for 16 hours after stopping isoflurane to a maximum mean concentration of 25.34 nanomol/mL; thereafter, levels gradually declined to normal values by the fifth day. Despite the increased plasma fluoride ion concentrations, no biochemical or clinical evidence of deterioration in renal function was found. Giving isoflurane for 34 days to a patient with tetanus who required sedation to facilitate mechanical ventilation resulted[3] in sustained fluoride ion concentrations of 50 nanomol/mL and a peak concentration of 87 nanomol/mL. Although such concentrations are considered to be potentially nephrotoxic no clinical effect on renal function was found.

1. Kong KL, *et al.* Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects. *Br J Anaesth* 1990; **64:** 159–62.
2. Spencer EM, *et al.* Plasma inorganic fluoride concentrations during and after prolonged (>24h) isoflurane sedation: effect on renal function. *Anesth Analg* 1991; **73:** 731–7.
3. Stevens JJWM, *et al.* Prolonged use of isoflurane in a patient with tetanus. *Br J Anaesth* 1993; **70:** 107–109.

Uses and Administration

Isoflurane is a volatile halogenated anaesthetic given by inhalation. It is an isomer of enflurane and has anaesthetic actions similar to those of halothane (p.1785). Isoflurane has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) ranging from 1.05% in the elderly to 1.87% in infants. It is used in the induction and maintenance of general anaesthesia (p.1780) although induction is more often carried out using an intravenous anaesthetic. Isoflurane is also used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures.

Isoflurane is given using a calibrated vaporiser. If it is used for induction then it is given with oxygen or oxygen and nitrous oxide mixtures and induction should start with an isoflurane concentration of 0.5% v/v increased to 1.5 to 3% v/v which generally produces surgical anaesthesia within 10 minutes. Its pungency may limit the rate of induction. Anaesthesia may be maintained with a concentration of 1 to 2.5% v/v with oxygen and nitrous oxide mixtures; 1.5 to 3.5% v/v may be required if used only with oxygen. Isoflurane 0.5 to 0.75% v/v with oxygen and nitrous oxide mixtures is suitable to maintain anaesthesia for caesarean section. Although isoflurane is reported to possess muscle relaxant properties, neuromuscular blockers may nevertheless be required. Recovery is rapid.

Anaesthesia. ***CAESAREAN SECTION.*** Isoflurane 0.8% v/v has been found to be a suitable supplement to nitrous oxide-oxygen anaesthesia for patients undergoing caesarean section.[1] It has been suggested[2] that an overpressure technique might be of use to further reduce awareness in such patients. Giving isoflurane at a concentration of 2% v/v for 5 minutes followed by concentrations of 1.5% v/v for the next 5 minutes and 0.8% v/v thereafter produced higher arterial concentrations of isoflurane in patients undergoing caesarean section than when it was given at a concentration of 1% v/v throughout.[2]

1. Dwyer R, *et al.* Uptake of halothane and isoflurane by mother and baby during Caesarean section. *Br J Anaesth* 1995; **74:** 379–83.
2. McCrirrick A, *et al.* Overpressure isoflurane at Caesarean section: a study of arterial isoflurane concentrations. *Br J Anaesth* 1994; **72:** 122–4.

Pain. Isoflurane is used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures but studies[1,2] have been unable to confirm that it had an analgesic effect at subanaesthetic concentrations. The use of isoflurane 0.2 or 0.25% v/v in a mixture of nitrous oxide 50% v/v and oxygen 50% v/v has been studied.[3,4]

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.
2. Roth D, *et al.* Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials. *Br J Anaesth* 1996; **76:** 38–42.
3. Wee MYK, *et al.* Isoflurane in labour. *Anaesthesia* 1993; **48:** 369–72.
4. Bryden FM, *et al.* Isoflurane for removal of chest drains after cardiac surgery. *Br J Anaesth* 1994; **73:** 712P–713P.

Sedation. ***INTENSIVE CARE.*** The various drugs used to provide sedation in intensive care are discussed on p.957. Isoflurane is not usually considered for such a purpose but in a comparative 24-hour study[1] in 60 patients requiring mechanical ventilation, isoflurane 0.1 to 0.6% v/v in an air-oxygen mixture produced satisfactory sedation for a greater proportion of time than did the continuous infusion of midazolam 10 to 200 micrograms/kg per hour. Patients given isoflurane also recovered more rapidly. Isoflurane has also been used successfully for sedation over 5 days in a 3-year-old infant who required ventilation for pneumonia, a complication of the child's myasthenia gravis.[2] However, there has been some concern over high plasma fluoride concentrations after prolonged use of isoflurane (see under Metabolism in Pharmacokinetics, above).

1. Kong KL, *et al.* Isoflurane compared with midazolam for sedation in the intensive care unit. *BMJ* 1989; **298:** 1277–80.
2. McBeth C, Watkins TGL. Isoflurane for sedation in a case of congenital myasthenia gravis. *Br J Anaesth* 1996; **77:** 672–4.

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. Despite rare reports of seizures associated with the use of isoflurane in anaesthetic procedures (see Effects on the Nervous System, above) it has been used successfully,[1-3] typically in concentrations of 0.5 to 1% v/v, to control refractory convulsive status epilepticus. Although some[4] consider that isoflurane-induced coma may be more easy to control than barbiturate-induced coma, the use of isoflurane may be limited by the need for special anaesthetic equipment and continuous EEG monitoring.

1. Meeke RI, *et al.* Isoflurane for the management of status epilepticus. *DICP Ann Pharmacother* 1989; **23:** 579–81.
2. Hilz MJ, *et al.* Isoflurane anaesthesia in the treatment of convulsive status epilepticus. *J Neurol* 1992; **239:** 135–7.
3. Mirsattari SM, *et al.* Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol* 2004; **61:** 1254–9.
4. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Forane; Zuflax; ***Austral.:*** AErrane; Forthane; ***Austria:*** Forane; ***Belg.:*** Forene†; ***Braz.:*** Forane; Isoforine; Isothane†; ***Canad.:*** Forane; ***Chile:*** Forene; ***Cz.:*** AErrane; Forane; ***Denm.:*** Forene; ***Fin.:*** Forene; ***Ger.:*** Forene; ***Gr.:*** Forenium; ***Hong Kong:*** Forane; ***Hung.:*** AErrane; Forane; ***Indon.:*** AErrane; Forane; ***Irl.:*** Forane; ***Israel:*** AErrane; Forane; ***Ital.:*** AErrane; Forane; ***Malaysia:*** Forane; ***Mex.:*** Forane; Lisorane†; Sofloran; ***Neth.:*** AErrane; Forene; ***Norw.:*** Forene; ***NZ:*** AErrane; Forane; ***Philipp.:*** AErrane; Forane; ***Pol.:*** AErrane; Forane; ***Port.:*** Forene; ***Rus.:*** Forane (Форан)†; ***S.Afr.:*** AErrane; Forane; ***Singapore:*** Forane; ***Spain:*** AErrane; Forane; ***Swed.:*** Forene; ***Switz.:*** Forene; ***Thai.:*** AErrane; Forane; ***Turk.:*** AErrane; Forane; ***UK:*** AErrane; ***USA:*** Forane; Terrell; ***Venez.:*** Forene.

Ketamine Hydrochloride

(BANM, USAN, rINNM)

CI-581; CL-369; CN-52372-2; Hidrocloruro de ketamina; Ketamiinihydrokloridi; Ketamin Hidroklorür; Kétamine, chlorhydrate de; Ketamin-hidroklorid; Ketamin-hydrochlorid; Ketaminhydroklorid; Ketamini hydrochloridum; Ketamino hidrochloridas; Ketaminy chlorowodorek. (±)-2-(2-Chlorophenyl)-2-methylaminocyclohexanone hydrochloride.

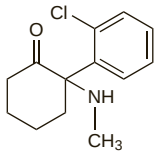
Кетамина Гидрохлорид

$C_{13}H_{16}ClNO,HCl$ = 274.2.

CAS — 6740-88-1 (ketamine); 1867-66-9 (ketamine hydrochloride).

ATC — N01AX03.

ATC Vet — QN01AX03.



(ketamine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of ketamine:
Animal trank; Animal tranquilizer; Bump; Cat tranquilizer; Cat valium; Elephant tranquilizer; Green; Honey oil; Horse tranquilizer; Jet; Jet fuel; K; "K"; K wire; Kay Jay; K-blast; Keets; Keezy; Keller; Kellys day; Kenny; Ket; Keta; Ketaset; KFC; Kit kat; Kit-Kat; Kitty; KKK; Klarko K Kat; Klarky Kat; Kustard; Lady K; Naughty horsey; Old Man; Property of Sir John; Purple; Regretamine; Special K; Special "K"; Special la coke; Super acid; Super C; Super K; Tranquilizer; Triple K; Vetamine; Vitamin K; Wonky.

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

Ph. Eur. 6.2 (Ketamine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 4.1. Protect from light.

USP 31 (Ketamine Hydrochloride). A white crystalline powder having a slight characteristic odour. Soluble 1 in 4 of water, 1 in 14 of alcohol, 1 in 60 of dehydrated alcohol and of chloroform, and 1 in 6 of methyl alcohol; practically insoluble in ether. pH of a 10% solution in water is between 3.5 and 4.1. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. Ketamine hydrochloride is incompatible with soluble barbiturates. The US licensed product information recommends that when use of diazepam and ketamine is required they should be given separately and not mixed in the same giving equipment.

Esketamine Hydrochloride *(BANM, rINNM)*

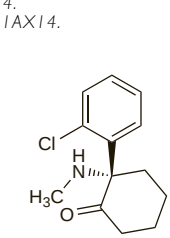
Esketamiinihydrokloridi; Eskétamine, Chlorhydrate d'; Eskétamine, chlorhydrate de; Esketamin-hydrochlorid; Esketaminhydroklorid; Esketamini hydrochloridum; Esketamino hidrochloridas; Hidrocloruro de esketamina; *S*-Ketamine Hydrochloride.

Эскетамина Гидрохлорид

CAS — 33643-46-8 (esketamine).

ATC — N01AX14.

ATC Vet — QN01AX14.



(esketamine)

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

Ph. Eur. 6.2 (Esketamine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 4.5. Protect from light.

Adverse Effects

Emergence reactions are common during recovery from ketamine anaesthesia and include vivid often unpleasant dreams, confusion, hallucinations, and irrational behaviour. Children and elderly patients appear to be less sensitive. Patients may also experience increased muscle tone, sometimes resembling seizures. Blood pressure and heart rate may be temporarily increased by ketamine; hypotension, arrhythmias, and bradycardia have occurred rarely.

Respiration may be depressed after rapid intravenous injection or with high doses. Apnoea and laryngospasm have occurred. Diplopia and nystagmus may occur. Nausea and vomiting, lachrymation, hypersalivation, and raised intra-ocular and CSF pressure have also been reported. Transient skin rashes and pain at the site of injection may occur.

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

Effects on the cardiovascular system. Ketamine has been advocated by some for maintaining or increasing cardiovascular performance in selected patients during induction of anaesthesia as it may increase blood pressure and heart rate.[1] However, there have been reports of reduced cardiac and pulmonary performance in severely ill patients[1] and of arrhythmias.[2]

Some of the cardiovascular effects of ketamine may be attenuated by premedication with diazepam[2] or clonidine.[3]

1. Waxman K, *et al*. Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg* 1980; **59:** 355–8.
2. Cabbabe EB, Behbahani PM. Cardiovascular reactions associated with the use of ketamine and epinephrine in plastic surgery. *Ann Plast Surg* 1985; **15:** 50–2.
3. Tanaka M, Nishikawa T. Oral clonidine premedication attenuates the hypertensive response to ketamine. *Br J Anaesth* 1994; **73:** 758–62.

Effects on the liver. Changes in liver enzyme values have occurred after ketamine in an initial dose of 1 mg/kg followed by continuous infusion as a 0.1% solution.[1]

1. Dundee JW, *et al*. Changes in serum enzyme levels following ketamine infusions. *Anaesthesia* 1980; **35:** 12–16.

Effects on mental state. Mental disturbances following ketamine anaesthesia may vary in incidence from less than 5% to greater than 30%.[1] See also Abuse, below.

1. White PF, *et al.* Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 1982; **56:** 119–36.

Effects on the skin. Harlequin-like colour skin changes were reported[1] in a 9-month-old boy during anaesthesia with ketamine 15 mg.

1. Wagner DL, Sewell AD. Harlequin color change in an infant during anesthesia. *Anesthesiology* 1985; **62:** 695.

Malignant hyperthermia. Malignant hyperthermia has been reported in a patient given ketamine.[1]

1. Rasore-Quartino A, *et al.* Forma atipica di ipertermia maligna: osservazione di un caso da ketamina. *Pathologica* 1985; **77:** 609–17.

Precautions

Ketamine is contra-indicated in patients in whom elevation of blood pressure would be a serious hazard including those with hypertension or a history of cerebrovascular accident. Cardiac function should be monitored in patients found to have hypertension or cardiac decompensation. Ketamine should be used with caution in patients with elevated CSF pressure. It can raise intra-ocular pressure and should not be used in the presence of eye injury or increased intra-ocular pressure.

Ketamine does not reliably suppress pharyngeal and laryngeal reflexes and mechanical stimulation of the pharynx should be avoided unless a muscle relaxant is used.

The use of ketamine should be avoided in patients prone to hallucinations or psychotic disorders. Verbal, tactile, and visual stimuli should be kept to a minimum during recovery in an attempt to reduce the risk of emergence reactions.

See also Precautions for General Anaesthetics, p.1779.

Abuse. Health care workers in the USA were alerted to the dangers associated with the abuse of ketamine as long ago as 1979.[1] Similar concern had also been voiced in the UK[2] over the abuse of ketamine at social gatherings where it has been taken intranasally or orally. A WHO expert committee[3] considered in 2006 that the available information on ketamine was not sufficient to warrant international control. Studies in *animals* have shown that ketamine can produce dependence, however, reports of dependence in humans are limited (see below). Although tolerance may occur there is no evidence of a withdrawal syndrome (but see below). Ketamine abuse has been reported in a number of countries.

Ketamine produces a state of psychological dissociation resulting in hallucinations and out of body or near death experiences. It can induce a state of helplessness in which the user loses awareness of the environment and this together with severe loss of coordination and pronounced analgesia can put the user at great risk. Furthermore, some users experience a state in which they are unconcerned about whether they live or die. Ketamine has the potential for compulsive repeated use and there have been reports of users self-injecting ketamine several times a day for prolonged periods. Dependency may develop[4,5] and withdrawal symptoms requiring detoxification can occur.[4] Frequent use may produce long-lasting memory impairment.[6] Other adverse effects include a report[7] of an acute dystonic reaction in a 20-year old man following self-administration of ketamine intravenously.

In one case series[8] of 20 patients presenting to hospital after ketamine abuse the most common symptoms included anxiety, chest pain, and palpitations. Frequent complications included agitation and rhabdomyolysis. Symptoms were generally short lived with most patients discharged within 5 hours.

Some[2] suggest that patients seeking medical attention are best placed in a quiet darkened room to recover with diazepam being given for unresponsive panic attacks while others advocate that such patients should be admitted to an intensive care unit for close monitoring.[9] The use of intravenous fluids to prevent rhabdomyolysis has also been recommended.[8]

Long-term and frequent abuse of ketamine has been associated with adverse effects on the urinary tract.[10-12] Patients may present with symptoms of dysuria, frequency, urgency, urinary incontinence, suprapubic pain, and haematuria. Examination has shown in some cases a contracted shrunken bladder and ulcerative cystitis. Complications have included hydronephrosis and renal impairment.

Ketamine is tasteless, odourless, and colourless and has been misused to incapacitate the victim and produce amnesia in sexual assaults and drug-facilitated rape ('date rape').[4]

1. Anonymous. Ketamine abuse. *FDA Drug Bull* 1979; **9:** 24.
2. Jansen KLR. Non-medical use of ketamine. *BMJ* 1993; **306:** 601–2.
3. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 06/08/08)
4. Smith KM, *et al*. Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59:** 1067–76.
5. Jansen KLR, Darracot-Cankovic R. The nonmedical use of ketamine, part two: A review of problem use and dependence. *J Psychoactive Drugs* 2001; **33:** 151–8.
6. Curran HV, Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. *Addiction* 2001; **96:** 749–60.
7. Felser JM, Orban DJ. Dystonic reaction after ketamine abuse. *Ann Emerg Med* 1982; **11:** 673–5.
8. Weiner AL, *et al*. Ketamine abusers presenting to the emergency department: a case series. *J Emerg Med* 2000; **18:** 447–51.
9. Gill PA. Non-medical use of ketamine. *BMJ* 1993; **306:** 1340.
10. Chu PSK, *et al.* 'Street ketamine'-associated bladder dysfunction: a report of ten cases. *Hong Kong Med J* 2007; **13:** 311–13.
11. Shahani R, *et al*. Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007; **69:** 810–12.
12. Cottrell AM, *et al*. Urinary tract disease associated with chronic ketamine use. *BMJ* 2008; **336:** 973.

Neurosurgery. Although the idea that ketamine should not be used in patients at risk from rises in intracranial pressure has limited its use in neurosurgical patients, a review[1] considered that if used with controlled ventilation and a GABA receptor agonist, and without nitrous oxide, it did not appear to have adverse effects in this group, and there was some evidence from *animal* studies that it might have neuroprotective properties.

1. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? *Anesth Analg* 2005; **101:** 524–34.

Interactions

Inhalational anaesthetics, such as ether and halothane, and other cerebral depressants may prolong the effect of ketamine and delay recovery. Prolonged recovery has also occurred when barbiturates and/or opioids have been given with ketamine. It has been recommended that ketamine should not be used with ergometrine.

See also Interactions of General Anaesthetics, p.1779.

Neuromuscular blockers. For the enhancement of the effect of *tubocurarine* or *atracurium* by ketamine, see p.1904.

Thyroid drugs. For a reference to increased cardiovascular adverse effects with *levothyroxine*, see p.2173.

Xanthines. For a reference to seizures and tachycardia attributed to an interaction between ketamine and *theophylline*, see p.1145.

Pharmacokinetics

After intravenous boluses, ketamine shows a bi- or triexponential pattern of elimination. The alpha phase lasts about 45 minutes with a half-life of 10 to 15 minutes. This first phase, which represents ketamine's anaesthetic action, is terminated by redistribution from the CNS to peripheral tissues and hepatic biotransformation to an active metabolite norketamine. Other