blood, then to the brain; recovery is a function of the removal of the anaesthetic from the brain. With injectable anaesthetics their activity is similarly dependent on their ability to penetrate the blood/brain barrier and recovery in turn is governed by their redistribution and excretion. The potency of inhalational anaesthetics is often expressed in terms of *minimum alveolar concentrations*, known as MAC values. The MAC of an anaesthetic is the concentration at 1 atmosphere that will produce immobility in 50% of subjects exposed to a noxious stimulus. Values given under the individual monographs are based on use without nitrous oxide as the latter can reduce the MAC. Other factors including age, body temperature, and concurrent medication such as opioid analgesics can also affect MAC values.

◊ General references.

1. Royston D, Cox F. Anaesthesia: the patient's point of view. *Lancet* 2003; **362:** 1648–58.
2. García-Miguel FJ, *et al.* Preoperative assessment. *Lancet* 2003; **362:** 1749–57.
3. Buhre W, Rossaint R. Perioperative management and monitoring in anaesthesia. *Lancet* 2003; **362:** 1839–46.
4. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; **362:** 1921–8.
5. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; **25:** 1773–88.
6. Stachnik J. Inhaled anesthetic agents. *Am J Health-Syst Pharm* 2006; **63:** 623–34. Correction. *ibid.* 2436.
7. Nathan N, Odin I. Induction of anaesthesia: a guide to drug choice. *Drugs* 2007; **67:** 701–23.

Anaesthesia. Many drugs are involved in achieving and maintaining conditions suitable for surgery. Conventional general anaesthesia may be divided into a number of stages including:

- premedication
- induction
- muscle relaxation and intubation
- maintenance
- analgesia
- reversal

A brief outline of the drugs typically used in each stage follows.

For **premedication**, benzodiazepines and some phenothiazines such as promethazine or alimemazine may be given to sedate and relieve *anxiety* in apprehensive patients. Butyrophenones such as droperidol have also been used. The benzodiazepines have useful amnesic and muscle-relaxant properties and short-acting oral forms are common in current regimens. The phenothiazines and butyrophenones are rarely used now although their antiemetic actions may be useful to control *postoperative nausea and vomiting* (see p.1700). Cloral hydrate is still used in some countries for pre-operative sedation. The use of barbiturates has largely ceased. For sedation of children the oral route is often preferred to injections, or the rectal route may be used in exceptional circumstances.

Antimuscarinics such as atropine, glycopyrronium, and hyoscine may be given to inhibit excessive *bronchial* and *salivary secretions* induced by intubation and some anaesthetics, although such use is less common nowadays. Antimuscarinics are also given as premedicants to reduce the intra-operative bradycardia and hypotension induced by drugs such as suxamethonium, halothane, or propofol or by vagal stimulation. Hyoscine also provides some degree of amnesia.

Opioids, including morphine and its derivatives, papaveretum and pethidine, have been widely used before surgery to reduce anxiety, smooth induction of anaesthesia, reduce overall anaesthetic requirements, and provide pain relief during and after surgery. The routine use of opioids as premedicants is now rare and generally restricted to patients already in pain. However, they continue to find a role at induction (below).

Patients may also be given drugs that reduce the danger from regurgitation and *aspiration* of gastric contents (see under Aspiration Syndromes, p.1693), such as the histamine H_2-antagonists, cimetidine and ranitidine, and the proton pump inhibitor, omeprazole. Cardiovascular drugs may be needed during surgery to control *blood pressure* and counteract *arrhythmias*.

The aim of **induction** is to produce anaesthesia rapidly and smoothly. Induction may be achieved with intravenous or inhalational anaesthetics but intravenous induction may be more pleasant for the patient. Intravenous drugs used include the barbiturate thiopental, the benzodiazepine midazolam, and other anaesthetics such as etomidate, propofol, or ketamine. Small doses of short-acting opioids, for example alfentanil, fentanyl, or remifentanil, given before or at induction allow the use of smaller induction doses of some drugs used for anaesthesia, and this technique is particularly suitable for poor-risk patients.

After induction, **muscle relaxation** with a rapidly acting depolarising neuromuscular blocker such as suxamethonium aids **intubation** of the patient. Longer acting, competitive neuromuscular blockers may then be given to allow procedures such as abdominal surgery to be carried out under lighter anaesthesia. For more detail, see Anaesthesia, p.1900.

Maintenance of anaesthesia may be achieved with an inhalational anaesthetic, an intravenous anaesthetic, or an intravenous opioid, either alone or in combination.

Opioid analgesics may also be given for **analgesia** as supplements during general anaesthesia (see also Balanced Anaesthesia, under Anaesthetic Techniques, below). Long-acting opioids such as morphine or papaveretum may cause postoperative respiratory depression. The short-acting opioid fentanyl, and its congeners alfentanil and sufentanil, appear to produce fewer circulatory changes and may be preferred to other opioids, especially in cardiovascular surgery; remifentanil may be valuable for its very short duration of action. Various combinations of analgesic techniques, including the use of pre-emptive analgesia, are used or are being investigated for the management of surgical pain (see Postoperative Analgesia, p.4).

At the end of surgery drugs are sometimes given to accelerate recovery by **reversal** of the effects of the various agents used during anaesthesia. The *neuromuscular block* produced by competitive neuromuscular blockers may be reversed with anticholinesterases such as neostigmine and edrophonium but atropine or glycopyrronium are also needed to prevent bradycardia and other muscarinic actions developing. The opioid antagonist naloxone has been given to reverse opioid-induced *respiratory depression*. However, it may antagonise the analgesic effects of the opioids in the control of postoperative pain and the increasing use of short-acting intravenous opioid analgesics should reduce the need for its use. Flumazenil is a benzodiazepine antagonist that is used to reverse the *central sedative effects* of benzodiazepines in anaesthetic procedures.

ANAESTHETIC TECHNIQUES. A balanced combination of drugs with different actions is often used to provide the various components of general anaesthesia including unconsciousness, muscle relaxation, and analgesia. This technique, termed **balanced anaesthesia**, has been reported to minimise intra-operative cardiovascular depression, to facilitate a rapid return of consciousness, and to have a low incidence of postoperative adverse effects such as nausea and vomiting, and excitation. Typically an opioid is given before or with induction and anaesthesia is induced using nitrous oxide and an intravenous barbiturate such as thiopental. The opioid is then given in small incremental doses to achieve and maintain adequate analgesia during surgery. Opioid analgesics commonly used in this technique include morphine, fentanyl, sufentanil, and alfentanil; buprenorphine and nalbuphine have also been used.

In **total intravenous anaesthesia** (TIVA), induction and maintenance of anaesthesia is achieved with one or more anaesthetics given intravenously. This allows high inspired oxygen concentrations in situations where hypoxaemia may otherwise occur, and is advantageous in surgery where delivery of inhaled anaesthetic may be difficult (for example in bronchoscopy). Combinations used in TIVA include propofol with alfentanil or fentanyl, and midazolam with alfentanil. Neuromuscular blockers are given to produce muscle relaxation but there can be difficulty in assessing the depth of anaesthesia in patients who are paralysed for mechanical ventilation, and there have been reports of awareness during procedures under total intravenous anaesthesia (see also Intraoperative Awareness under Precautions, above).

Although now largely obsolete, use of a neuroleptic with an opioid analgesic produces an altered state of consciousness known as **neuroleptanalgesia** in which the patient is calm and indifferent to the surroundings yet is responsive to commands. The technique was used for diagnostic or therapeutic procedures such as minor surgery, endoscopy, and changing dressings. Neuroleptanalgesia can be converted to **neuroleptanaesthesia** by the concurrent administration of nitrous oxide in oxygen; a muscle relaxant may also be included. Neuroleptanaesthesia is particularly useful if the patient's cooperation is required, as consciousness soon returns once the nitrous oxide is stopped. The neuroleptic most commonly employed was droperidol and it was usually used with fentanyl although other opioids have also been used. These procedures have since evolved into **conscious sedation** and **monitored anaesthetic care** techniques employing newer drugs.

Ketamine used alone can produce a state of **dissociative anaesthesia** similar to that of neuroleptanalgesia in which the patient may appear to be awake but is unconscious. Marked analgesia and amnesia are produced, but there may be an increase in muscle tone and emergence reactions. Dissociative anaesthesia is considered suitable for use in various diagnostic procedures, dressing changes, and in minor surgery not requiring muscle relaxation.

Techniques using **local anaesthetics** are discussed on p.1853.

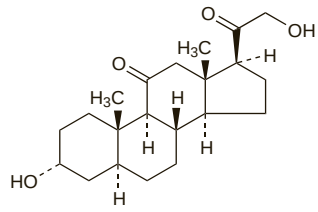
Alfadolone Acetate *(BANM, rINNM)*

Acetato de alfadolona; Alfadolone, Acétate d'; Alfadoloni Acetas; Alphadolone Acetate; GR-2/1574. 3α,21-Dihydroxy-5α-pregnane-11,20-dione 21-acetate.

Альфадолона Ацетат

$C_{23}H_{34}O_5$ = 390.5.

CAS — 14107-37-0 (alfadolone); 23930-37-2 (alfadolone acetate).



(alfadolone)

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Alfadolone Acetate). A white to creamy white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol; freely soluble in chloroform.

Profile

Alfadolone acetate has been used to enhance the solubility of alfaxalone (below). It possesses some anaesthetic properties and is considered to be about half as potent as alfaxalone.

Alfaxalone *(BAN, rINN)*

Alfaksaloni; Alfaxalon; Alfaxalona; Alfaxalonum; Alphaxalone; GR-2/234. 3α-Hydroxy-5α-pregnane-11,20-dione.

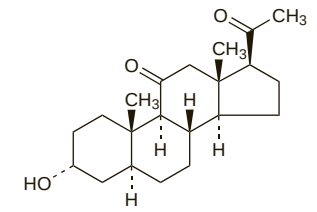
Альфаксалон

$C_{21}H_{32}O_3$ = 332.5.

CAS — 23930-19-0.

ATC — N01AX05.

ATC Vet — QN01AX05.



Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Alfaxalone). A white to creamy white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol; freely soluble in chloroform.

Profile

Alfaxalone was formerly used with alfadolone acetate (above) ['Althesin'], as an intravenous anaesthetic for induction and maintenance of general anaesthesia.

Adverse reactions associated with polyethoxylated castor oil (present as a vehicle) led to the general withdrawal of alfaxalone with alfadolone acetate from human use. It is still used in veterinary medicine.

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

Chloroform

Chloroformium Anesthesicum; Chloroformum; Chloroformum pro Narcosi; Cloroformo. Trichloromethane.

$CHCl_3$ = 119.4.

CAS — 67-66-3.

ATC — N01AB02.

ATC Vet — QN01AB02.

Pharmacopoeias. In *Br.*, *Chin.*, and *Viet.*

BP 2008 (Chloroform). A colourless volatile liquid with a characteristic odour. Not more than 5.0% v/v distils below 60° and the remainder distils at 60° to 62°. It contains 1.0 to 2.0% v/v of ethyl alcohol; amylene 50 micrograms/mL is permitted as an alternative to ethyl alcohol.

Slightly soluble in water; miscible with dehydrated alcohol, with ether, with fixed and volatile oils, and with most other organic solvents. Store in containers with glass stoppers or other suitable closures. Protect from light. The label should state whether it contains ethyl alcohol or amylene.

Stability. The addition of a small percentage of alcohol greatly retards the gradual oxidation that occurs when chloroform is exposed to air and light, and which results in its becoming contaminated with the very poisonous carbonyl chloride (phosgene) and with chlorine; the alcohol also serves to decompose any carbonyl chloride that may have been formed.

From a study[1] of chloroform losses from chloroform water and from 6 typical BPC mixtures under various conditions of storage the following shelf-lives were recommended: chloroform solutions and non-sedimented mixtures could be stored in well-closed well-filled containers for 2 months at ambient temperatures; when stored in partially-filled containers and periodically opened the shelf-life should not exceed 2 weeks; sedimented mixtures could be stored for 2 months in well-closed well-filled containers, but because loss of chloroform could be expected in containers periodically opened such mixtures should be prepared as required or packed in their final containers; for chloroform-containing mixtures in the home a shelf-life of 2 weeks was suggested.

1. Lynch M, *et al*. Chloroform as a preservative in aqueous systems: losses under "in-use" conditions and antimicrobial effectiveness. *Pharm J* 1977; **219:** 507–10.

Storage. It has been recommended[1] that if the period of use would exceed 6 weeks, PVC bottles should not be used for storing or dispensing: Chloroform and Morphine Tincture, or aqueous mixtures containing more than 5% thereof; mixtures or dispersions in which chloroform is present in excess of its aqueous solubility; aqueous mixtures containing chloroform and high concentrations of electrolytes; or of mixtures containing chloroform water.

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

Adverse Effects and Precautions

Chloroform depresses respiration and produces hypotension. Cardiac output is reduced and arrhythmias may develop. Poisoning can lead to respiratory depression and cardiac arrest. Delayed hepatotoxic and nephrotoxic reactions have occurred 6 to 24 hours after a dose; symptoms may include abdominal pain, vomiting, and, at a later stage, jaundice.

Liquid chloroform is irritant to the skin and mucous membranes and may cause burns if spilt on them. Suitable precautions should be taken to avoid skin contact with chloroform as it can penetrate skin and produce systemic toxicity. Chloroform is not flammable. Care should be taken not to vaporise chloroform in the presence of a flame because of the production of toxic gases.

In the UK medicinal products are limited to a chloroform content of not more than 0.5% (w/w or v/v as appropriate) of chloroform. Exceptions include supply by a doctor or dentist, or in accordance with his prescription, to a particular patient, and supply for anaesthetic purposes.

In the USA the FDA has banned the use of chloroform in medicines and cosmetics, because of reported carcinogenicity in *animals*. It has also been withdrawn from systemic use in other countries.

The sale within or import into England and Wales and Scotland of food containing any added chloroform is prohibited.

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

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

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)

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

Uses and Administration

Chloroform is a volatile halogenated anaesthetic that was used by inhalation, but safer drugs are now preferred in general anaesthesia.

Chloroform is used as a carminative and as a flavouring agent and preservative. For these purposes it is usually employed as Chloroform Spirit (BP 2008) or Double-strength Chloroform Water (BP 2008) but doubts have been cast on the safety of the long-term use of chloroform in mixtures.

Externally, chloroform has a rubefacient action.

Chloroform is also used as a solvent.

Anaesthesia. An historical review of the use of chloroform in clinical anaesthesia.[1]

1. Payne JP. Chloroform in clinical anaesthesia. *Br J Anaesth* 1981; **53:** 11S–15S.

Preparations

BP 2008: Chloroform and Morphine Tincture; Chloroform Spirit; Double-strength Chloroform Water.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Dentophar; ***Rus.:*** Eludril (Элюдрил); Espol (Эспол); ***S.Afr.:*** Diphenhydramine Expectorant Syrup; Mrs Johnsons American Soothing Syrup; SB Toothache Drops; Tandpyndruppels; Vicks Acta Plus; ***Venez.:*** Fiometil†; Gamasol†; Iodex†; Rubefric†.

Cyclopropane *(rINN)*

Ciclopropano; Cyclopropanum; Trimethylene.

Циклопропан

C_3H_6 = 42.08.

CAS — 75-19-4.

Pharmacopoeias. In *US.*

USP 31 (Cyclopropane). A colourless highly flammable gas with a characteristic odour and pungent taste. Freely soluble in alcohol; soluble in fixed oils. One volume dissolves in about 2.7 volumes of water at 15°.

Stability. CAUTION. Mixtures of cyclopropane with oxygen or air at certain concentrations are explosive. Cyclopropane should not be used in the presence of an open flame or of any electrical apparatus liable to produce a spark. Precautions should be taken against the production of static electrical discharge.

Storage and supply. Cyclopropane is supplied compressed in metal cylinders. National standards are usually in operation for the labelling and marking of such cylinders.

Adverse Effects and Precautions

Cyclopropane depresses respiration to a greater extent than many other anaesthetics. Laryngospasm, cardiac arrhythmias, or hepatic injury may occur. Cyclopropane increases the sensitivity of the heart to sympathomimetic amines. Malignant hyperthermia has also been reported. Postoperative nausea, vomiting, and headache are frequent.

Cyclopropane should be used with caution in patients with bronchial asthma and cardiovascular disorders. Premedication with atropine may be advisable to reduce vagal tone.

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

Abuse. Two of 4 deaths from abuse of volatile anaesthetics in operating rooms were attributed to cyclopropane.[1]

1. Bass M. Abuse of inhalation anesthetics. *JAMA* 1984; **251:** 604.

Malignant hyperthermia. Malignant hyperthermia was associated with cyclopropane.[1]

1. Lips FJ, *et al*. Malignant hyperthermia triggered by cyclopropane during cesarean section. *Anesthesiology* 1982; **56:** 144–6.

Interactions

Care is advised if adrenaline or other sympathomimetics are given during cyclopropane anaesthesia. Potentiation of competitive neuromuscular blockers occurs after use of cyclopropane.

See also Interactions for General Anaesthetics, p.1779.

Uses and Administration

Cyclopropane is an anaesthetic that has been given by inhalation for analgesia and induction and maintenance of general anaesthesia. It produces skeletal muscle relaxation, is non-irritant, and induction and recovery are rapid, but it is difficult to use and handle and other anaesthetics are generally preferred. Because of the risk of explosion, it has usually been given by means of a closed circuit. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) of 9.2%.

Desflurane *(USAN, rINN)*

Desfluraani; Desfluran; Desflurano; Desfluranum; I-653. (±)-2-Difluoromethyl 1,2,2,2-tetrafluoroethyl ether.

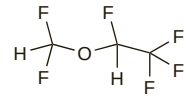
Десфлуран

$C_3H_2F_6O$ = 168.0.

CAS — 57041-67-5.

ATC — N01AB07.

ATC Vet — QN01AB07.



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

Ph. Eur. 6.2 (Desflurane). A clear, colourless, mobile, heavy liquid. B.p. about 22°. Practically insoluble in water; miscible with anhydrous alcohol. Store in a glass bottle fitted with a polyethylene-lined cap. Before opening the bottle, cool the contents to below 10°.

USP 31 (Desflurane). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Replace cap securely after each use. Protect from light.

Adverse Effects and Precautions

As with other halogenated anaesthetics, respiratory depression, hypotension, and arrhythmias may occur. Desflurane may rarely precipitate malignant hyperthermia in susceptible individuals. It appears to sensitise the myocardium to sympathomimetics to a lesser extent than halothane or enflurane. Nausea and vomiting have been reported in the postoperative period.

Desflurane is irritant to the airways and may provoke breath holding, apnoea, coughing, increased salivation, and laryngospasm. It is therefore not recommended for induction of anaesthesia in paediatric patients.

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with desflurane. Desflurane may increase CSF pressure and should therefore be used with caution in patients with, or at risk from, raised intracranial pressure.

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 desflurane (see below).

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

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. CSM/MCA. Safety issues in anaesthesia: volatile anaesthetic 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. A review[1] of *animal* and human studies concluded that the cardiorespiratory effects of desflurane were similar to those of isoflurane but that there might be better control of arterial pressure with desflurane during stressful stimuli. A study[2] in patients undergoing coronary artery bypass surgery showed that a state of haemodynamic stability suitable for patients at risk of myocardial ischaemia could be maintained when desflurane was used with the opioid analgesic fentanyl.

1. Warltier DC, Pagel PS. Cardiovascular and respiratory actions of desflurane: is desflurane different from isoflurane? *Anesth Analg* 1992; **75:** S17–S31.
2. Parsons RS, *et al*. Comparison of desflurane and fentanyl-based anaesthetic techniques for coronary artery bypass surgery. *Br J Anaesth* 1994; **72:** 430–8.

Effects on the liver. Although considered to be less hepatotoxic than some other halogenated anaesthetics (see under Adverse Effects of Halothane, p.1784), delayed hepatotoxicity has occurred in a 65-year-old woman after maintenance anaesthesia involving desflurane.[1] She had received halothane on two previous occasions which may have caused sensitisation. Investigation of