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.

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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.

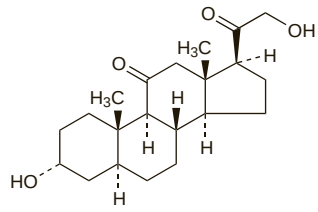
Alfadolone Acetate *(BANM, rINNM)*

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.

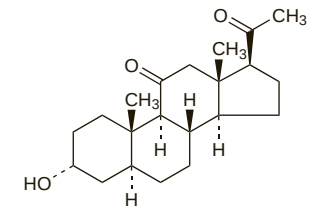
Альфаксалон

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