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# WHO Model Prescribing Information

## Drugs used in Anaesthesia



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# Preface

WHO's revised drug strategy, as adopted in Resolution WHA39.27 of the Thirty-ninth World Health Assembly in 1986, calls for the preparation of model prescribing information which is being developed to complement WHO's Model List of Essential Drugs.<sup>1</sup> The objective is to provide source material for adaptation by national authorities, particularly in developing countries, that wish to develop national drug formularies, drug compendia and similar material.

The information is to be regarded as illustrative rather than normative. It is appreciated that it is not possible to develop an information sheet on a specific drug that is appropriate to circumstances prevailing in each of WHO's Member States and that some countries have already formally adopted texts of their own that have a statutory connotation.

This volume has been reviewed by individual internationally accredited experts and the World Federation of Societies of Anaesthesiologists, which stands ready to provide advice to any national administration on how a basic anaesthetic service may best be organized. For practical details of anaesthetic techniques suitable for use in hospitals of first referral, the reader is referred to Dobson, M.B., *Anaesthesia at the district hospital* (Geneva, World Health Organization, 1988).

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<sup>1</sup>WHO Technical Report Series, No. 770, 1988 (*The use of essential drugs: third report of the WHO Expert Committee*).

### **Drug dosage**

Most drug doses are given per kilogram of body weight or as fixed doses calculated for adults of 60 kg.

### **Storage conditions**

Readers are referred to *The International Pharmacopoeia*, 3rd edition, vol. 1 & vol. 2 (Geneva, World Health Organization, 1979 & 1981) for definitions concerning containers for drugs.

### **Abbreviations used**

i.m. intramuscular(ly)  
i.v. intravenous(ly)

# Introduction

Sound theoretical and practical training followed by several years of supervised experience in the administration of anaesthetics is essential to develop the skills of the anaesthetist. Even within the recommended dosage range, anaesthetic agents can cause death when inappropriately used and only as a last resort should they be administered by non-specialized personnel.

## Emergency care

Ideally, fully equipped emergency services should be provided in every health centre. Where this is not feasible, selected health workers should be trained in basic anaesthetic techniques. It is important that transportation facilities should be available to ensure that as many patients as possible are brought within reach of the nearest emergency service. In the absence of transportation, efforts should be made to bring a trained anaesthetist to the side of the patient. Before injured or seriously ill patients are transported, consideration must be given to the need for respiratory support, supplementary oxygen, control of bleeding, relief of pain, fluid replacement and immobilization of fractures. In order to maintain the circulatory volume of seriously injured patients until more effective measures can be taken, and to allow for rapid parenteral delivery of the necessary drugs, an infusion of isotonic saline should be set up as soon as possible. Provided the patient is not shocked and there is no evidence of head injury, morphine should be administered immediately to relieve severe pain.

## Anaesthetic techniques

To produce a state of prolonged full surgical anaesthesia reliably and safely a variety of drugs is needed. Irrespective of whether a general or conduction (regional or local) anaesthetic technique is used, it is essential that facilities for intubation and mechanically assisted ventilation are available.

Whenever possible, anaesthesia, whether conduction or general, should be deferred for at least 4 hours from the time the patient last ingested either solids or liquids. Since trauma significantly delays gastric emptying time, regurgitation or vomiting may still

occur even when this rule is observed. At all times a properly functioning suction machine, tested prior to anaesthesia, must be available.

## **Premedication**

Pre-anaesthetic medication is generally advisable prior to both conduction and general anaesthetic procedures for the following reasons:

- Sedatives improve the course of subsequent anaesthesia in apprehensive patients. Diazepam, promethazine syrup and chloral hydrate are effective. Diazepam can be administered orally, intravenously or rectally. Promethazine syrup, which has antihistaminic and antiemetic properties as well as a sedative effect, is of particular value in children, as is chloral hydrate. Intramuscular injection of promethazine is preferred in adults.
- Potent analgesics such as morphine or pethidine should be administered preoperatively to patients in severe pain or to provide analgesia during and after surgery. Sedatives should then be withheld since they may cause restlessness or confusion.
- Anticholinergic drugs such as atropine are additionally used prior to general anaesthetic procedures. They inhibit excessive bronchial and salivary secretions induced, in particular, by ether and ketamine. Intramuscular administration is most effective, but oral administration is more convenient in children.

## **Conduction anaesthesia**

Conduction anaesthesia has many applications. It is used very widely in dental practice; for brief and superficial interventions; for obstetric procedures; and for specialized techniques of regional anaesthesia calling for highly developed skills. It can be particularly useful when the patient is required to collaborate during the intervention.

### **Local infiltration**

Many simple surgical procedures that neither involve the body cavities nor require muscle relaxation (but including lower-segment caesarean section) can be performed under local infiltration anaesthesia. The local anaesthetic drug of choice is 0.5%



lidocaine with or without epinephrine. No more than 4 mg/kg of plain lidocaine or 7 mg/kg of lidocaine with epinephrine should be administered on any one occasion.

***Regional block***

Regional nerve blocks can provide safe and effective anaesthesia but their execution requires considerable training and practice. Nevertheless, where the necessary skills are available, techniques such as axillary or ankle blocks can be invaluable. Either lidocaine 1.0% or bupivacaine 0.5% is suitable.

***Spinal anaesthesia***

Spinal anaesthesia is one of the most useful of all anaesthetic techniques and can be used widely for surgery of the abdomen and lower limbs. Either lidocaine (5%) or bupivacaine (0.75%) can be used but the latter is often chosen because of its longer duration of action.

**General anaesthesia**

***Induction***

Anaesthesia may be induced with an intravenous barbiturate, intravenous or intramuscular ketamine, or an inhalational agent. The first two methods are more pleasant for the patient but they are absolutely contraindicated when the anaesthetist is not confident of maintaining an airway.

Intravenous induction using thiopental or methohexital is rapid and excitement does not occur in patients sedated with diazepam. Neither agent can be used alone as an anaesthetic since large or repeated doses severely depress respiration and delay recovery. Before intubation is attempted, a muscle relaxant must be given or deep inhalational anaesthesia achieved.

Ketamine is used both intravenously and intramuscularly for induction, and for maintenance of anaesthesia of short duration that does not call for muscular relaxation. Diazepam or another benzodiazepine should be given beforehand in order to reduce the incidence of emergence reactions during recovery. Before intubation is attempted a muscle relaxant must be administered. Ketamine in low doses is also a potent analgesic. It is thus of particular value in children, when burns are dressed and during radiotherapeutic procedures and marrow sampling.

One of the volatile anaesthetics — ether, halothane or trichloroethylene (with or without nitrous oxide) — must be used for

induction when intravenous agents are contraindicated and particularly when intubation is likely to be difficult. Halothane is preferred in these circumstances. Because it is non-irritant, induction is smoother and more pleasant for the patient. Once anaesthesia is established ether may be substituted.

### ***Inhalational techniques***

Ether is the safest and most reliable anaesthetic in inexperienced hands. It must, however, be used with care since it is flammable in air and explosive when mixed with high concentrations of oxygen or nitrous oxide or mixtures of these. It produces good muscle relaxation and, if necessary, it can be used alone for induction and maintenance of anaesthesia in all branches of surgery.

Halothane may also be used for induction and maintenance of anaesthesia. Induction is smooth and rapid but, since halothane is cardiodepressant, the concentration that can be administered with safety to maintain anaesthesia is strictly limited. When it is used in abdominal surgery, muscle relaxants must also be given as soon as anaesthesia is established. It must always be administered from a calibrated vaporizer in order to reduce the risk of cardiorespiratory depression.

Trichloroethylene is a weak hypnotic agent but a potent analgesic. It can be used economically in conjunction with halothane in a draw-over system but it must never be used with a soda lime system for carbon dioxide absorption. In analgesic doses it can be used for the relief of pain in labour.

Nitrous oxide is costly and has to be transported and stored in cylinders. It is used widely in conjunction with other agents for induction and maintenance of anaesthesia. It should never be used alone for these purposes since it is a weak anaesthetic, but it allows the dosage of other anaesthetic agents to be reduced. In subanaesthetic doses (50% with oxygen) it is of value as an analgesic in obstetric procedures and in the emergency management of injured patients.

Oxygen should be added routinely to inhalational agents, even when air is used as the carrier gas, to protect against hypoxia. This is an essential precaution whenever halothane is used. When oxygen is not available, ether is the safest agent for maintenance of anaesthesia. Oxygen is most simply given with

volatile anaesthetics (provided adequate precautions are taken when it is mixed with ether) using the economical draw-over technique, but it may also be used in an anaesthetic machine for compressed gases.

## **Muscle relaxants**

Muscle relaxants are classified according to their mode of action as depolarizing or non-depolarizing neuromuscular blocking agents. Their use allows abdominal surgery to be carried out under light anaesthesia. They should never be given until it is certain that general anaesthesia has been established, and ventilation must be mechanically assisted until they have been completely inactivated.

Suxamethonium is the only widely used depolarizing muscle relaxant. It produces rapid, complete paralysis which is very short-lasting in most patients and is of particular value for laryngoscopy and intubation. Should paralysis be prolonged, ventilation must be assisted until muscle function is fully restored. Powder formulations of suxamethonium are recommended because they retain activity during storage. Liquid formulations must be kept under refrigeration during transportation and storage.

Gallamine and alcuronium are both non-depolarizing muscle relaxants with a duration of action of about 30 minutes. Their effects may be rapidly reversed after surgery by the anticholinesterase agent neostigmine, provided atropine is given to prevent excessive autonomic activity. Alcuronium has little effect on the cardiovascular system but the vagolytic action of gallamine tends to produce a tachycardia.

Pancuronium is another potent synthetic agent with a duration of action of about 30 minutes but it requires refrigerated storage as does the newer agent atracurium. Vecuronium, another relatively new and expensive non-depolarizing muscle relaxant, has the advantage of a shorter duration of action (15–20 minutes), which frequently averts the need for postoperative neostigmine. The powder formulation has a long shelf-life.

## **Analgesics**

For relief of mild postoperative pain, acetylsalicylic acid or paracetamol suffices. Opioid analgesics such as morphine and

pethidine should be reserved for severe pain. Opioids are also used during prolonged operations to supplement general anaesthesia. When doses producing respiratory depression are used, vital functions must be closely monitored and assisted ventilation maintained until spontaneous breathing is fully restored. Naloxone, a specific opioid antagonist, helps to restore breathing but its effect is short-lasting and it counteracts the analgesic effect as well as the respiratory depression. To avoid unnecessarily high dosages, it can be given in small divided doses until the respiratory depressant effect of the opioid is overcome but, because its action is not long sustained, the patient will continue to need careful respiratory monitoring.

### **Ancillary drugs used in anaesthesia**

Various drugs may be needed to modify normal physiological functions or otherwise to maintain the patient in a satisfactory condition during surgery. These include:

- antidysrhythmic agents such as lidocaine, propranolol and verapamil
- hypotensive agents such as hydralazine and sodium nitroprusside for controlled reduction of blood pressure
- vasoactive agents including ephedrine or methoxamine to maintain blood pressure after spinal or epidural block
- osmotic diuretics such as mannitol hexanitrate to reduce intracranial pressure
- bronchodilators such as salbutamol and aminophylline.

Special precautions and close monitoring of the patient are often required when these drugs are administered. Certain vasoactive agents, and particularly sodium nitroprusside, can be given safely only by means of an infusion pump.

### **Fluid replacement therapy**

Fluid requirements must be assessed before, during and after major surgery. Any preoperative loss of blood, plasma or gastrointestinal fluid must be replaced and account must also be taken of sweating, chronic malnutrition and preoperative starvation. Cumulative fluid losses can attain many litres. Replacement fluids should correspond as nearly as possible in volume and composition to those lost. When, as in emergency, adequate fluid

replacement is impossible, general anaesthesia can become hazardous and conduction anaesthesia should be preferred.

Blood transfusion should be avoided, unless absolutely necessary, whenever screening for human immunodeficiency viruses and hepatitis B virus is impracticable. None the less, blood becomes essential to restore oxygen-carrying capacity when more than 15% of the circulating volume is lost, particularly in patients with pre-existing anaemia. Isotonic sodium chloride solution may be used for short-term volume replacement. Plasma expanders such as albumin concentrates (which carry no risk of human immunodeficiency virus or hepatitis B virus transmission) or less expensive substitutes such as dextran 70, polygeline or hetastarch may additionally be required.

During surgery extracellular fluid is sequestered in traumatized tissue. As a general rule one-third to one-half of the estimated 24-hour fluid requirement should be administered parenterally during a major operation in addition to the total measured fluid loss. Provided renal function is maintained, fluid is most simply replaced by intravenous administration of sodium chloride solution 9 mg/ml or the more physiologically appropriate compound solution of sodium lactate.

Isotonic glucose/saline mixtures (most commonly glucose 4% / saline 0.18%) are preferred in children to avoid the danger of sodium overload and hypoglycaemia. These solutions are also preferred both before and after major surgery. For an adult patient whose condition is stable, 2–3 litres of glucose/saline provide the average daily requirement of both water and sodium in a temperate climate.

When fluids are administered intravenously over long periods, potassium chloride is required to prevent potassium depletion. In order to avoid serious dysrhythmias, especially in patients with impaired renal function, the required dosage should be determined, whenever possible, by monitoring blood levels of potassium.

## **Anaesthesia during pregnancy**

Throughout pregnancy the safety of the fetus as well as of the mother must be considered; there is a greater risk of vomiting and aspiration during induction, and airway obstruction is also more likely to occur as a result of localized oedema.

Thiopental is generally preferred for induction and anaesthesia may be maintained safely with halothane, nitrous oxide and oxygen. Suxamethonium may be used for intubation. When pregnancy is advanced the patient must be placed in the “wedge” position to avoid supine hypotension.

In obstetric practice intramuscular pethidine is effective in relieving the pain of early labour but it should be used only when naloxone can be administered to the neonate to reverse respiratory depression. A subanaesthetic concentration of nitrous oxide or trichloroethylene may be administered on demand during labour and delivery. Alternatively, pain may be relieved by epidural nerve block with bupivacaine.

The danger of aspiration of gastric contents is reduced by fasting and routine oral administration of antacids. Sodium citrate is commonly used before induction to neutralize the gastric contents. Magnesium trisilicate is less satisfactory since it is slow-acting and bulky and has been implicated as a cause of gastric aspiration. A histamine  $H_2$ -receptor antagonist (cimetidine or ranitidine) may additionally be given either orally, at least 2 hours before surgery, or intravenously, immediately before induction, to reduce the acidity and volume of gastric secretions. The antiemetic metoclopramide is also used to promote gastric emptying and to increase tone in the lower oesophageal sphincter. However, its effects are antagonized by atropine.

In emergency, caesarean section must often be carried out under general anaesthesia. Because this can be unpredictably hazardous, spinal block is often preferred for elective caesarean section. This technique avoids drug-induced fetal depression and is of particular value in premature labour. It can also be used for procedures such as the removal of a retained placenta, where rapid onset of anaesthesia is of value. However, “postspinal headache” is particularly common in obstetric patients. Epidural nerve block is also used in many hospitals but should only be undertaken by a skilled anaesthetist.

# Premedication

## Atropine

Group: anticholinergic agent

Tablet: 1 mg (sulfate)

Injection: 1 mg (sulfate) in 1-ml ampoule

### General information

Atropine is an alkaloid of *Atropa belladonna* that competitively antagonizes the muscarinic action of acetylcholine and other cholinergic drugs.

Atropine is readily absorbed from the gastrointestinal tract. Its half-life in plasma ranges from 2 to 3 hours. It is largely metabolized in the liver and excreted in the urine.

### Clinical information

#### Uses

In general surgery:

- to inhibit salivary and bronchial secretions particularly during ether or ketamine anaesthesia (preoperative medication)
- to inhibit cardiac dysrhythmias, bradycardia and hypotension resulting from excessive vagal stimulation
- to block the parasympathomimetic effects of anticholinesterase agents used to restore muscular activity on completion of surgery.

#### Dosage and administration

##### Pre-anaesthetic medication

Adults: 20 micrograms/kg i.m. 30–60 minutes before induction, or up to a maximum of 500 micrograms i.v. immediately before induction.

Children: 20 micrograms/kg i.m. 30–60 minutes before induction, or the same dose orally 2 hours before induction.

##### Inhibition of cardiac dysrhythmias

Adults: 400–1000 micrograms i.v.

Children: 10–30 micrograms/kg i.v.

##### Restoration of muscular activity

Adults: 600–1200 micrograms i.v. 2–3 minutes before administration of the anticholinesterase agent.

Children: 20 micrograms/kg administered as above.

#### Precautions

Atropine should be used at reduced dosage in the elderly and in patients with cardiovascular insufficiency, hyperthyroidism, hypertension or hepatic or renal insufficiency.

#### Use in pregnancy

Atropine should be used during pregnancy only when the need outweighs any possible risk to the fetus.

#### Adverse effects

Signs of parasympathetic blockade commonly occur within the therapeutic dosage range. These include dry mouth, blurred vision, raised ocular tension, flushing and dryness of skin, skin rashes and difficulty in micturition, which occasionally results in urinary retention.

Less common are atrial dysrhythmias, ventricular tachycardia or fibrillation and confusional states.

Heat prostration and convulsions can occur, especially in febrile children. This risk is intensified in a hot, humid environment.

#### Overdosage

Serious overdosage is characterized by signs of parasympathetic blockade, central excitation, skin rash and hyperpyrexia. Hallucinations, mania and delirium may be followed by convulsions. Circula-

### **Atropine (continued)**

tory and respiratory collapse are terminal events.

Treatment consists of symptomatic and supportive therapy. Activated charcoal should be administered followed by gastric aspiration. Neostigmine (250 micrograms subcutaneously) will reverse the peripheral but not the central effects of

atropine. Small doses of diazepam may help delay excitation. Fever may be reduced by sponging with tepid water. Mechanically assisted respiration may be required.

### **Storage**

Atropine injection and tablets should be stored in hermetically closed containers protected from light, and should not be allowed to freeze.

## **Chloral hydrate**

*Group: sedative*

*Syrup: 200 mg in 5 ml*

### **General information**

Chloral hydrate is a sedative and hypnotic. The depressant effect on the central nervous system is believed to be due to an active metabolite, trichloroethanol. Its mechanism of action is unknown.

Chloral hydrate is rapidly absorbed from the gastrointestinal tract following oral or rectal administration. The depressant effect, which is evident within 30 minutes to 1 hour, persists for 6 to 8 hours. It is metabolized in the liver to the active metabolite trichloroethanol, which is subsequently excreted in the urine. The plasma half-life is 7 to 10 hours.

### **Clinical information**

#### **Uses**

Preoperative medication to allay anxiety and to produce sedation.

#### **Dosage and administration**

Adults and children: 30 mg/kg 30 minutes before surgery.

#### **Contraindications**

- Known hypersensitivity to chloral hydrate.
- Hepatic or renal impairment.

### **Precautions**

The dosage should be reduced in patients with cardiac disease.

Ambulatory patients should be warned that chloral hydrate may impair their ability to drive or operate machinery for up to 24 hours.

### **Use in pregnancy**

Chloral hydrate should be used during pregnancy only when the need outweighs any potential risk to the fetus.

### **Adverse effects**

Gastric irritation is the most frequent adverse effect. Skin rashes may also occur.

### **Drug interactions**

The hypoprothrombinaemic effect of coumarin anticoagulants may be intensified if such drugs are given concurrently with chloral hydrate.

### **Overdosage**

Signs of overdose include increasing confusion, severe drowsiness leading to coma, hypotension, hypothermia and respiratory depression.

### **Treatment**

Induction of emesis or gastric lavage may be of value if undertaken within a few



hours of ingestion. Otherwise, reliance must be placed on supportive measures such as maintenance of circulatory volume and mechanically assisted respiration.

## Storage

Chloral hydrate syrup should be stored in tightly closed containers protected from light, below 25 °C.

# Diazepam

*Group: sedative*

*Tablet: 2 mg, 5 mg*

*Injection: 5 mg/ml in 2-ml ampoule*

## General information

Diazepam is a benzodiazepine with anxiolytic properties, a centrally mediated muscle-relaxant effect and, when used intravenously, an anticonvulsant action. It is metabolized in the liver to several active metabolites, which are mainly excreted in the urine as glucuronides.

The response, which persists for 12–24 hours, becomes evident 30–90 minutes after oral administration and 1–5 minutes after intravenous injection. The plasma half-life is 20–50 hours.

## Clinical information

### Uses

In general surgery:

- premedication before major or minor surgery
- to relieve anxiety and provide light sedation for endoscopic procedures and surgery under local anaesthesia
- in combination with pethidine, when other anaesthetic agents are not available, for emergency reduction of fractures.

## Dosage and administration

### Premedication

Adults and children over 12 years: 5–10 mg orally 2 hours before surgery.

### Anxiety relief and light sedation

Adults and children over 12 years: 200 micrograms/kg i.v. immediately before medical or surgical intervention.

In order to ensure stability, diazepam for injection should not be mixed with other drugs in syringes or infusion fluids, nor should it be diluted before use except in saline or glucose solution. Unused diazepam solutions should be discarded within 6 hours.

It should be administered directly into the cubital vein at a rate of no more than 1 ml/min to reduce the risk of thrombophlebitis. Preparations of diazepam in an oil-in-water emulsion are available which reduce the risk of thrombophlebitis after injection.

Accidental intra-arterial injection can cause severe local necrosis.

### Contraindications

- Age less than 12 years.
- Known hypersensitivity to benzodiazepines.
- Parenteral administration is contraindicated in shocked or comatose patients.

### Precautions

Equipment for resuscitation should be immediately available.

Diazepam should be administered with particular caution to patients with myas-

### **Diazepam (continued)**

thenia gravis. Patients with chronic obstructive airway disease are at particular risk of respiratory depression.

Diazepam should be used with great caution, in much reduced doses, and only when essential in elderly and debilitated patients, and in patients with chronic pulmonary insufficiency or chronic renal or hepatic disease.

Ambulatory patients should be warned that diazepam may impair their ability to drive or operate machinery for up to 24 hours.

#### **Use in pregnancy**

Use in pregnancy should be avoided whenever possible. An increased incidence of malformations has been reported in some studies among infants born to mothers who have received diazepam during the first trimester of pregnancy, although other, large-scale prospective studies have failed to confirm this.

Use of diazepam during labour can result in marked fetal sedation and hypotonia.

#### **Adverse effects**

Paradoxical reactions including irritability, excitability, hallucinations, increased muscle spasticity and sleep disturbances have been reported, particularly in elderly patients and in children.

Rare but serious adverse reactions include leukopenia, jaundice and hypersensitivity reactions.

#### **Drug interactions**

The effects of phenothiazines, barbiturates, monoamine oxidase inhibitors and other antidepressants may be potentiated.

#### **Overdosage**

Signs include somnolence, ataxia, dysarthria, diminished reflexes, confusion and coma. Paradoxical excitement may occur in children. Unless the specific benzodiazepine antagonist flumazenil is available, treatment should be symptomatic and directed to the management of respiratory depression and shock.

#### **Storage**

Diazepam should be stored in tightly closed containers protected from light.

## **Promethazine**

*Group: sedative*

*Tablet: 10 mg, 25 mg (hydrochloride)*

*Elixir or syrup: 5 mg (hydrochloride) in 5 ml*

*Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule*

### **General information**

Promethazine is an antihistaminic and sedative phenothiazine derivative with antiemetic and anticholinergic properties. It acts for about 12 hours following oral administration and is excreted in the urine, largely as metabolites, within 24 hours.

### **Clinical information**

#### **Uses**

Premedication prior to surgical anaesthesia and sedation in obstetrics.

#### **Dosage and administration**

Adults: 25 mg i.m. 1 hour prior to induction.

Children over 1 year: 0.5–1 mg/kg orally as syrup or tablet, 1 hour prior to induction.

### **Contraindications**

- Known hypersensitivity to promethazine or to other phenothiazine derivatives (since cross-sensitivity may occur).
- Age under 1 year.
- Impaired consciousness due to cerebral depressants or of other origin.

### **Precautions**

Ambulatory patients should be warned that promethazine may impair their ability to drive or operate machinery for up to 24 hours.

### **Use in pregnancy and lactation**

Promethazine should be used in pregnancy only when the need outweighs any potential risk to the fetus. Sufficient promethazine is excreted in maternal milk to sedate breast-fed infants.

### **Adverse effects**

Adverse effects, which occur less frequently than with other phenothiazines, are usually referable to gastrointestinal irritation, allergic phenomena and dose-related central and anticholinergic effects.

Gastrointestinal effects include anorexia, nausea, vomiting, epigastric distress, constipation and diarrhoea. They may be attenuated by taking the drug with meals.

Allergic phenomena include urticaria and dermatitis. Agranulocytosis is very rare. Cholestatic jaundice, which is usually reversible on withdrawal of treatment, has been reported.

Central effects include sedation, dizziness, fatigue, insomnia, nightmares, hallucinations, nervousness, tremor, tinnitus, inco-ordination, diplopia and blurred vision.

Anticholinergic effects include dryness of the mouth, urinary frequency and palpitations.

### **Drug interactions**

The sedative effect of alcohol and other cerebral depressants is augmented.

Concurrent use of epinephrine may result in hypotension and tachycardia due to partial adrenergic blockade.

### **Overdosage**

Serious poisoning is characterized by muscular twitching, convulsions, restlessness, irritability, confusion, hallucinations and coma. Gastric lavage is of value if undertaken within a few hours of ingestion. Emetics may be ineffective. Oxygen and assisted ventilation are required in the event of respiratory depression. Seizures may be controlled with diazepam.

### **Storage**

Promethazine should be stored in well-closed containers protected from light and should not be allowed to freeze. The syrup is less stable than the other dosage forms.

# General anaesthetics and oxygen

## Ketamine

*Group: parenteral anaesthetic agent*

*Injection: 50 mg (hydrochloride)/ml in 10-ml ampoule*

### General information

Ketamine is a phencyclidine derivative. In anaesthetic doses it produces a trance-like state known as "dissociative anaesthesia".

#### Advantages

Anaesthesia persists for up to 15 minutes after a single intravenous injection and is characterized by profound analgesia. Ketamine may be used as the sole agent for diagnostic and minor surgical interventions. It is less likely than other anaesthetic agents to induce vomiting. Since it does not induce hypotension the patient does not have to remain supine and its sympathomimetic effects are of particular value in patients who are shocked, severely dehydrated or severely anaemic. Because pharyngeal and laryngeal reflexes are only slightly impaired, the airway may be less at risk than is the case with other general anaesthetic techniques. It is of particular value in children and poor-risk patients, and also in asthmatic patients, because it rarely induces bronchospasm.

#### Disadvantages

Ketamine produces no muscular relaxation. It tends to raise heart rate and intracranial and intraocular pressure. In hypertensive patients it may raise blood pressure unduly. Hallucinations can occur during recovery (although rarely in children), but they are avoided if ketamine is used solely as an induction agent and followed by a conventional inhalational anaesthetic. Their incidence may also be greatly reduced by administration of diazepam both as a premedication and after the procedure.

### Clinical information

#### Uses

Subanaesthetic concentrations of ketamine may be used to provide analgesia for painful procedures of short duration such as the dressing of burns, radiotherapeutic procedures, marrow sampling and minor orthopaedic procedures.

Ketamine may be used for induction of anaesthesia prior to administration of inhalational anaesthetics, or for both induction and maintenance of anaesthesia for short-lasting diagnostic and surgical interventions, including dental procedures, that do not require skeletal muscle relaxation. It is of particular value for children requiring frequent repeated anaesthetics.

Its use in conjunction with a muscle relaxant and controlled ventilation for more prolonged anaesthesia should be considered only by specialist anaesthetists because experience is required in assessing the depth of anaesthesia. Emergence from the anaesthetic state is heralded, in these circumstances, by tachycardia, a rise in blood pressure, nystagmus and attempts at swallowing.

#### Dosage and administration

Administration of ketamine should always be preceded by premedication with atropine to reduce salivary secretions.

Premedication with diazepam reduces the subsequent requirement for ketamine and the incidence of emergence reactions but in this case there is a need for endotracheal intubation.

Dosage requirements vary with age, the physical condition of the patient and rate of administration.

As a general guide the following regimens are recommended:

### **Induction**

Intravenous route:

1–2 mg/kg by slow intravenous injection over a period of 60 seconds. More rapid administration may result in respiratory depression or apnoea and an enhanced pressor response. A dose of 2 mg/kg produces surgical anaesthesia within 1–2 minutes which may be expected to last 5 to 10 minutes.

Intramuscular route:

6–8 mg/kg by deep intramuscular injection. This dose produces surgical anaesthesia within 3–5 minutes and may be expected to last up to 25 minutes.

### **Induction and maintenance**

Following induction, as above, serial doses of 50% of the original intravenous dose or 25% of the intramuscular dose are administered as required. The need for supplementary doses is established largely by movement in response to surgical stimuli.

Intravenous infusion:

Anaesthesia may also be maintained by slow microdrip infusion of ketamine at a rate of 1–2 mg/minute, augmented with diazepam 2–5 mg administered intravenously, as required, from a separate syringe to a maximum of 20 mg.

Tonic and clonic movements resembling seizures occur in some patients. These are not indicative of a light plane of anaesthesia or of a need for additional doses of the anaesthetic.

As an analgesic:

500 micrograms/kg i.m. or i.v. followed, if necessary, by a dose of 250 micrograms/kg.

### **Recovery**

Return to consciousness is gradual. Emergence reactions with delirium may occur during the recovery period. Their incidence is reduced if unnecessary disturbance of the patient is avoided during recovery (although vital signs may be monitored) and they are unlikely to occur if diazepam is administered preoperatively and supplemented, if necessary, by a further 5–10 mg i.v. at the end of the procedure. Hypnotic doses of thiopental (50–100 mg i.v.) may be required to suppress overt reactions but this will considerably prolong the recovery period.

### **Contraindications**

- Hypersensitivity to ketamine.
- Moderate to severe hypertension, congestive cardiac failure, or a history of cerebrovascular accident.
- Acute or chronic alcohol intoxication.
- Cerebral trauma, intracerebral mass or haemorrhage or other causes of raised intracranial pressure.
- Eye injury and increased intraocular pressure.
- Psychiatric disorders such as schizophrenia and acute psychoses.

### **Precautions**

Ketamine should, whenever possible, be used under the supervision of an experienced specialist anaesthetist who is confident of intubating the patient should this become necessary. Equipment for resuscitation and endotracheal intubation should be immediately available and ready for use.

Pulse and blood pressure should be closely monitored, particularly in patients with hypertension, congestive cardiac failure or thyrotoxicosis. Mechanical stimulation of the pharynx should be avoided unless muscle relaxants are used.

Supplementary analgesia is often required in surgical procedures involving visceral pain pathways. Morphine may be used

### **Ketamine (continued)**

but the addition of nitrous oxide will often suffice.

During recovery, patients must remain undisturbed and under observation. Outpatients must be discharged in the care of a responsible adult and advised not to drive or operate machinery for at least 24 hours.

#### **Use in pregnancy**

Ketamine is contraindicated in pregnancy before term, since it has oxytocic activity. It is also contraindicated in patients with eclampsia or pre-eclampsia. It may be used for assisted vaginal delivery by an experienced anaesthetist, but the dosage has to be adjusted within wide limits to individual circumstances. It is better suited for use during caesarean section; ketamine results in less fetal and neonatal depression than do other anaesthetics and the short exposure required has not been associated with emergence reactions when diazepam is used concomitantly.

#### **Adverse effects**

The emergence reactions experienced during recovery are sometimes accompanied by irrational behaviour. These effects rarely persist for more than a few hours but recurrences can occur at any time within 24 hours of exposure.

Transient elevation of pulse rate and blood pressure is common, and dysrhythmias have occurred. Conversely, hypotension and bradycardia are occasionally reported.

Infrequent reactions include:

- anorexia, nausea and vomiting
- local pain and exanthema at the injection site
- transient generalized erythema and morbilliform rashes
- transient postoperative diplopia, nystagmus and elevated intraocular pressure
- laryngospasm and other forms of airway obstruction.

#### **Drug interactions**

Barbiturates and diazepam are chemically incompatible with ketamine. They should never be administered from the same syringe or via the same infusion set.

Ether, halothane and other cerebral depressants may considerably prolong the effect of ketamine and delay recovery.

#### **Overdosage**

Transient respiratory depression may necessitate mechanical support of ventilation.

#### **Storage**

Ketamine injection should be protected from light.

## **Thiopental**

*Group: intravenous anaesthetic agent*

*Powder for injection: 0.5 g, 1 g and 2.5 g (sodium salt) in ampoule*

### **General information**

Thiopental is a very short-acting barbiturate which, administered parenterally, rapidly induces hypnosis and anaesthesia without analgesia. It is extensively bound to plasma albumin and is initially

distributed most extensively in the highly vascular tissues of the brain and other organs. It subsequently diffuses selectively into fatty tissues where it is pharmacologically inactive. It is slowly but almost entirely metabolized in the liver. Traces are excreted unchanged in the urine.

## **Advantages**

Thiopental usually exerts its cerebral depressant effect within 30 seconds and it persists for about 4–7 minutes. Anaesthesia is induced rapidly, pleasantly and without excitement.

## **Disadvantages**

Thiopental has little analgesic action. Any muscular relaxation that occurs is too short to be of practical value. In contrast to ketamine, it cannot be used alone as an anaesthetic agent because the large and repeated doses required accumulate in fatty tissues and are subsequently only slowly released; this results in prolonged anaesthesia and delayed recovery characterized by somnolence and respiratory and circulatory depression.

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## **Clinical information**

### **Uses**

Induction of anaesthesia prior to administration of inhalational and other anaesthetics.

### **Dosage and administration**

Adults and children: 3–5 mg/kg given by slow intravenous injection over 10–15 seconds and repeated, if necessary, after 20–30 seconds.

Dosage requirements vary; they are reduced in the elderly, in hypovolaemic patients, and in patients heavily premedicated with narcotics or other cerebral depressants.

The injection should be administered slowly until the patient becomes unconscious. Recovery after a single dose is rapid because of redistribution of the drug from the central nervous system into other tissues.

Solutions of 25 mg/ml should be freshly prepared by mixing 20 ml of water for injection with the contents of the 0.5-g ampoule, 40 ml with the 1-g ampoule or

100 ml with the 2.5-g ampoule. Any solution made up over 24 hours previously or in which cloudiness, precipitation or crystallization is evident should be discarded.

## **Contraindications**

- Thiopental should not be used if there is doubt that a clear airway can be maintained.
- Hypersensitivity to barbiturates.
- Severe cardiovascular disease or hypotension.
- Dyspnoea or obstructive respiratory disease.
- Status asthmaticus.
- Addison's disease.
- Hepatic dysfunction.
- Myxoedema.
- A history of acute intermittent or variegate porphyria.

## **Precautions**

Thiopental should, whenever possible, be administered under the supervision of an experienced specialist anaesthetist.

Equipment for resuscitation and endotracheal intubation should be immediately available and ready for use.

The patient must always lie supine as even a small overdose can cause hypotension.

Concentrations greater than 25 mg/ml are liable to cause thrombophlebitis. Local extravasation can result in extensive necrosis and sloughing. Intra-arterial injection causes intense pain and may result in arteriospasm necessitating local use of vasodilators, supplemented, if necessary, by brachial plexus block and anticoagulants.

Outpatients must be discharged in the care of a responsible adult and advised against driving, operating machinery and taking alcohol for 24 hours.

## **Use in pregnancy and lactation**

Thiopental should be used during preg-

### **Thiopental (continued)**

nancy only when the need outweighs any potential risk to the fetus; repeated doses should not be administered during labour. It readily crosses the placental barrier and appears in breast milk.

#### **Adverse effects**

A short period of apnoea may follow intravenous injection.

Rapid injection may result in severe hypotension and hiccoughs. Coughing, sneezing or laryngeal spasm may occur during induction.

Allergic reactions and hypersensitivity have been documented.

Acute attacks of variegate or acute intermittent porphyria may be triggered in susceptible individuals.

#### **Drug interactions**

Other cerebral depressants may augment the action of thiopental. Antihypertensives or diuretics may augment the hypotensive effect.

#### **Overdosage**

Serious overdosage results in respiratory depression necessitating assisted ventilation with oxygen, and hypotension progressing to circulatory collapse. In the latter event the head of the table must immediately be tilted down. Plasma expanders and pressor agents may be of value in patients who are unresponsive to this measure.

#### **Storage**

Thiopental should be stored in ampoules.

## **Ether**

*Group: volatile inhalational anaesthetic agent*

### **General information**

Ether (diethyl ether) is a colourless, highly volatile and flammable liquid that, in anaesthetic dosage, depresses cerebral activity.

#### **Advantages**

Ether is a reliable and potent anaesthetic that is particularly useful when elaborate apparatus is not available and cost is an important consideration. It may be used safely in closed circuits containing soda lime. The vasomotor centre is resistant to the doses required for full surgical anaesthesia. Because it is highly soluble in body tissues induction is slow and follows the classical stages of general anaesthesia. Full muscle relaxation is achieved in deep anaesthesia. Although irritant to the upper airway, ether is a bronchodilator and it

can be of value in treating bronchospasm resistant to other drugs. It does not potentiate the dysrhythmic effect of sympathomimetic agents as much as other potent inhalational anaesthetics.

#### **Disadvantages**

Because ether is both flammable and explosive it can be used in hot dry climates only when special precautions are taken to prevent sparking and combustion; diathermy is contraindicated when ether is used with oxygen. Premedication with atropine is essential to avoid excessive bronchial and salivary secretion. Laryngeal spasm may occur during induction and intubation. Localized capillary bleeding can be troublesome. Postoperative nausea and vomiting are frequent and recovery time is slow, particularly after prolonged administration.



## Clinical information

### Uses

Induction and maintenance of anaesthesia during surgery.

### Dosage and administration

Ether may be administered from many types of vaporizer. In emergency it may be dropped on to an open mask.

Premedication with atropine is necessary to reduce salivary and bronchial secretions.

When supplementary oxygen is used it can be fed under an open mask or into an open-ended T-piece connected to a draw-over vaporizer.

### Administration from vaporizers

Concentrations of ether vapour in the inspired gases should not exceed 15% during induction and should subsequently be reduced during maintenance of anaesthesia. Light anaesthesia (with or without muscle relaxants) can be sustained using 3–5% in air. Deep anaesthesia requires concentrations of up to 10%.

### “Open drop” technique

This technique should be used only when no other means of delivering a general anaesthetic is available.

Ether is applied from a drop bottle to an open mask covered with multilayered gauze. During induction 12 drops/minute are applied for 2 minutes, then 1 drop/second until the patient loses consciousness (usually within 5 minutes). The rate is subsequently adjusted to provide the required depth of anaesthesia. Deep levels of surgical anaesthesia cannot be achieved with this technique in less than 20–30 minutes.

### Contraindications

- Severe liver disease.
- Raised cerebrospinal fluid pressure.

### Precautions

In febrile children exposure to ether increases the risk of potentially fatal convulsions. If convulsions occur, ether should immediately be withdrawn, and the child's body temperature reduced by sponging with tepid water. Small doses of diazepam or thiopental should be administered intravenously until convulsions cease.

Diathermy must not be used when ether/oxygen mixtures are in use and the operating theatre and its equipment should be designed to minimize the risk of static discharge, particularly in hot, dry climates. Electrical sockets and switches situated within 1 metre of the floor should be spark-proof. No potential source of combustion or sparking should be allowed within 30 cm of an expiratory valve emitting ether vapour.

### Use in pregnancy

Ether should be used during pregnancy only when the need outweighs any possible risk to the fetus.

Low concentrations (no more than 4%) should be employed in obstetric procedures to avoid loss of uterine tone, excessive postpartum haemorrhage and respiratory depression in the neonate.

### Adverse effects

Laryngeal spasm is common during induction.

Severe nausea, vomiting and bronchopneumonia are liable to occur postoperatively, particularly after prolonged, deep anaesthesia.

Transient postoperative effects include impairment of liver function and leucocytosis.

Dependence can occur in individuals who are repeatedly exposed to ether.

### **Ether (continued)**

#### **Drug interactions**

The action of non-depolarizing neuromuscular blocking agents is potentiated. In patients receiving  $\beta$ -adrenoceptor-blocking agents such as propranolol, ether may cause myocardial depression.

#### **Overdosage**

Overdosage leads to severe central depression, characterized first by respiratory failure and later by cardiac arrest.

Spontaneous respiration is usually restored if intermittent positive pressure ventilation with oxygen is instituted promptly.

#### **Storage**

Ether should be stored in sealed containers protected from light, below 25 °C. Naphthols, polyphenols, aromatic amines and aminophenols may be added in trace amounts to commercial supplies as stabilizers.

## **Halothane**

*Group: volatile inhalational anaesthetic agent*

### **General information**

Halothane is a colourless, volatile, non-irritant liquid with a sweet odour. It is neither flammable nor explosive. In anaesthetic dosage it depresses both cerebral function and sympathetic activity and produces little, if any, preliminary excitement.

#### **Advantages**

Halothane is a potent non-flammable inhalational anaesthetic. Induction is smooth and rapid and surgical anaesthesia can be produced in 2–5 minutes. It does not augment salivary or bronchial secretions and coughing is less readily provoked than with ether. The recovery time is rapid and the incidence of postoperative nausea and vomiting is low. It does not react with soda lime and can be used in a closed-circuit system.

#### **Disadvantages**

Severe hepatitis, which may be fatal, is a recognized complication of halothane anaesthesia with an incidence of 1:50 000. It is more likely to occur in patients who are repeatedly anaesthetized with halothane within a short period.

Little margin exists between the doses needed to produce respiratory and vasomotor depression. Because of its cardio-depressant effect halothane is usually combined with another inhalational agent, such as nitrous oxide or trichloroethylene, to produce surgical anaesthesia. Muscle relaxants are additionally required to prepare the patient for abdominal surgery.

Although it suppresses endogenous sympathetic activity halothane sensitizes the heart to the dysrhythmic effects of catecholamines.

### **Clinical information**

#### **Uses**

Induction and maintenance of anaesthesia for all types of surgery.

#### **Dosage and administration**

##### **Method of administration**

Halothane should always be administered using a specially calibrated vaporizer. Vaporizers should be drained at regular intervals and any discoloured halothane discarded.

If draw-over machines or inhalers are used, supplementary oxygen or assisted ventilation may be necessary to maintain full oxygenation, even when air is used as the carrier gas.

Halothane is not suitable for "open drop" anaesthesia, although a few drops applied to a face mask may smooth the subsequent administration of ether.

### **Induction**

A flow of gas containing at least 30% oxygen should be maintained. Halothane should be introduced gradually and the concentration increased every few breaths until the inspired gases contain 2–3% halothane (for adults) or 1.5–2% (for children).

### **Maintenance**

Concentrations of 0.5–1.5% are usually adequate for adults and children.

### **Recovery**

Recovery time is relatively fast but it varies with the concentrations used and the period of administration. Shivering is common during recovery but it is readily controlled by covering the patient with a warm blanket and, if this is insufficient, by administering chlorpromazine (10 mg i.m.). When it is available, oxygen should be given.

### **Contraindications**

- A history of unexplained jaundice following previous exposure to halothane.
- A family history of malignant hyperthermia.
- Raised cerebrospinal fluid pressure.

### **Precautions**

The patient's anaesthetic history should be carefully taken to determine previous exposure and previous reactions to halothane.

At least 3 months should be allowed to elapse between each re-exposure to halothane. Repeated and frequent administration increases the risk of liver damage.

Premedication with atropine reduces the risk of hypotension and bradycardia. Nevertheless, the pulse and blood pressure must be monitored throughout anaesthesia and the inspired concentration of halothane reduced should hypotension develop. Halothane should be withdrawn if the patient's condition gives rise to concern.

Use of epinephrine increases the risk of ventricular dysrhythmias. It should be used only by a specialist anaesthetist and if the following precautions are taken:

- The total dose should not exceed 20 ml of a 5 micrograms/ml (1:200 000) solution in 10 minutes or 30 ml in 1 hour. Higher concentrations should not be employed.
- Ventilation should be adjusted to avoid any risk of hypoxia or hypercapnia.

### **Use in pregnancy**

Halothane should be used during pregnancy only when the need outweighs any possible risk to the fetus.

Low concentrations (no more than 0.5%) should be employed in operative delivery to avoid loss of uterine tone and excessive postpartum haemorrhage.

### **Adverse effects**

Cardiac dysrhythmias may be induced, in particular atrioventricular dissociation, nodal rhythm and ventricular extrasystoles.

Hepatic damage occurs in a small proportion of exposed patients. Typically fever develops 2 or 3 days after anaesthesia accompanied by anorexia, nausea and vomiting. In more severe cases this is followed by transient jaundice or, very rarely, fatal hepatic necrosis.

### **Drug interactions**

Halothane potentiates the response to:

- hypotensive agents, including hexa-

### **Halothane (continued)**

methonium bromide and trimetaphan camsilate

- non-depolarizing muscle relaxants.

Recovery from anaesthesia may be prolonged when ketamine is used for induction.

Concurrent use of suxamethonium may increase the risk of malignant hyperthermia.

### **Overdosage**

Death due to overdosage results from cardiovascular depression. No specific antidote exists.

### **Storage**

Halothane should be stored in tightly closed amber-glass containers protected from light, below 25 °C. Thymol is added as a stabilizing agent to commercially produced supplies at a concentration of 100 micrograms/ml.

## **Trichloroethylene**

*Group: volatile inhalational anaesthetic agent*

### **General information**

Trichloroethylene is a colourless slightly volatile liquid with a sweet smell. It is normally artificially coloured blue for ready identification.

### **Advantages**

Trichloroethylene is non-flammable and cheap. It has a strong analgesic effect; it does not irritate the respiratory tract and does not promote capillary oozing.

### **Disadvantages**

The hypnotic effect is weaker than that of other commonly used volatile inhalational agents. Trichloroethylene must generally be used with other inhalational agents and muscle relaxants to produce a state of full surgical anaesthesia. Breathing can become very rapid and shallow. Trichloroethylene must never be used in a closed-circuit system with soda lime since it is then converted into toxic compounds. Epinephrine should generally not be used concurrently since it increases the danger of dysrhythmias.

### **Clinical information**

#### **Uses**

- Maintenance of light anaesthesia.
- To supplement nitrous oxide–oxygen or halothane anaesthesia during major surgery.
- In subanaesthetic doses, to provide analgesia for obstetrics, emergency treatment of traumatic injury, and other acutely painful conditions.

### **Dosage and administration**

Trichloroethylene may be used alone, with halothane in a draw-over apparatus, or with nitrous oxide and oxygen in a continuous-flow anaesthetic machine.

It is preferably administered from a calibrated vaporizer. To avoid oxidation a fresh supply of trichloroethylene should be placed in the vaporizer every few days; unused anaesthetic should be discarded.

In general, trichloroethylene is used in concentrations of 0.5–1.5% to maintain light anaesthesia and 0.35–0.5% as an analgesic.

Recovery time is slow after prolonged administration. Trichloroethylene is consequently used at low vapour concentrations to maintain anaesthesia and it is preferably withdrawn some 20 minutes before the end of the surgical intervention.

### **Contraindications**

- Raised cerebrospinal fluid pressure.

### **Precautions**

Prolonged tachypnoea can result in carbon dioxide retention and hypoxia, which predispose the patient to cardiac dysrhythmias. Tachypnoea can often be averted by reducing the inspired concentration of vapour. Otherwise, ventilation must be controlled or pethidine 25 mg administered intravenously.

Dysrhythmias occasionally necessitate the administration of a  $\beta$ -adrenoceptor-blocking agent such as propranolol.

Epinephrine should not be used concurrently with trichloroethylene since

it increases the risk of ventricular dysrhythmias.

### **Use in pregnancy**

Trichloroethylene should be used in pre-term pregnancy only when the need outweighs any possible risk to the fetus. It is widely used as an analgesic in obstetric practice.

### **Adverse effects**

Postoperative nausea, vomiting and headache occasionally occur. Tachypnoea and cardiac dysrhythmias are dose-related. Cardiorespiratory depression occurs with the doses of trichloroethylene needed to produce deep anaesthesia.

### **Storage**

Trichloroethylene should be stored in well-closed containers protected from light, below 25 °C. Thymol (100 micrograms/ml) is added to commercial supplies as a stabilizing agent. Waxoline blue (5 micrograms/ml) is also added for identification purposes.

## **Nitrous oxide**

*Group: inhalational anaesthetic gas*

### **General information**

Nitrous oxide is a colourless gas with a slightly sweetish odour. It is neither flammable nor explosive. It is a cerebral depressant and produces light anaesthesia without demonstrably depressing the respiratory or vasomotor centre provided that normal oxygen tension is maintained.

### **Advantages**

Nitrous oxide reduces the requirement for other more potent and intrinsically more toxic anaesthetic agents. It has a strong analgesic action. Induction is rapid and not unpleasant although transient

excitement may occur. Recovery time rarely exceeds 1–4 minutes even after prolonged administration.

### **Disadvantages**

Nitrous oxide is expensive to buy and to transport. It must be used in conjunction with more potent anaesthetics and muscle relaxants to produce a state of full surgical anaesthesia.

## **Clinical information**

### **Uses**

- Maintenance of surgical anaesthesia in combination with other anaesthetic

### **Nitrous oxide (continued)**

agents (halothane, ether, thiopental or ketamine) and muscle relaxants.

- In subanaesthetic doses, to provide analgesia for obstetric practice, for emergency management of injuries, during postoperative physiotherapy and for refractory pain in terminal illness.

### **Dosage and administration**

For the maintenance of anaesthesia, nitrous oxide must always be mixed with at least 30% oxygen. This is usually accomplished using a compressed-gas anaesthetic machine.

For analgesia, a concentration of 50% nitrous oxide with 50% oxygen usually suffices.

### **Contraindications**

Any closed gas-filled space tends to expand during administration of nitrous oxide. It is therefore contraindicated in patients with demonstrable collections of air in the pleural, pericardial or peritoneal space; intestinal obstruction; occlusion of the middle ear; arterial air embolism; decompression sickness; chronic obstructive airway disease; or emphysema. It is also contraindicated in patients who have recently undergone pneumoencephalography.

### **Precautions**

Continued administration of oxygen may be necessary during recovery especially in elderly patients.

### **Adverse effects**

The incidence of nausea and vomiting increases with the duration of anaes-

thesia. Because prolonged and repeated exposure may be associated with bone-marrow depression and a teratogenic risk, precautions should be taken to minimize ambient concentrations in operating theatres.

### **Drug interactions**

Addition of 50% nitrous oxide/oxygen mixture to an inhalational anaesthetic reduces the required dosage of the latter by about 50%.

### **Storage**

Nitrous oxide is supplied under pressure in cylinders, which must be kept below 25 °C. It must be obtained from a reliable source since contamination with higher oxides of nitrogen, including nitric oxide and nitrogen peroxide, has caused deaths.

Cylinders containing premixed oxygen 50% and nitrous oxide 50% are available for analgesia in some countries. However, the constituents separate out at -6 °C, in which case adequate mixing must be assured before use. When the two components are supplied from separate cylinders a safety device must be installed that interrupts the flow of nitrous oxide should the oxygen pressure fall.

### **Identification of cylinders**

An ISO standard<sup>1</sup> requires that cylinders containing nitrous oxide should bear the name of the contents in legible and permanent characters and, preferably, also the chemical symbol N<sub>2</sub>O. The neck, from the valve to the shoulder, should be coloured blue. Cylinders containing nitrous oxide and oxygen mixtures should be similarly labelled, and the neck coloured white and blue.

<sup>1</sup> International Standard 32. Gas cylinders for medical use — marking for identification of content. Switzerland, International Organization for Standardization, 1977.

# Oxygen

Group: inhalational gas

## General information

Pressurized oxygen cylinders for industrial use that contain gas at about 13 000 kPa are acceptable for use in anaesthesia. Cylinders intended for anaesthetic use are supplied with pin-index valves. They contain more than 99% oxygen by volume with small residues of nitrogen or argon. Cylinders should always be connected to anaesthetic apparatus by a suitable pressure-reducing valve and they should be replaced as soon as the cylinder pressure falls below 800 kPa.

Oxygen concentrators have recently been developed that offer a more economical source of oxygen and avert the need for frequent delivery and storage of cylinders.

## Clinical information

### Uses

To maintain an adequate oxygen tension in inhalational anaesthesia.

### Dosage and administration

The concentration of oxygen in inspired anaesthetic gases should never be less than 21%.

It may be administered with the anaesthetic gases, or from a face mask or via a nasal catheter.

### Precautions

Combustion or sparking creates a danger of fire or explosion at high oxygen tensions. Use of cautery is contraindicated whenever oxygen is used in combination with ether. Reducing valves should not be greased, since this creates a danger of explosion.

Oxygen should not be used for longer or at a greater concentration than is necessary to prevent hypoxaemia.

### Adverse effects

After prolonged administration, concentrations greater than 80% at atmospheric pressure have a toxic effect on the lungs, which presents initially as a mild substernal irritation progressing to pulmonary congestion, exudation and atelectasis.

Use of unnecessarily high concentrations of oxygen in incubators has led to the development of retrolental fibroplasia and permanent blindness in premature infants.

### Storage

Oxygen is supplied under pressure in cylinders, which must be kept below 25 °C.

Cylinders containing premixed oxygen 50% and nitrous oxide 50% are available for analgesia in some countries. However, the constituents separate out at -6 °C, in which case adequate mixing must be assured before use. When the two components are supplied from separate cylinders a safety device must be installed that cuts off the flow of nitrous oxide should the oxygen pressure fall.

### Identification of cylinders

An ISO standard<sup>1</sup> requires that cylinders containing oxygen intended for medical use should bear the name of the contents in legible and permanent characters and, preferably, also the chemical symbol O<sub>2</sub>. The neck, from the valve to the shoulder, should be coloured white. Cylinders containing nitrous oxide and oxygen mixtures should be similarly labelled, and the neck coloured white and blue.

<sup>1</sup> International Standard 32. Gas cylinders for medical use — marking for identification of content. Switzerland, International Organization for Standardization, 1977.

# Local anaesthetics

## Bupivacaine

*Group: local anaesthetic agent*

*Injection (hydrochloride): 2.5 mg/ml (0.25%) or 5 mg/ml (0.5%) in 10-ml ampoule; 5 mg/ml (0.5%) in 1.8-ml cartridge for dental anaesthesia; 7.5 mg/ml (0.75%) with glucose 82.5 mg/ml (8.25%) in 4-ml ampoule*

### General information

Bupivacaine is a long-acting local anaesthetic. Addition of epinephrine is thus rarely required. It blocks initiation and transmission of nerve impulses at the site of application by stabilizing the neuronal membrane. The compound is ultimately metabolized in the liver. Depending upon the site of injection and the concentration used, anaesthesia usually lasts 2–4 hours.

### Clinical information

#### Uses

- Infiltration anaesthesia.
- Peripheral and sympathetic nerve block.
- Dental anaesthesia.
- Spinal anaesthesia.
- Epidural and caudal anaesthesia (these techniques produce prolonged regional anaesthesia, and should be attempted only by experienced specialist anaesthetists).

Bupivacaine is unsuitable for intravenous regional anaesthesia or for topical application.

#### Dosage and administration

The aim is to administer the smallest effective dose. This varies with the proce-

cedure adopted, the degree of anaesthesia required, the rate of absorption from the injection site and the size and responsiveness of the patient. Higher initial blood levels are attained with more concentrated solutions.

The maximum cumulative safe dose for adults and children of a 0.25% solution of bupivacaine is 1.5 mg/kg. The table provides a general guide to dosage in adults. Smaller dosages should be administered to debilitated, elderly, epileptic and acutely ill patients.

Bupivacaine is generally not recommended for children aged less than 12 years since there is insufficient information on the effects of its use in this age group.

Solutions containing preservatives should not be used for spinal, epidural or caudal anaesthesia.

#### Spinal anaesthesia

Spinal anaesthesia should be attempted only by a person fully trained in the technique and competent to treat possible complications. A "heavy" solution (0.75% bupivacaine in 8.25% glucose) will provide the muscular relaxation required for abdominal surgery. Full aseptic technique must be employed for the injection and

Anaesthetic procedure	Concentration (%)	Dose	
		ml	mg
Local infiltration	0.25	up to 60	up to 150
Peripheral nerve block	0.5	up to 30	up to 150
Dental anaesthesia	0.5	1.8–3.6	9.0–18.0
Spinal anaesthesia	0.75 (+ 8.25% glucose)	1–1.5	7.5–11.25



the patient must be appropriately tilted to ensure safety and the required level of analgesia.

Spinal anaesthesia always causes hypotension as a result of sympathetic blockade. It should never be used in patients with any condition resulting in hypovolaemia. The hypotensive response may largely be averted by preliminary intravenous infusion of 500–1000 ml of physiological saline (9 mg/ml) but blood pressure should always be measured every 2 minutes for at least 10 minutes. Postoperative headache can be prevented by instructing the patient to remain supine for 24 hours.

### **Obstetric practice**

Lumbar epidural block has largely replaced caudal epidural block for relief of pain in labour. It requires less local anaesthetic, carries less risk of infection and is readily extended should caesarean section become necessary. However, because of the risk to both the mother and the fetus, it should be attempted only by an experienced specialist anaesthetist. Concentrations of bupivacaine greater than 0.5% are contraindicated for this purpose in view of reports of cardiac arrest and maternal death. Maternal blood pressure, fetal heart rate and uterine contractions should be monitored throughout the procedure. Paracervical block is no longer recommended during labour because it results in very high levels of the drug in fetal blood.

### **Contraindications**

- Known or suspected hypersensitivity to bupivacaine.
- Skin infection adjacent to the intended site of injection, concomitant anticoagulant therapy or an abnormal bleeding tendency.
- Severe anaemia or heart disease.
- Spinal and epidural anaesthetics should never be administered to dehydrated or hypovolaemic patients.

### **Precautions**

Facilities and equipment for resuscitation should be readily available at all times.

Assurance must be obtained that the patient is psychologically prepared to accept the proposed procedure.

High blood levels of bupivacaine must be avoided in patients with hepatic impairment.

Care must always be taken to avoid inadvertent intravascular injection.

### **Use in pregnancy**

Safe use in early pregnancy has not been established. However, there is no clinical evidence to suggest that exposure of the mother to bupivacaine is harmful to the fetus.

### **Adverse effects**

These may result from excessive dosage, inadvertent intravascular injection, or injection into highly vascular tissues. Initial signs of light-headedness, dizziness, blurred vision, restlessness, tremors and, occasionally, convulsions are rapidly followed by drowsiness, unconsciousness and respiratory failure. Myocardial depression and hypotension can result in hypoxia, acidosis, heart block and cardiac arrest.

Hypersensitivity and allergic reactions may also occur.

Epidural anaesthesia is occasionally complicated by urinary retention, faecal incontinence, headache, backache or loss of perineal sensation. Transient paraesthesiae and paraplegia are very rare complications.

### **Drug interactions**

Co-administration of oxytocic drugs postpartum may cause severe and prolonged hypertension. The use of bupivacaine preparations containing epinephrine during or following the administration of

### **Bupivacaine (continued)**

halothane or trichloroethylene creates a risk of cardiac dysrhythmias.

### **Overdosage**

Overdosage or accidental intravascular injection is characterized by the systemic effects described above. Treatment is symptomatic. There is no specific anti-

dote. A clear airway should be maintained and ventilation assisted as required. Convulsions may be controlled by diazepam or thiopental.

### **Storage**

Bupivacaine injection should be kept protected from light and should not be allowed to freeze. Ampoules should not be used if the solution is discoloured.

## **Lidocaine**

*Group: local anaesthetic agent*

*Injection (hydrochloride): 5 mg/ml (0.5%), 10 mg/ml (1%) in 20-ml ampoule; 10 mg/ml (1%) + epinephrine 5 micrograms/ml (1:200 000) in 20-ml ampoule; 20 mg/ml (2%) + epinephrine 12.5 micrograms/ml (1:80 000) in 2.2-ml cartridge for dental anaesthesia; 50 mg/ml (5%) in 2-ml ampoule to be mixed with 75 mg/ml (7.5%) glucose solution*

*Topical forms: 20–40 mg (hydrochloride)/ml (2–4%) as gel or solution*

### **General information**

Lidocaine is a moderately long-acting local anaesthetic. It blocks initiation and transmission of nerve impulses at the site of application by stabilizing the neuronal membrane. The compound is ultimately metabolized in the liver. Anaesthesia, which persists for 1–3 hours, is induced within 1–5 minutes following mucosal application, infiltration and spinal or dental nerve block, and within 10–15 minutes following other methods of administration.

techniques produce prolonged regional anaesthesia and should be attempted only by experienced specialist anaesthetists).

### **Dosage and administration**

The aim is to administer the smallest effective dose. This varies with the procedure adopted, the degree of anaesthesia required, the rate of absorption from the injection site and the size and responsiveness of the patient. Higher initial blood levels are attained with more concentrated solutions.

Solutions are available with or without epinephrine at 5 micrograms/ml (1:200 000) or, for dental anaesthesia, 12.5 micrograms/ml (1:80 000). Epinephrine is contraindicated for ring block of digits or the penis and for other procedures associated with risk of ischaemia.

The maximum cumulative safe doses of lidocaine for adults and children are:

0.5%, 1% lidocaine	4 mg/kg
0.5%, 1% lidocaine + epinephrine 5 µg/ml (1:200 000)	7 mg/kg.

### **Clinical information**

#### **Uses**

- Surface anaesthesia of mucous membranes.
- Infiltration anaesthesia.
- Peripheral and sympathetic nerve block.
- Dental anaesthesia.
- Spinal anaesthesia.
- Intravenous regional anaesthesia.
- Epidural and caudal anaesthesia (these

Anaesthetic procedure	Concentration (%)	Epinephrine	Dose	
			ml	mg
Local infiltration and peripheral nerve block	0.5	No	<50	<250
	1.0	No	<25	<250
	0.5	Yes	<80	<400
	1.0	Yes	<40	<400
Surface anaesthesia				
Pharynx, larynx, trachea	4	No	1–5	40–200
Urethra	4	No	10	400
Dental anaesthesia	2	Yes	1–5	20–100
Spinal anaesthesia	5	No	1–1.5	50–75
	(+ 7.5% glucose)			

The table provides a general guide to dosage in adults. Smaller dosages should be administered to debilitated, elderly, epileptic and acutely ill patients.

Solutions containing preservatives should not be used for spinal, epidural, caudal and intravenous regional anaesthesia.

### Spinal anaesthesia

Spinal anaesthesia should only be attempted by a person trained in the technique and competent to treat possible complications. A "heavy" solution (5% lidocaine in 7.5% glucose) will provide the muscular relaxation required for abdominal surgery. Full aseptic technique must be employed for the injection and the patient must be appropriately tilted to ensure safety and the required level of analgesia.

Spinal anaesthesia always causes hypotension as a result of sympathetic blockade. It should never be used in patients with any condition resulting in hypovolaemia. The hypotensive response may largely be averted by preliminary intravenous infusion of 500–1000 ml of physiological saline (9 mg/ml) but blood pressure should always be measured every 2 minutes for at least 10 minutes. Postoperative headache can be prevented by instructing the patient to remain supine for 24 hours.

### Obstetric practice

Lumbar epidural block has largely replaced caudal epidural block for relief of pain in labour. It requires less local anaesthetic, carries less risk of infection and is readily extended should caesarean section become necessary. However, because of the risk to both the mother and the fetus, it should be attempted only by an experienced specialist anaesthetist. Maternal blood pressure, fetal heart rate and uterine contractions should be monitored throughout the procedure. Paracervical block is no longer recommended during labour because it results in very high levels of the drug in fetal blood.

### Contraindications

- Known or suspected hypersensitivity to lidocaine.
- Skin infection adjacent to the proposed site of injection, concomitant anticoagulant therapy or an abnormal bleeding tendency.
- Severe anaemia or heart disease.
- Spinal and epidural anaesthesia should never be used in dehydrated or hypovolaemic patients.

### Precautions

Facilities and equipment for resuscitation should be readily available at all times.

### **Lidocaine (continued)**

Assurance must be obtained that the patient is psychologically prepared to accept the proposed procedure.

Caution is required in patients with hepatic impairment when the dosage or route of administration is liable to result in high blood levels.

Care must always be taken to avoid inadvertent intravascular injection.

#### **Use in pregnancy**

Safe use in early pregnancy has not been established. However, there is no clinical evidence to suggest that exposure of the mother to lidocaine is harmful to the fetus.

#### **Adverse effects**

These may result from excessive dosage, inadvertent intravascular injection or injection into highly vascular tissues. Initial signs of light-headedness, dizziness, blurred vision, restlessness, tremors and, occasionally, convulsions are rapidly followed by drowsiness, unconsciousness and respiratory failure. Myocardial depression and hypotension may result in hypoxia, acidosis, heart block and cardiac arrest.

Hypersensitivity and allergic reactions may also occur.

Epidural anaesthesia is occasionally complicated by urinary retention, faecal incontinence, headache, backache or loss of perineal sensation. Transient paraesthesiae and paraplegia are very rare complications.

#### **Drug interactions**

Co-administration of oxytocic drugs postpartum may cause severe and prolonged hypertension. The use of lidocaine preparations containing epinephrine during or following the administration of halothane or trichloroethylene creates a risk of cardiac dysrhythmias.

#### **Overdosage**

Overdosage or accidental intravascular injection is characterized by the systemic effects described above. Treatment is symptomatic. There is no specific antidote. A clear airway should be maintained and ventilation assisted as required. Convulsions may be controlled with diazepam or thiopental.

#### **Storage**

Lidocaine injection should be kept protected from light and should not be allowed to freeze. Methylene blue may be added to topical formulations for ease of identification.

## **Tetracaine**

*Group: local anaesthetic agent*

*Solution (eye drops): 5 mg (hydrochloride)/ml (0.5%)*

### **General information**

Tetracaine is a local anaesthetic that penetrates the cornea and conjunctiva. It is effective after topical application to the eye within 30 seconds and anaesthesia persists for at least 15 minutes.

### **Clinical information**

#### **Uses**

Short-lasting local anaesthesia of the cornea and conjunctiva.

#### **Dosage and administration**

One or 2 drops of 0.5% solution should be instilled into the conjunctival sac.

### Contraindications

- Known hypersensitivity to tetracaine.
- Ocular inflammation or infection.

### Precautions

The anaesthetized eye should be protected from dust and bacteriological contamination until sensation is fully restored.

Prolonged use has resulted in corneal opacities.

### Adverse effects

A localized burning sensation may occur and, more rarely, lacrimation and photophobia.

### Storage

Tetracaine eye drops should be kept in well-closed containers protected from light, and should not be allowed to freeze.

## Epinephrine (for use with local anaesthetics)

*Group: additive to local anaesthetic agents*

*Injection: 1 mg (as hydrochloride) in 1-ml ampoule*

### General information

Epinephrine is a sympathomimetic agent that activates both  $\alpha$ - and  $\beta$ -adrenoceptors. It is secreted together with norepinephrine by the adrenal medulla in response to stress. Epinephrine is transient in its effect when administered parenterally because it is rapidly metabolized.

### Clinical information

#### Uses

To retard systemic absorption of infiltrated local anaesthetics.

#### Dosage and administration

The addition of epinephrine 5 micrograms/ml (1:200 000) as a vasoconstrictor to local anaesthetic solutions slows systemic absorption and prolongs the anaesthetic effect. In dental surgery, in which small volumes are injected, concentrations of 12.5 micrograms/ml (1:80 000) are commonly used.

Epinephrine should not be used in ring block of digits or the penis or in other

situations where there is a danger of local ischaemia.

### Precautions

Solutions containing epinephrine should be used with particular caution in patients with hypertension, atherosclerotic heart disease, cerebral vascular insufficiency, heart block, thyrotoxicosis or diabetes since severe and sustained variations in blood pressure may occur.

### Drug interactions

The risk of cardiac dysrhythmias is increased when epinephrine is administered to patients receiving halogenated hydrocarbon anaesthetic agents (such as halothane and trichloroethylene), digitalis glycosides, quinidine, tricyclic antidepressants or thyroid hormones.

### Overdosage

An abrupt rise in blood pressure and dysrhythmias may be counteracted by propranolol or other  $\beta$ -adrenoceptor-blocking agents.

### Storage

Epinephrine injection should be stored protected from light.

# Non-opioid analgesics

## Acetylsalicylic acid

*Group: non-opioid analgesic*

*Tablet: 100–500 mg*

*Suppository: 50–150 mg*

### General information

Acetylsalicylic acid has anti-inflammatory, analgesic, antipyretic, antirheumatic and antithrombotic activity. In part these effects are due to inhibition of the synthesis of endogenous prostaglandins.

It is hydrolysed primarily in the gut and the liver and excreted mainly in the urine, both as free salicylic acid and as inactive metabolites. The plasma half-life of salicylate resulting from doses of 2–3 g of acetylsalicylic acid is approximately 3 hours. With higher doses it is significantly longer.

### Clinical information

#### Uses

Symptomatic relief of mild to moderate pain.

#### Dosage and administration

Adults: 300–900 mg every 4–6 hours as required (max 4 g/day).

Children:

6–12 years: 300–400 mg every 6 hours.

3–5 years: 200–300 mg every 8 hours.

1–2 years: 50–150 mg every 6 hours.

Treatment should not be continued for more than 5 days except on medical advice.

Administration with food or a full glass of water reduces gastric irritation. Rectal absorption is slow and incomplete, but suppositories are of value in patients unable to take oral dosage forms.

#### Contraindications

- Hypersensitivity to acetylsalicylic acid.
- Bleeding disorders, anticoagulant

therapy, haemorrhagic stroke, active peptic ulcer or gastritis.

- Chronic renal insufficiency.

Reye's syndrome (a rare but often fatal non-inflammatory encephalopathy and fatty metamorphosis of the liver) has been reported in children and adolescents with influenza or chickenpox who have received acetylsalicylic acid. The risk is remote but it is readily avoided by withholding the drug in these circumstances.

To avoid the risk of haemorrhage acetylsalicylic acid should not be administered within 7 days of an elective surgical operation.

#### Precautions

Symptoms of hypersensitivity are more likely to occur in:

- patients with asthma, urticaria or chronic rhinitis
- patients who have developed skin rashes or anaphylactic phenomena after exposure to other nonsteroidal anti-inflammatory agents.

A mild haemolytic reaction may occur in patients with glucose-6-phosphate dehydrogenase deficiency.

Young children are particularly susceptible to the dose-related toxic effects of acetylsalicylic acid. They should never receive more than the maximum recommended dose and stocks of tablets should never be left within their reach.

#### Use in pregnancy

Normal use of acetylsalicylic acid carries no apparent risk during early pregnancy. However, it should not be taken in the last 3 months of pregnancy since it has been reported to prolong labour and contribute to maternal and neonatal bleeding.

### Adverse effects

Hypersensitivity reactions, which may occasionally be severe, include urticaria, angio-oedema, pruritus and anaphylactic phenomena.

Gastrointestinal effects including dyspepsia, heartburn, epigastric distress and nausea are common and sometimes severe. Gastrointestinal bleeding can result from acute mucosal erosion or reactivation of peptic ulceration. It is commonly occult but occasionally profuse and even fatal.

Inhibition of platelet aggregation may result in prolongation of bleeding time. Leukopenia, thrombocytopenia, purpura and pancytopenia have rarely been reported.

### Drug interactions

The therapeutic actions of anticoagulants may be potentiated.

Conversely, the efficacy of uricosuric agents and spironolactone may be reduced.

Co-administration of acetylsalicylic acid and corticosteroids greatly increases the risk of gastrointestinal bleeding.

### Overdosage

Acute ingestion of 20–25 g by an adult, or 4 g by a small child, can be lethal and smaller quantities can cause serious toxic effects.

Characteristic early signs of overdosage include nausea and vomiting, abdominal pain and tinnitus that may ultimately progress to deafness. These are followed by flushing, sweating and hyperventilation with respiratory alkalosis. In severe cases metabolic acidosis and coma supervene.

Gastric lavage should be carried out immediately. Failing this, vomiting should be induced. Hyperthermia, dehydration, acidosis and potassium deficiency should be corrected symptomatically.

Whole blood transfusion may be necessary in the event of spontaneous haemorrhage. It is unnecessary additionally to prescribe vitamin K routinely.

Forced alkaline diuresis accelerates excretion of salicylate. However, when the serum salicylate concentration is dangerously high or when grave signs develop, such as unresponsive acidosis, impaired urinary output, pulmonary oedema, persistent seizures or coma, haemodialysis may offer the only hope of survival.

### Storage

Acetylsalicylic acid tablets should be kept in tightly closed containers. If an odour of acetic acid is perceptible on opening the container, the tablets should be discarded. Suppositories should be stored below 15 °C.

## Paracetamol

*Group: non-opioid analgesic*

*Tablet: 100–500 mg*

*Suppository: 100 mg*

*Syrup: 125 mg in 5 ml*

### General information

Paracetamol is a synthetic derivative of *p*-aminophenol with analgesic and antipyretic activity but no anti-inflammatory

action. Its plasma half-life is about 2 hours. It is extensively metabolized in the liver and subsequently excreted in the urine.

**Paracetamol (continued)**

## Clinical information

### Uses

Symptomatic relief of mild to moderate pain.

### Dosage and administration

Adults: 0.5–1 g repeated, as necessary, every 4–6 hours to a maximum of 4 g daily.

Children: 20–30 mg/kg daily in divided doses.

Dosages should be reduced in patients with renal failure.

Suppositories are available for patients unable to take the drug orally.

Treatment should not be continued for more than 5 days except on medical advice.

### Contraindications

- Hypersensitivity to paracetamol.
- Repeated administration is contraindicated in patients with hepatic insufficiency.

### Adverse effects

At doses within the therapeutic range paracetamol is usually well tolerated.

Hypersensitivity, dermatological reactions, neutropenia and thrombocytopenic purpura have rarely been reported.

### Overdosage

In overdosage paracetamol is dangerously hepatotoxic; potentially fatal hepatic necrosis can occur after ingestion of as little

as a single dose of 10–15 g. Signs of mild gastrointestinal irritation are commonly followed 2 days later by anorexia, nausea, malaise, abdominal pain, progressive evidence of liver failure and, ultimately, hepatic coma.

Gastric lavage should be performed or emesis induced whenever there is a possibility that paracetamol remains in the stomach. When feasible, plasma paracetamol concentrations should be determined to assess the risk of liver failure. This is likely when the plasma concentration is greater than 200 micrograms/ml at 4 hours after ingestion, 100 micrograms/ml at 8 hours, 50 micrograms/ml at 12 hours, 25 micrograms/ml at 16 hours and 6 micrograms/ml at 24 hours.

Either methionine or acetylcysteine may be used as a specific antidote. To be effective the antidote must be administered within 16 hours and before signs of hepatic damage become evident. A loading dose of 140 mg/kg administered orally or through a nasogastric tube is supplemented by 70 mg/kg every 4 hours until the results of liver function tests have returned to normal. If this has not occurred within 3 days, no further improvement can be expected.

Fluid and electrolyte balance must be maintained and ventilation must be assisted when respiration is depressed.

### Storage

Paracetamol tablets and syrup should be stored in tightly closed containers protected from light, below 25 °C. Suppositories should be stored below 15 °C.



# Opioid analgesics and antagonists

## Morphine

*Group: opioid analgesic*

*Injection: 10 mg (sulfate or hydrochloride) in 1-ml ampoule*

*Oral solution: 10 mg (sulfate or hydrochloride) in 5 ml*

*Tablet: 10 mg (sulfate or hydrochloride)*

### General information

Morphine is the principal alkaloid of opium. It is the most potent of the narcotic analgesics and a dangerous drug of addiction. Its supply is controlled under Schedule 1 of the Single Convention on Narcotic Drugs, 1961. It is extensively absorbed following oral administration but parenteral administration produces a more reliable and more rapid response. The plasma half-life is 2–3 hours. It is largely metabolized in the liver and subsequently excreted in the urine.

### Clinical information

#### Uses

- Preoperative management of musculoskeletal and visceral pain.
- Premedication prior to general surgery.
- An adjunct to inhalational and other anaesthetic agents during major surgical interventions.
- Postoperative analgesia.

#### Dosage and administration

##### **Premedication**

Adults: 150–200 micrograms/kg i.m. or subcutaneously 1 hour before operation.

Children: 50–100 micrograms/kg as above, to a maximum of 10 mg.

##### **Preoperative analgesia**

Adults: 150–200 micrograms/kg i.m. or i.v.

Children: 50–100 micrograms/kg i.m.

##### **During anaesthesia**

Adults and children: 100 micrograms/kg i.v. repeated every 40–60 minutes as required.

##### **Postoperative analgesia**

Adults: 150–300 micrograms/kg i.m. every 4 hours or, by continuous intravenous infusion, 8–10 mg in 30 minutes, then 2–2.5 mg/hour.

Children: 100–200 micrograms/kg i.m. or subcutaneously repeated as necessary. No more than 10 mg should be administered as a single dose.

Rarely, morphine is administered by epidural or intrathecal injection to provide postoperative analgesia. These procedures should be attempted only by experienced specialist anaesthetists and must be used only when facilities for close monitoring of the patient are available. The preparations used must be free of preservatives.

Morphine should be administered at reduced dosage to patients who are elderly or who have cardiorespiratory disease or renal insufficiency.

#### Contraindications

- Bronchial asthma, emphysema or heart failure secondary to chronic lung disease.
- Increased intracranial pressure, head injury or brain tumour.
- Severe hepatic impairment, adrenocortical insufficiency, hypothyroidism.
- Convulsive disorders, acute alcoholism, delirium tremens.
- Diverticulitis and other spastic conditions of the colon, biliary colic and recent surgery on the biliary tract.
- Use of monoamine oxidase inhibitors within the previous 14 days.

#### Precautions

Vital signs must be monitored regularly in the immediate postoperative period when

### **Morphine (continued)**

morphine is administered during anaesthesia since respiratory depression may persist for several hours. In addition, marked respiratory depression may occur up to several hours after epidural administration. Facilities for intermittent positive pressure ventilation must therefore be immediately available.

To reduce risk of dependence, opioids should not normally be used for postoperative analgesia for longer than 7 days.

### **Use in pregnancy**

Morphine should be used during pregnancy only when the need outweighs any possible risk to the fetus. Its use during labour may produce respiratory depression in the infant, who may require administration of naloxone, 10 micrograms/kg i.m., immediately after birth.

### **Adverse effects**

Acute dose-related effects include respiratory depression; anorexia, nausea, vomiting and constipation; euphoria, dizziness, drowsiness and confusion; dry mouth and spasm of the urinary and biliary tract; hypotension, bradycardia and palpitations.

Allergic phenomena are uncommon but anaphylactoid reactions have been reported.

Prolonged administration may result in physical dependence.

### **Drug interactions**

Morphine potentiates the effects of other cerebral depressants. Its effect is counteracted by naloxone within 2 minutes.

Sedatives should be withheld if a patient has been given morphine since they may cause restlessness or confusion.

### **Overdosage**

Serious overdosage is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, and pin-point pupils. Cardiovascular collapse and cardiac arrest are terminal events.

Supportive therapy includes mechanically assisted ventilation and administration of pressor drugs and fluids to maintain the circulating blood volume. Except in dependent individuals, in whom specific opioid antagonists induce an intense acute withdrawal reaction, naloxone (200 micrograms i.v.), should be administered, as necessary, at 2-minute intervals.

### **Storage**

Morphine tablets, solution and injection should be kept in tightly closed containers and should not be allowed to freeze.

The requirements relating to drugs controlled under Schedule 1 of the Single Convention on Narcotic Drugs should be observed.<sup>1</sup>

<sup>1</sup> *Single convention on narcotic drugs, 1961*. New York, United Nations, 1977.

# Pethidine

*Group: opioid analgesic*

*Injection: 50 mg (hydrochloride) in 1-ml ampoule*

*Tablet: 50 mg (hydrochloride)*

## General information

Pethidine is a synthetic narcotic analgesic that competes for the same receptors as morphine in the central nervous system. It is a dangerous drug of addiction. Its supply is controlled under Schedule I of the Single Convention on Narcotic Drugs, 1961.

Pethidine is comparable to morphine in its sedative and tranquillizing effects, but the analgesia and respiratory depression it produces are of shorter duration, and it induces less smooth muscle spasm. Pethidine is preferred to morphine in the pre-operative management of biliary colic and in the management of acute diverticulitis.

It is well absorbed orally but parenteral administration is more effective. Its plasma half-life is about 3 hours. It is largely metabolized in the liver and the end-products are excreted in the urine.

## Clinical information

### Uses

- Preoperative management of musculoskeletal and visceral pain.
- Premedication prior to general anaesthesia.
- An adjunct to inhalational and other anaesthetic agents during major surgical interventions.
- To prevent tachypnoea induced by trichloroethylene.
- Postoperative and obstetric analgesia.
- In combination with diazepam, and in the absence of other agents, for reduction of fractures and other minor interventions.

## Dosage and administration

### Premedication

Adults: 50–100 mg i.m. or subcutaneously 1 hour before induction.

Children: 1 mg/kg i.m. or subcutaneously 1 hour before induction.

### Preoperative analgesia

Adults: 50–100 mg i.m. or i.v.

Children: 1 mg/kg i.m.

### During general anaesthesia

Adults and children: 0.25 mg/kg i.v. repeated every 40–60 minutes as required.

### Postoperative analgesia

Adults: 50–150 mg i.m. every 4 hours, or 15–35 mg/hour by continuous intravenous infusion.

Children: 1–2 mg/kg orally, i.m. or subcutaneously, repeated every 4 hours as necessary.

### Obstetric analgesia

A dose of 1 mg/kg, repeated as needed. The last dose should be administered, when possible, 1–3 hours prior to delivery in order to prevent neonatal depression.

Dosage should be reduced in elderly patients and those with cardiorespiratory disease.

## Contraindications

- Bronchial asthma, emphysema or heart failure secondary to chronic lung disease.
- Increased intracranial pressure, head injury or brain tumour.
- Severe hepatic impairment, adrenocortical insufficiency, hypothyroidism.
- Convulsive disorders, acute alcoholism, delirium tremens.

**Pethidine (continued)**

- Use of monoamine oxidase inhibitors within the previous 14 days.

**Precautions**

Vital signs must be monitored regularly in the immediate postoperative period when pethidine has been administered during anaesthesia since respiratory depression may persist for several hours.

Facilities for intermittent positive pressure ventilation must be immediately available.

To reduce risk of dependence, opioids should not normally be used for postoperative analgesia for longer than 7 days.

**Use in pregnancy**

Pethidine should be used during pregnancy only when the need outweighs any possible risk to the fetus. Its use during labour may produce respiratory depression in the infant, who may require administration of naloxone 10 micrograms/kg i.m. immediately after birth.

**Adverse effects**

Adverse effects include respiratory depression, nausea and vomiting, dizziness, drowsiness and confusion, hypotension, bradycardia and palpitations.

Allergic phenomena are uncommon but anaphylactoid reactions have been reported.

Physical dependence may occur with prolonged administration.

**Drug interactions**

Pethidine potentiates the effects of other cerebral depressants. Its effect is counteracted by naloxone within 2 minutes.

Sedatives should be withheld if a patient has been given pethidine since they may cause restlessness or confusion.

**Overdosage**

Serious overdosage is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, and pin-point pupils. Cardiovascular collapse and cardiac arrest are terminal events. Supportive therapy includes mechanically assisted ventilation and administration of pressor drugs and fluids to maintain the circulating blood volume. Except in dependent individuals, in whom specific opioid antagonists induce an intense acute withdrawal reaction, naloxone (200 micrograms i.v.) should be administered, as necessary, at 2-minute intervals.

**Storage**

Pethidine tablets and injection should be kept in tightly closed containers protected from light, and should not be allowed to freeze.

The requirements relating to drugs controlled under Schedule 1 of the Single Convention on Narcotic Drugs should be observed.<sup>1</sup>

<sup>1</sup> *Single convention on narcotic drugs, 1961*. New York, United Nations, 1977.

# Naloxone

*Group: opioid antagonist*

*Injection: 0.4 mg (hydrochloride) in 1-ml ampoule*

## General information

Naloxone is a semisynthetic opioid antagonist that competes with opioid analgesics for specific receptor sites in the central nervous system. Its effect, which persists for about 45 minutes, occurs within 1–2 minutes of intravenous administration.

## Clinical information

### Uses

To counteract respiratory depression induced by opioids administered during anaesthesia or by opioid overdose.

### Dosage and administration

#### **Post-anaesthetic administration**

Adults: 100–400 micrograms i.v. titrated to the needs of the patient and repeated, as necessary, at intervals of 2–3 minutes.

Children: 5–10 micrograms/kg i.v. repeated as above.

Neonates: 10 micrograms/kg i.v., i.m. or subcutaneously immediately after birth.

#### **Opioid overdose**

Adults: 200 micrograms i.v. repeated, as necessary, at 2-minute intervals to a maximum of 10 mg.

Dosage should be reduced in patients with cardiovascular conditions predisposing to dysrhythmias.

### Contraindications

- Known hypersensitivity to naloxone.

- Physical dependence on narcotics (naloxone will precipitate an acute withdrawal syndrome in dependent patients).

### Precautions

The use of naloxone to counteract respiratory depression complements other resuscitative measures including maintenance of a clear airway, control of ventilation, cardiac massage, maintenance of an effective circulatory volume and vasopressor therapy. The necessary facilities and equipment for such treatment must be immediately available.

### Use in pregnancy

Naloxone should be used during pre-term pregnancy only when the need outweighs any possible risk to the fetus.

### Adverse effects

Unnecessarily high doses may cause hypertension and tachycardia. Transient nausea, vomiting, sweating, tachycardia, hypertension and tremor have been reported. Seizures are rare.

Patients with pre-existing cardiovascular disease have occasionally developed ventricular dysrhythmias.

### Overdosage

Excessive dosage results in convulsions, raised blood pressure and loss of pre-existing opioid analgesia.

### Storage

Naloxone injection should be kept protected from light.

# Muscle relaxants and cholinesterase inhibitors

## Gallamine

*Group: non-depolarizing muscle relaxant*

*Injection: 40 mg (triethiodide)/ml in 2-ml ampoule*

### General information

Gallamine is a synthetic non-depolarizing neuromuscular blocking agent. Its effect becomes apparent within 2 minutes of intravenous administration and persists for up to 40 minutes. It is excreted in the urine largely unchanged.

### Clinical information

#### Uses

To produce relaxation of skeletal muscle during surgery.

#### Dosage and administration

Muscle relaxants should be administered only after induction of anaesthesia and when a secure airway has been established. The dosage must be adjusted according to the response. As a guide:

Adults: 1–1.5 mg/kg i.v. initially, then 0.5–1 mg/kg as required at about 40-minute intervals.

Children: 1.5 mg/kg initially, then 0.5 mg/kg as required.

Infants of less than 1 month: 250–750 micrograms/kg initially, then 100–500 micrograms/kg as required.

#### Contraindications

- Known hypersensitivity to gallamine.
- Myasthenia gravis.
- Shock and impaired renal function.
- Cardiac disease predisposing to dysrhythmias.

#### Precautions

Gallamine should be used, whenever possible, by an experienced specialist

anaesthetist. Facilities for endotracheal intubation and mechanically assisted ventilation should be immediately to hand and ready for use.

Gallamine should not be administered before evidence of recovery from the effect of any suxamethonium given previously.

#### Use in pregnancy

Gallamine should be used in pre-term pregnancy only when the need outweighs any possible risk to the fetus. Its use is best avoided in obstetric practice since gallamine crosses the placenta.

#### Adverse effects

Gallamine may produce vagolytic tachycardia. Anaphylactoid reactions rarely occur.

#### Drug interactions

The effect of gallamine may be appreciably prolonged by many other drugs including streptomycin, neomycin, polymyxin B, kanamycin, quinidine, propranolol and procainamide.

Ether and halothane potentiate the action of gallamine and other non-depolarizing muscle relaxants. The dose of gallamine should be reduced by 40% when used with ether, and by 20% when used with halothane.

Used concomitantly with gallamine, potassium-depleting agents, particularly thiazide diuretics and furosemide, may cause prolonged neuromuscular blockade.

#### Overdosage

Ventilation must be mechanically assisted until spontaneous respiration is fully

re-established and the patient must be closely monitored until all risk of recrudescence of muscular paralysis has passed.

Muscular paralysis can generally be rapidly reversed by neostigmine after atropine has been administered to prevent excessive autonomic stimulation. This

reversal occurs more rapidly if some return of muscle tone is evident before neostigmine is given.

### **Storage**

Gallamine injection should be kept protected from light, and should not be allowed to freeze.

## **Suxamethonium**

*Group: depolarizing muscle relaxant*

*Injection: 50 mg (chloride)/ml in 2-ml ampoule*

*Powder for injection (chloride or bromide)*

### **General information**

Suxamethonium is a short-acting muscle relaxant which exerts a depolarizing effect at the neuromuscular junction. It is metabolized rapidly, mainly by pseudocholinesterase, and excreted in the urine. Given intravenously it acts within 30 seconds and flaccid paralysis, preceded by fasciculation, lasts up to 5 minutes. This effect is not reversible pharmacologically.

### **Clinical information**

#### **Uses**

To produce brief muscular paralysis during:

- endotracheal intubation
- endoscopy
- orthopaedic manipulations
- electroconvulsive therapy.

The muscular relaxation produced by suxamethonium is generally more profound than that of the longer-acting non-depolarizing muscle relaxants, but the latter are more suitable when an extended effect is required.

#### **Dosage and administration**

Muscle relaxants should only be administered after induction of anaesthesia and when a secure airway has been established.

Adults: initially 1 mg/kg i.v. followed, when necessary, by supplements of 0.3 mg/kg. Repeat doses may cause bradycardia, which can be prevented by atropine 0.5–1 mg i.v.

Children: 1–2 mg/kg i.v. supplemented, when necessary, as above.

A more prolonged effect may be obtained in both adults and children by continuous intravenous infusion of 1–2 mg/minute. This sometimes results in a paradoxical and prolonged non-depolarizing muscle-relaxant action. Since this is only partially and temporarily reversible by neostigmine, ventilation must be assisted and subsequently monitored until spontaneous breathing is fully re-established.

#### **Contraindications**

- Suxamethonium is absolutely contraindicated if the anaesthetist is not confident of maintaining a clear airway.
- Known hypersensitivity to suxamethonium.
- Myasthenia gravis.
- A family history of malignant hyperthermia.
- Glaucoma and ocular surgery (since suxamethonium raises intraocular pressure).
- Genetically determined disorders of plasma pseudocholinesterase. (If effective enzyme levels are suspected to be

### **Suxamethonium (continued)**

low, a test dose of 5–10 mg should be administered. Patients who develop respiratory depression requiring mechanically assisted ventilation should not receive suxamethonium again.)

- Hyperkalaemia resulting from severe burns, crush injuries or denervation, which may persist for up to 9 months after injury to the spinal cord (suxamethonium can further raise serum potassium concentrations and cause cardiac arrest).

### **Precautions**

Suxamethonium should be used, whenever possible, by an experienced specialist anaesthetist. Facilities for endotracheal intubation and mechanically assisted ventilation should be immediately to hand and ready for use.

Restoration of muscle tone should always be allowed to occur before a long-acting muscle relaxant (such as gallamine) is administered.

### **Use in pregnancy**

Suxamethonium should be used in pre-term pregnancy only when the need outweighs any possible risk to the fetus. It can be administered by intravenous infusion in obstetric practice for caesarean section since, unlike gallamine, it does not readily cross the placental barrier.

### **Adverse effects**

Skin rashes and anaphylactoid reactions, including bronchospasm and hypotension, have been reported.

Transient postoperative muscular pain is common, especially in ambulant outpatients.

Suxamethonium is claimed to have triggered the onset of malignant hyperthermic crisis in rare cases, in particular in patients receiving either ether or halothane. Cyanosis and cardiac dysrhythmias are succeeded by facial spasms, generalized rigidity, tachycardia, rapid breathing and profound hyperpyrexia. Anaesthesia should be discontinued as rapidly as possible. Treatment is directed to supportive measures including the administration of 100% oxygen, the intravenous infusion of large volumes of cooled fluids, control of cardiac dysrhythmias and maintaining urinary output, if necessary with diuretics. Dantrolene can reduce spasticity by a direct action on skeletal muscle and, if available, should be administered intravenously as soon as possible if malignant hyperthermia is suspected (1 mg/kg initially repeated as necessary to a total of 10 mg/kg).

### **Drug interactions**

The effect of suxamethonium may be appreciably prolonged by cholinesterase inhibitors including ecothiopate eye drops and certain other drugs used in the treatment of glaucoma. Exposure to certain organophosphate insecticides may also prolong the effect of suxamethonium.

Cardiac dysrhythmias have been precipitated by suxamethonium in patients receiving cardiac glycosides.

### **Overdosage**

Ventilation must be assisted for as long as muscular paralysis prevents the re-establishment of spontaneous respiration.

### **Storage**

Suxamethonium injection is usually stable for 12 months when stored at 2–8 °C and the powder is stable for at least 5 years when stored below 37 °C and protected from light and moisture.



# Neostigmine

Group: cholinesterase inhibitor

Injection: 0.5, 2.5 mg (metilsulfate)/ml in 1-ml ampoule

## General information

Neostigmine is a cholinesterase inhibitor that raises the concentration of acetylcholine at the myoneural junction and other cholinergic nerve endings. Administered parenterally, the effect of a single dose persists for 2–4 hours. It is destroyed by plasma esterases and excreted in the urine.

## Clinical information

### Uses

- To counteract the effect of non-depolarizing muscle relaxants administered during surgery.
- Treatment of postoperative non-obstructive urinary retention.

### Dosage

#### **Reversal of muscle relaxation**

Adults: 2.5 mg by i.v. injection. Supplements of 0.5 mg may be administered as necessary up to a maximum of 5 mg. Atropine sulfate (600–1200 micrograms i.v.) administered immediately beforehand prevents autonomic excitation.

Children: 40 micrograms/kg i.v. after atropine sulfate (20 micrograms/kg i.v.) administered as above.

Titration of the required dose using a peripheral-nerve stimulator is advisable in small children and severely ill patients.

The initial dose should be reduced in patients with bronchial asthma, postoperative atelectasis, bradycardia, atrioventricular block and other cardiac dysrhythmias, epilepsy and parkinsonism.

#### **Postoperative non-obstructive urinary retention**

Adults: 500 micrograms i.m. or subcuta-

neously initially, repeated every 3 hours for at least 15 hours once the patient has voided the bladder. If urine is not passed within 1 hour of the initial dose the patient's bladder should be catheterized. Cystoscopy is indicated if retention persists.

### Contraindications

- Hypersensitivity to neostigmine.
- Peritonitis.
- Mechanical obstruction of the intestinal or urinary tracts.

### Precautions

Equipment for resuscitation and mechanically assisted respiration should be immediately available.

Neostigmine should be given only after halothane or ether administration has been discontinued.

Adequate ventilation must be maintained since respiratory acidosis predisposes the patient to cardiac dysrhythmias.

### Use in pregnancy

Neostigmine should be administered only when the need outweighs any possible risk to the fetus. Premature labour has been induced following intravenous administration near term.

### Adverse effects

Neostigmine may produce signs of excessive cholinergic activity, including nausea and vomiting, increased salivation, diarrhoea, abdominal cramps, cardiac dysrhythmias, syncope and hypotension.

Rash, urticaria and anaphylaxis have been reported.

### Drug interactions

Neostigmine potentiates the effect of depolarizing muscle relaxants. It should

**Neostigmine (continued)**

therefore not be used in conjunction with suxamethonium.

**Overdosage**

Sudden death may occur as a result of cardiac arrest. More frequently a “cholinergic crisis” is induced, characterized by nausea, vomiting, diarrhoea, excess sali-

vation and rapidly progressive paralysis. Ventilation must be mechanically assisted until spontaneous breathing returns. Atropine (1 mg i.v.) serves to block the autonomic effects.

**Storage**

Neostigmine should be stored in ampoules protected from light, and should not be allowed to freeze.

# Blood substitutes

## Albumin, human

*Group: plasma-volume expander*

*Injectable solution: 250 mg (dried albumin)/ml (25%)*

### General information

Concentrated human albumin solution is prepared from pooled blood, plasma, serum or placental tissue derived from healthy human donors. It is subsequently heat-treated to inactivate bacterial and viral organisms. All supplies should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives<sup>1</sup> to prevent any risk of transmitting hepatitis or acquired immunodeficiency syndrome.

Because it contributes to the colloid oncotic pressure of plasma, human albumin is an important determinant of plasma volume.

It has an inherent advantage over synthetic plasma expanders but its expense precludes its routine use.

### Clinical information

#### Uses

Human albumin should be reserved for maintaining plasma volume in conditions where there is loss of plasma protein over periods of several days or weeks, as in ulcerative colitis, peritonitis or acute bowel obstruction.

It can also be used as an immediate short-term measure in severe haemorrhage pending the availability of blood.

#### Dosage and administration

##### *Pre- and perioperative management of colloid deficit*

Adults: 25–100 ml of albumin solution may be required daily for several days before and after surgery.

#### **Acute blood loss**

Adults: 500–1000 ml of albumin solution infused intravenously over 15 minutes may compensate for moderate blood loss. However, albumin has no oxygen-carrying capacity and fresh blood should be transfused when losses exceed 15% of the normal blood volume.

#### **Precautions**

The erythrocyte volume fraction should be monitored and maintained by transfusions of fresh blood, if necessary, throughout the period of treatment.

Clinically dehydrated patients always require fluids and electrolytes in addition to albumin infusions.

The infusion must be stopped immediately if signs of pulmonary oedema develop.

#### **Adverse effects**

Adverse reactions are infrequent. Fever, nausea, urticaria and hypotension rarely occur.

#### **Storage**

Stored below 25 °C the solution will last 3 years. Stored between 2 °C and 5 °C it will last for 5 years. Solutions that have been allowed to freeze should not be used if they are turbid or contain sediment.

<sup>1</sup> WHO Technical Report Series (WHO Expert Committee on Biological Standardization: thirty-ninth report), Annex 4 (in press).

# Dextran 70

*Group: plasma-volume expander*  
*Injectable solution: 60 mg/ml (6%)*

## General information

Dextrans are long-chain glucose polysaccharides of various relative molecular masses. Dextran 70 (relative molecular mass 70 000) is retained in the intravascular space where, like albumin, it contributes to the colloid oncotic pressure of plasma. Unlike albumin, dextran 70, when given in large amounts, prevents platelet aggregation and facilitates fibrinolysis.

Commercially available solutions of dextran 70 are made up in either glucose 50 mg/ml or saline 9 mg/ml.

## Clinical information

### Uses

- Restoration of circulatory volume during surgery, in hypovolaemic shock due to trauma and dehydration, or following haemorrhage when:
  - blood loss is estimated to be less than 15%, or
  - full cross-matching of blood for transfusion has not been completed, or
  - blood supplies for transfusion have not been adequately screened for viable pathogens.
- Prevention of postoperative deep-vein thrombosis.

### Dosage and administration

#### **Acute blood loss**

Adults: 500–1000 ml of dextran 70 may be infused intravenously over 15 minutes to compensate for moderate blood loss.

#### **Prevention of thromboembolic phenomena.**

Adults: 500 ml preoperatively, repeated daily for 2–3 days postoperatively.

### Contraindications

- Known hypersensitivity to dextran 70.
- Thrombocytopenia (since dextran 70 interferes with platelet function).

### Precautions

Patients should be closely observed during the first minutes of administration as severe hypersensitivity reactions may occur. Equipment for resuscitation should be immediately available.

Blood samples for cross-matching should routinely be taken before administration of dextran 70 since it promotes rouleaux formation and thereby interferes with the cross-matching process.

The infusion must be stopped immediately if signs of pulmonary oedema develop.

### Adverse effects

When given in large amounts (> 15 ml/kg) dextran 70 may interfere with platelet function and produce a transient increase in bleeding time.

Urticaria, nasal congestion, wheezing, tightness of the chest and mild hypotension are reported and severe anaphylactoid reactions with circulatory collapse have also occasionally occurred.

### Storage

Dextran 70 solution should be stored at a constant temperature, preferably 25 °C. It should not be administered unless clear. Precipitates formed during storage may be dissolved by heating in a water bath at 100 °C.

# Solutions for correcting water and electrolyte imbalance

## Compound solution of sodium lactate

*Group: intravenous infusion fluid  
Injectable isotonic solution*

### General information

Two solutions are widely available that approximate the composition of extracellular fluid (see table).

Component	Concentration (mmol/litre)	
	I	II
Sodium	131.41	130.00
Potassium	5.37	4.02
Calcium	1.84	1.36
Lactate	28.70	27.60
Chloride	111.70	109.10

### Clinical information

#### Uses

- As an alternative to isotonic saline in the preoperative correction of severe fluid and sodium depletion.
- Replacement of extracellular fluid during surgery.
- Initial restoration of circulatory volume in hypovolaemic shock.

#### Dosage and administration

Individual fluid requirements must always be determined on the basis of clinical and, whenever possible, electrolyte monitoring. As a general guide in adults:

Preoperative fluid replacement: 500 ml at 50 ml/minute as an alternative to isotonic saline.

Fluid replacement during surgery: 5 ml/minute as an alternative to isotonic saline.

Acute hypovolaemic shock: as an alternative to isotonic saline until vasoconstriction disappears and systolic blood pressure reaches 100 mmHg (13.3 kPa).

### Contraindications

- Metabolic alkalosis.
- Isotonic sodium chloride solution should be used in preference to compound solution of sodium lactate in patients with:
- hypochloraemic alkalosis due to pyloric stenosis
  - respiratory or metabolic alkalosis
  - diabetes or severe liver impairment.

### Precautions

Solutions should not be used unless they are absolutely clear, and must not be administered through apparatus used for blood transfusion because of the risk of coagulation.

Careful monitoring is required throughout the infusion since intravascular overload can occur, particularly in patients with cardiac insufficiency and whenever large volumes are administered rapidly. In this event the infusion must be slowed or suspended and, if necessary, a rapidly acting diuretic administered (for example furosemide 40 mg i.v.).

### Adverse effects

Unduly rapid replacement may lead to pulmonary oedema.

### Overdosage

Excessive infusion may result in sodium and water retention. Symptoms of hypernatraemia include restlessness, weakness, thirst, dry swollen tongue, flushing of the skin, pyrexia and tachycardia. Symptoms of water retention range from mild lethargy and disorientation to delirium, coma and convulsions.

### Storage

Compound solution of sodium lactate should be stored in sealed containers and should not be allowed to freeze.

## Glucose

*Group: intravenous infusion fluid*

*Injectable isotonic solution: 50 mg/ml (5%)*

### Clinical information

#### Uses

- Postoperative fluid replacement in patients with no sodium deficit, until adequate fluid can be taken by mouth.
- Intravenous rehydration of patients suffering from water depletion for whom oral rehydration salts are not suitable.

#### Dosage and administration

Individual requirements should always be determined on the basis of clinical and, whenever possible, electrolyte monitoring.

#### Precautions

Patients must be monitored for signs of intravascular overload. In this event infusion must be slowed or suspended and, if necessary, a rapidly acting diuretic

administered (for example furosemide 40 mg i.v.).

Patients with overt or known diabetes additionally require insulin and close biochemical monitoring.

Prolonged parenteral infusion of glucose solutions may inhibit secretion of insulin. To minimize the risk of hyperglycaemia it may be necessary to add insulin to the infusion.

#### Adverse effects

Infusion of large volumes of glucose solution may cause hyponatraemia.

Unduly rapid replacement may lead to pulmonary oedema.

#### Storage

Glucose solution should be kept in sealed containers.

## Glucose with sodium chloride

*Group: intravenous infusion fluid*

*Injectable isotonic solution: 40 mg/ml (4%) glucose, 1.8 mg/ml (0.18%) sodium chloride; Na<sup>+</sup> 30 mmol/litre, Cl<sup>-</sup> 30 mmol/litre*

### General information

This isotonic preparation has a relatively low sodium content.

### Clinical information

#### Uses

- Postoperative fluid and electrolyte replacement, until adequate fluid can be taken by mouth.
- Replacement of fluid and electrolyte loss during surgery, particularly in children.

#### Dosage and administration

Individual requirements should always be determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Adults and children: during surgery the infusion rate is typically 5 ml/kg per hour.

#### Precautions

Patients must be carefully monitored throughout the infusion for signs of intravascular overload. Should this occur, the infusion must be slowed or suspended and, if necessary, a rapidly acting diuretic administered (for example furosemide 40 mg i.v.).

### Adverse effects

Unduly rapid replacement may lead to pulmonary oedema.

### Storage

Glucose with sodium chloride solution should be stored in sealed containers.

## Sodium chloride

*Group: intravenous infusion fluid*

*Injectable isotonic solution: 9 mg/ml (0.9%); Na<sup>+</sup> 154 mmol/litre, Cl<sup>-</sup> 154 mmol/litre*

### General information

Sodium is the major extracellular cation. Maintenance of physiological concentrations is vital to effective regulation of the osmotic pressure of blood and tissues.

### Clinical information

#### Uses

- Preoperative correction of fluid and sodium depletion.
- Replacement of extracellular fluid during surgery.
- Initial restoration of circulatory volume in hypovolaemic shock.

#### Dosage

Individual fluid requirements must be determined on the basis of clinical and, whenever possible, electrolyte monitoring. As a general guide in adults:

Preoperative fluid replacement: 50 ml/minute as an alternative to compound solution of sodium lactate.

Fluid replacement during surgery: 5 ml/minute as an alternative to compound solution of sodium lactate.

Acute hypovolaemic shock: as an alternative to compound solution of sodium lactate until vasoconstriction disappears and systolic blood pressure reaches 100 mmHg (13.3 kPa).

#### Precautions

Patients must be carefully monitored throughout the infusion for signs of intravascular overload, particularly when large volumes are administered rapidly. Should this occur, the infusion must be slowed or suspended and, if necessary, a rapidly acting diuretic administered (for example furosemide 40 mg i.v.).

#### Adverse reactions

Unduly rapid replacement can lead to pulmonary oedema.

#### Overdosage

Excessive infusion may result in sodium retention. Symptoms of hypernatraemia include restlessness, weakness, thirst, dry swollen tongue, flushing of the skin, pyrexia and tachycardia.

#### Storage

Sodium chloride solution should be stored in sealed containers.

## Potassium chloride

*Group: electrolyte-replacement solution*

*Injectable solution: 1.5 mmol/ml in 20-ml ampoule*

### General information

Potassium is the major intracellular ion. Maintenance of physiological concentra-

tions is vital for many essential intracellular metabolic processes.

**Potassium chloride (continued)**

## Clinical information

### Uses

Prevention and treatment of potassium depletion during prolonged parenteral fluid therapy.

### Dosage and administration

Individual requirements must be determined by clinical assessment and, whenever possible, by estimating plasma potassium concentrations, which should be maintained between 3.5 and 5 mmol/litre.

Potassium chloride solution (1.5 mmol/ml) must always be diluted before use. The normal daily requirement of 3 g (40 mmol) of potassium chloride should be thoroughly mixed in 1 litre of infusion fluid. The rate of infusion should not exceed 10 mmol/hour except in cases of severe hypokalaemia when the rate of administration may be raised to as much as 40 mmol/hour.

Electrocardiographic and electrolyte monitoring is essential, particularly at high infusion rates.

### Contraindications

- Severe renal impairment.
- Untreated Addison's disease.

Potassium should never be administered when the plasma concentration exceeds 5 mmol/litre. Since release of intracellular potassium from traumatized tissues results in hyperkalaemia, potassium chloride solution should not be given to patients with severe burns or crush injuries, or within 24 hours of major surgery.

### Precautions

An adequate urine flow must be established before potassium chloride solution is infused. Close clinical observation for

signs of hyperkalaemia and, whenever possible, biochemical monitoring of plasma potassium concentrations should be continued throughout therapy.

Patients additionally receiving digitalis glycosides require particularly careful clinical and biochemical monitoring since they are at particular risk of ventricular dysrhythmias.

### Overdosage

Hyperkalaemia can result in sudden death from cardiac dysrhythmia. Warning signs and symptoms include distal paraesthesiae, apathy, muscular weakness, listlessness, mental confusion, cold skin and grey pallor. Cardiovascular collapse secondary to cardiac dysrhythmia or cardiac arrest is a terminal event.

### Treatment of hyperkalaemia

Infusion of potassium chloride solution should be suspended immediately when there is clinical or laboratory evidence of hyperkalaemia. Glucose (50 ml of a 500 mg/ml solution) together with 5 International Units of soluble insulin should be administered intravenously to facilitate intracellular uptake of potassium. If metabolic acidosis is present, an infusion of 50 ml of 84 mg/ml sodium bicarbonate should then be given at 1 ml/minute, whenever possible under continuous cardiac monitoring. Should a potentially serious dysrhythmia develop, calcium gluconate (10 ml of a 100 mg/ml solution) should be given intravenously. This dose may be repeated at 2-minute intervals for as long as electrocardiographic abnormalities persist.

Rapid reduction of serum potassium concentrations in "digitalized" patients may induce digitalis toxicity.

### Storage

Potassium chloride solution should be stored in ampoules.



# ***Antacid for use in obstetric practice***

## **Sodium citrate**

*Group: antacid*

*Oral solution: 88.2 mg/ml (8.82%, 0.3 mmol/ml)*

### **General information**

Sodium citrate is an alkalinizing agent which depends for its activity upon conversion to bicarbonate.

### **Clinical information**

#### **Uses**

To protect against the risk of aspiration of acidic gastric contents in women undergoing operative obstetric procedures.

#### **Dosage and administration**

A dose of 10–20 ml of the solution should be given immediately before the procedure.

#### **Contraindications**

- Severe renal impairment.

#### **Precautions**

Sodium citrate solution should be used with particular care in patients with hypertension or toxæmia in pregnancy.

#### **Adverse effects**

It is generally well tolerated. Metabolic alkalosis may occur in patients with renal dysfunction.

#### **Storage**

The solution should be stored in tightly closed containers.

