

ISDB WHO Section Review
Drugs used in anaesthesia (Sections 1.1 - 1.4)

by

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Part 1: Summary of Recommendations

Thiopental (subsection 1.1.1)	<p>STATUS: retain</p> <p>PRODUCT: Powder in vials containing 250 mg, 500 mg, 1 g, 2.5 g or 5 g of thiopental sodium</p> <p>INDICATIONS: Induction of anaesthesia prior to administration of inhalational anaesthetic; anaesthesia of short duration</p>
Ketamine (subsection 1.1.1)	<p>STATUS: retain.</p> <p>PRODUCT: ketamine (as hydrochloride) 50 mg/ml, 10ml vial</p> <p>INDICATIONS: Induction and maintenance of anaesthesia, analgesia for painful procedures of short duration</p> <p>SPECIAL COMMENT The abuse potential needs to be mentioned in the WHO Formulary, and its use as an analgesic needs to be highlighted.</p>
Ether (anaesthetic) (subsection 1.1.2)	<p>STATUS: retain</p> <p>PRODUCT: volatile liquid</p> <p>INDICATIONS: induction and maintenance of anaesthesia</p>
Halothane (subsection 1.1.2)	<p>STATUS: retain</p> <p>PRODUCT: volatile liquid</p> <p>INDICATIONS: induction and maintenance of anaesthesia</p>
Nitrous oxide (subsection 1.1.3)	<p>STATUS: retain</p> <p>PRODUCT: inhalation gas</p> <p>INDICATIONS: maintenance of anaesthesia in combination with other anaesthetic agents and muscle relaxants; analgesia for obstetric practice, for emergency management of injuries, during postoperative physiotherapy and for refractory pain in terminal illness.</p>

<p>Oxygen (subsection 1.1.3)</p>	<p>STATUS: retain</p> <p>PRODUCT: inhalation gas</p> <p>INDICATIONS: to maintain an adequate oxygen tension in inhalational anaesthesia.</p> <p>SPECIAL COMMENT: The uses and dosage sections in the WHO Formulary should be expanded.</p>
<p>Bupivacaine hydrochloride (subsection 1.2)</p>	<p>STATUS: retain</p> <p>PRODUCT: solution for injection, bupivacaine hydrochloride 2.5mg/ml (0.25%), 10-ml ampoule; 5mg/ml (0.5%), 10-ml ampoule; 5mg/ml (0.5%) with glucose 75mg/ml (7.5%), 4-ml ampoule</p> <p>INDICATIONS: infiltration anaesthesia; peripheral and sympathetic nerve block; spinal anaesthesia; postoperative pain relief.</p> <p>SPECIAL COMMENT: The dosage section in the WHO Formulary should be expanded.</p>
<p>Lidocaine hydrochloride (subsection 1.2)</p>	<p>STATUS: retain</p> <p>PRODUCT: lidocaine (hydrochloride) solution for injection 5mg/ml (0.5%), 20-ml ampoule; 10mg/ml (1%), 20-ml ampoule; 50mg/ml (5%), 2-ml ampoule to be mixed with glucose 75mg (7.5%).</p> <p>lidocaine (hydrochloride) solution for injection with epinephrine, lidocaine hydrochloride 10mg/ml (1%) with epinephrine 5 micrograms/ml (1 in 200,000), 20 ml ampoule.</p> <p>lidocaine (hydrochloride) solution for injection with epinephrine (dental use), lidocaine hydrochloride 20mg/ml (2%) with epinephrine 12.5 micrograms/ml (1 in 80,000), 2.2 ml dental cartridge.</p> <p>Topical gel or solution, lidocaine hydrochloride 20-40 mg/ml (2-4%)</p> <p>INDICATIONS: surface anaesthesia for mucous membranes; infiltration anaesthetic, peripheral and sympathetic nerve block; dental anaesthesia, spinal anaesthesia; intravenous regional anaesthesia; arrhythmia (not assessed here).</p> <p>SPECIAL COMMENT The dosage section in the WHO Formulary should be expanded.</p>

Ephedrine hydrochloride (subsection 1.2)	<p>STATUS: retain</p> <p>PRODUCT: ephedrine hydrochloride solution for injection 30mg/ml, 1-ml ampoule</p> <p>INDICATIONS: prevention of hypotension during delivery under spinal or epidural anaesthesia.</p>
Epinephrine (adrenaline) (subsection 1.2)	<p>STATUS: retain</p> <p>PRODUCT: solution for injection</p> <p>INDICATIONS: vasoconstrictor to retard systemic absorption of infiltrated local anaesthetics</p>
Atropine sulfate (subsection 1.3)	<p>STATUS: retain</p> <p>PRODUCT: atropine sulfate 600 microgrames solution for injection, 1-ml ampoule</p> <p>INDICATIONS: to inhibit salivary secretions; to inhibit arrhythmias resulting from excessive vagal stimulation; to block the parasympathomimetic effects of anticholinesterases such as neostigmine; organophosphate poisoning; antispasmodic (not discussed here); mydriasis and cycloplegia (not discussed here)</p>
Diazepam (subsection 1.3)	<p>STATUS: retain</p> <p>PRODUCT: tablets 2mg, 5mg Injection (solution for injection) diazepam 5mg/ml, 2-ml ampoule</p> <p>INDICATIONS: representative benzodiazepine for premedication before major or minor surgery; sedation with amnesia for endoscopic procedures and surgery under local anaesthesia; epilepsy; anxiety disorders</p>
Promethazine hydrochloride (subsection 1.3)	<p>STATUS: retain</p> <p>PRODUCT: tablets - promethazine hydrochloride 10mg, 25 mg Elixir (oral solution) - promethazine hydrochloride 5mg/ml Injection (solution for injection) - promethazine hydrochloride 25mg/ml, 2-ml ampoule</p> <p>INDICATIONS: premedication prior to surgery; antiemetic.</p>
Alcuronium chloride (subsection 1.4)	<p>STATUS: delete</p> <p>PRODUCT: injection (solution for injection) alcuronium chloride 5mg/ml, 2-ml ampoule</p>

	<p>INDICATIONS: as representative non-depolarising muscle relaxant for muscle relaxation during surgery.</p>
<p>Vecuronium bromide (subsection 1.4)</p>	<p>STATUS: retain</p> <p>PRODUCT: injection (powder for solution for injection), vecuronium bromide 10-mg vial.</p> <p>INDICATIONS: as complementary non-depolarising muscle relaxant for muscle relaxation during surgery</p> <p>SPECIAL COMMENT: to be listed as the representative non-depolarising muscle relaxant.</p>
<p>Atracurium besilate (add to subsection 1.4)</p>	<p>STATUS: add (as a complementary agent)</p> <p>PRODUCT: to be determined</p> <p>INDICATIONS: non-depolarising peripheral neuromuscular blocking agent for muscle relaxation during surgery, facilitating endotracheal intubation and, in intensive care units, facilitating controlled pulmonary ventilation.</p>
<p>Suxamethonium chloride (subsection 1.4)</p>	<p>STATUS: retain</p> <p>PRODUCT: injection (solution for injection), suxamethonium chloride 50mg/ml, 2-ml ampoule.</p> <p>(powder for solution for injection), suxamethonium chloride.</p> <p>INDICATIONS: brief muscular paralysis during endotracheal intubation, endoscopy, and electroconvulsive therapy.</p>
<p>Neostigmine metilsulfate (subsection 1.4)</p>	<p>STATUS: retain</p> <p>PRODUCT: injection (solution for injection) neostigmine metilsulfate 500 micrograms/ml, 1-ml ampoule; 2.5mg/ml, 1-ml ampoule</p> <p>INDICATIONS: counteract the effect of non-depolarising muscle relaxants administered during surgery; postoperative non-obstructive urinary retention; myasthenia gravis.</p>

2.1 Thiopental sodium (subsection 1.1.1)

Introduction

Thiopental is a rapid and ultra-short acting barbiturate widely used for the induction of general anaesthesia by the intravenous route. It is listed as a representative intravenous general anaesthetic in the 2004 WHO Model Formulary.¹ Ketamine is the other listed agent in this class.

In addition to induction of anaesthesia prior to administration of inhalational general anaesthetics, thiopental can be used for maintenance of anaesthesia of short duration. Thiopental is also used in the emergency management of refractory status epilepticus, when first line agents have failed, and as a pharmacological option to reduce intracranial pressure in neurosurgical cases.

The product^{2,3}

Thiopental is available in the form of a powder in vials containing 250 mg, 500 mg, 1 g, 2.5 g or 5 g of thiopental sodium. It is mixed with 6% anhydrous sodium carbonate to increase its solubility in water.

The powder is reconstituted with an appropriate quantity of water for injection (e.g. 20 mL to 0.5 g, 40 mL to 1 g or 100 mL to 2.5 g) to the usual concentration of 2.5%. A 5% solution has been used but is not recommended for reasons stated below. Sodium chloride 0.9% and dextrose 5% are the other compatible diluents, although solutions in dextrose are relatively unstable.

Thiopental sodium injections are strongly alkaline and incompatible with many drugs, including suxamethonium, other neuromuscular blockers, morphine, pentazocine, glycopyrrolate and many antibiotics. Solutions should be protected from light and used up within 24 hours unless refrigerated at 2 - 8 °C. Those showing cloudiness or precipitation should not be used. It is best to use freshly prepared solutions.

In some countries, thiopental sodium is available as a rectal preparation.

Dosage^{2,3}

Induction of general anaesthesia, by intravenous injection (directly into a vein or into a fast-running infusion) over 10 - 15 seconds, ADULT 100 - 150 mg (maximum 5 mg/kg), followed by a further quantity, if necessary according to response, after 30 - 60 seconds; CHILD 2 - 7 mg/kg.

To exclude inadvertent intra-arterial injection, it is preferable to avoid the medial side of the antecubital fossa, in case the pulsation of an aberrant ulnar artery is not detected or is obliterated by a tight tourniquet. It must be noted that the dose and speed of injection is tailored to the age and condition of the patient, the premedication used and pre-treatment with opioids immediately prior to induction. In obese patients, dose should be calculated based on lean body mass. It is usual

practice, in unfit patients, to inject a small initial test dose (e.g. 1 - 2 mL) and then proceed with the full injection if no problems occur. Smooth induction can be facilitated by a small dose of a short-acting opioid (e.g. fentanyl 1 - 2 microgram/kg intravenously) given before thiopental. In patients aged over 60 years, dose requirements decline markedly and 2 - 2.5 mg/kg may suffice in the elderly. Dose requirements may be increased in subjects with a history of dependence on opioids, sedative-hypnotics or alcohol. No special problems are reported during pregnancy or breast-feeding.

To maintain anaesthesia, intermittent doses may be given but care has to be taken to avoid respiratory depression. For short operations, thiopental may be used as the sole agent, but for longer procedures it should be supplemented by oxygen-nitrous oxide or a parenteral opioid or both.

In status epilepticus, by intravenous injection, loading dose of 5 mg/kg, followed after 30 minutes by intravenous infusion at 1 - 3 mg/kg or adjusted to maintain a plasma level of 60 - 100 microgram/mL. Administration should continue for at least 12 hours after seizure activity has ceased and then slowly discontinued.

Adverse drug reactions^{3,4}

- Hypotension: Risk is increased if large doses are used or the anaesthetic is administered to shocked, hypovolaemic or previously hypertensive patients. Lightening of anaesthesia does not necessarily reverse the hypotension, and it may continue into the postoperative period. If accompanied by respiratory depression, this will lead to hypoxia. Thiopental should not be administered in the sitting position.
- Apnoea and respiratory depression: Risk is increased if large doses or heavy opioid premedication is used
- Heightening of laryngeal reflexes, particularly in light anaesthesia, and laryngospasm induced by minor stimuli. Bronchospasm is rare but may occur in asthmatic subjects.
- Thrombophlebitis: This is uncommon if the 2.5% solution is used.
- Tissue necrosis following extravasation: Median nerve damage can occur in the antecubital fossa, which is another reason why this site is not preferred.
- Intra-arterial injection: Inadvertent intra-arterial injection has occurred in the brachial artery, aberrant ulnar artery in the antecubital fossa and also aberrant arteries at the wrist. Following intra-arterial injection, symptoms include intense burning pain, blanching of the forearm or hand, and the development of blisters distally. Depending on the intensity of vasospasm and the extent of the thrombosis, and the anatomical distribution of the affected vascular bed, sequelae can vary from transient hyperaesthesia to loss of digits. The risk is greater with the 5% solution.
- Inhibition of platelet function: The clinical significance of this is unknown, though it has been suggested that anaesthetic-induced platelet inhibition may lead to higher transfusion rates and prolonged operation times.^{5,6}
- Allergic reactions: Severe anaphylactic or anaphylactoid reactions have been reported but are rare.

Contraindications^{3,4}

- Anticipated difficulty in accessing and maintaining an open airway or lack of resuscitative facilities.

- Porphyria – barbiturates may precipitate lower motor neurone paralysis or severe cardiovascular collapse.
- Known hypersensitivity to barbiturates.
- Marked hypovolaemia, including acute blood loss.
- Cardiovascular disease e.g. myocardial disease, valvular stenosis, constrictive pericarditis.
- Asthma and obstructive respiratory disease.
- Severe hepatic disease.
- Renal failure.
- Neuromuscular disorders e.g. myasthenia gravis, myotonic dystrophy.
- Reduced metabolic rate e.g. myxoedema, adrenocortical insufficiency.
- Obstetrics – Excessive doses may result in cardiovascular or respiratory depression of the neonate, especially if the interval between induction and delivery is short.
- Outpatient anaesthesia when there is lack of facilities for recovery, lack of attendants to take home or the subject needs to be ambulant on the same day.⁷

Apart from the first three, all other contraindications are relative and thiopental may be used with care, at reduced doses if necessary or given more slowly than usual. The experience of the anaesthetist and availability of resuscitation facilities also count.

Evidence of value

Thiopental is a time-tested intravenous induction agent in general anaesthesia and therefore recent controlled studies on its effectiveness are scarcely reported in literature. However, comparative studies with new intravenous agents are being reported.

Propofol is one such new agent that offers the advantages of rapid induction and rapid recovery. Initial studies have suggested that propofol may be associated with a lower incidence of post-operative morbidity than thiopental.⁸ In day care surgery, prompt recovery from anaesthesia and minimal postoperative morbidity, helps ease the issues surrounding a high case burden. Propofol may be superior to thiopental in this respect,^{7,8} specially in ocular surgery.¹⁰ In elderly patients, propofol induction may produce more stable haemodynamics after intubation than thiopental induction.¹¹ Further, propofol - nitrous oxide anaesthesia may be associated with significantly less post-operative nausea and vomiting than thiopental - nitrous oxide.¹²

However, there are also various situations where propofol induction has not been found to offer significant advantage over thiopental.^{13,14} Propofol has been advocated for sedation in intensive care because of superior recovery characteristics. However, at least one comparative study has reported that propofol may offer no clinical benefit in short-term sedation, over opioid-thiopental combination, following cardiac surgery.¹⁵ Despite more stable haemodynamics, when compared to thiopental, propofol may not facilitate improved cognitive recovery in geriatric patients undergoing prolonged surgery.¹⁶ Clonidine premedication provides better haemodynamics with thiopental than with propofol.¹⁷ Economic advantage probably still rests with thiopental.¹⁸

Intravenous propofol injection is usually painful and a small dose of thiopental, before or with propofol, may reduce the pain considerably.^{19,20}

Thiopental has been found to facilitate maintenance of haemodynamic stability during semi-elective nasotracheal intubation in neonates than in un-premedicated babies.²¹ Rapid intravenous induction of general anaesthesia is indicated in infants at risk of vomiting or regurgitation to reduce the risk of aspiration of gastric contents. Thiopental can be used safely in this situation and compares well with propofol in haemodynamic stability.²²

The combination of a short acting opioid and thiopental is used routinely in rapid sequence induction-intubation with muscle relaxants.²³ It has also been used for intubation without muscle relaxants.²⁴

Large controlled studies on use of thiopental in refractory status epilepticus have not been reported recently. However, a meta-analysis has reported thiopental to be better than diazepam.²⁵ Thiopental has been used in the anaesthetic management of electroconvulsive therapy and is comparable to sevoflurane in this regard.²⁶

Thiopental can be used with minimal risk in patients with intracranial hypertension.²⁷ It produces cerebral metabolic depression and cerebral vasoconstriction. By reducing the metabolic rate it may offer cerebral neuroprotection in critical situations. However, this aspect of use of thiopental is still experimental.²⁸

Recommendation

Thiopental remains one of the most widely used intravenous anaesthetics offering the advantages of efficacy, convenience of use and economy. It is safe if recommendations are followed. Pharmacokinetic aspects of the drug have been studied intensively to determine which parameters (in patient characteristics, diseases and administration modalities) influence effective dose and concentrations in individual patients.²⁹ Thiopental should be retained in the WHO Model List of Essential Medicines.

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2.2 Ketamine (subsection 1.1.1)

Introduction

Ketamine is an intravenous general anaesthetic listed in the 2004 WHO Model Formulary.¹ Ketamine anaesthesia persists for up to 15 minutes following a single intravenous injection and is characterised by profound analgesia. It can be used, intravenously or intramuscularly, as an inducing agent or as the sole anaesthetic for minor surgical interventions not requiring muscle relaxation. In sub-anaesthetic concentrations, ketamine can provide analgesia for painful procedures of short duration, such as burn dressing, cardiac catheterization, bone marrow sampling and brief orthopaedic procedures.

Thiopental sodium is the only other intravenous general anaesthetic currently listed in the WHO Model Formulary.

The product^{2,3}

Ketamine, as ketamine hydrochloride, is supplied as a colourless solution for injection, pH 3.5 - 5.5, in concentrations of 1, 5 and 10%. It contains preservatives such as benzethonium chloride. The injection is intended for intravenous or intramuscular use, or, after suitable dilution (generally in 5% dextrose or 0.9% sodium chloride), for intravenous infusion. The product needs to be protected from light and not frozen. Once made up, infusion solutions should be used up within 24 hours.

Dosage¹

Ketamine should only be administered by anaesthetists or personnel trained in its use. Resuscitative facilities must be at hand.

Induction, by intramuscular injection, ADULT and CHILD 6 - 8 mg/kg; NEONATE 12.5 mg/kg.

Induction, by intravenous injection over at least 1 minute, ADULT and CHILD 1- 4.5 mg/kg.

Induction, by intravenous infusion of a solution containing 1 mg/mL, ADULT and CHILD total induction dose 0.5 - 2 mg/kg; maintenance (by microdrip infusion), 10 - 45 micrograms/kg/minute, rate adjusted according to response.

Use as sole anaesthetic agent, ADULT and CHILD, half the intramuscular or intravenous inducing dose is repeated when there are signs of purposeful response to painful stimuli.

Analgesia, by intramuscular injection, ADULT and CHILD 1.5 - 4 mg/kg initially.

Ketamine has been administered by epidural and caudal routes. Epidural administration of low doses of ketamine may provide more effective relief from postoperative pain than does intravenous administration. The sustained higher plasma concentration attained might account for the difference in analgesic effects.⁴ The suggested dose for epidural or caudal route (as an adjuvant for local anaesthetic

agents to intensify and to prolong the duration of postoperative analgesia) is 0.5 mg/kg.^{5,6}

It has also been reported that oral ketamine 8 mg/kg is an effective premedication in children undergoing elective surgery⁷ and in dental practice.⁸ The use of concurrent sedatives, like midazolam, may allow lower doses of ketamine to be used as effective oral premedicant.⁹ However, some studies report that ketamine may not be an effective oral premedicant in uncooperative children.¹⁰

Adverse drug reactions

- Cardiovascular stimulant effect: This is in contrast to most other intravenous general anaesthetics that depress rather than stimulate the cardiovascular system. Variable rise in blood pressure and tachycardia occurs. The rise in systolic arterial pressure can be dangerous in cardiac patients. Concurrent use of pancuronium as muscle relaxant increases risk. The pituitary-adrenal axis is stimulated with release of adrenal catecholamines. There is also rise in plasma norepinephrine levels. Arrhythmias, bradycardia and hypotension have been reported but are uncommon.
- Emergence reactions: Hallucinations, vivid dreams, out-of-body floating sensations, confusion and occasionally, frank delirium, may occur during emergence from ketamine anaesthesia. These psychotomimetic reactions can be distressing for the patient and disturbing for surrounding personnel. Some patients become aggressive. Although they seldom last for more than a few hours, there may be recurrences any time within 24 hours. Age (over 16 years), gender (being female), larger doses, rapid administration, and a history of personality problems increases risk. Verbal, tactile and visual stimuli should be kept at a minimum during recovery. Diazepam in small doses, at the start or end of the procedure, can reduce these reactions.
- Increased salivary secretion: An anticholinergic is usually administered before ketamine is given.
- Raised intracranial pressure: In subjects with already raised intracranial tension, this carries the risk of cloning.
- Raised intraocular pressure: This is undesirable in glaucoma and can be dangerous in presence of penetrating eye wounds or ocular surgery requiring opening of the globe.
- The dependence, and abuse, potential of ketamine is causing increasing concern.^{11,12} Abuse can induce a state of helplessness in the user leaving them open to assault. However, there is no evidence of a physical withdrawal syndrome.¹³ Abuse occurs by oral, parenteral and intranasal routes. In France, ketamine and its salts are subject to control under national legislation on narcotics and psychotropic substances.¹⁴

Contraindications

- Uncontrolled hypertension or thyrotoxicosis.
- Angina or recent myocardial infarction.
- History of cerebrovascular accidents.
- Head injury or raised intracranial tension.
- Glaucoma, penetrating eye injuries, open ocular surgery.
- History of psychiatric disorders, particularly hallucinations.
- History of alcohol abuse.
- Operations on the pharynx, larynx and tracheobronchial tree.

- Eclampsia or pre-eclampsia.

Evidence of value

Unlike most general anaesthetics, inhalational or intravenous ketamine does not cause a dose-related depression of the cardiovascular and respiratory systems. It is thus a very safe agent in this respect, even in critically ill patients. In children the incidence of emergence reactions is low and therefore it is valuable in paediatric practice. It has been used extensively in neonates, both to induce anaesthesia and also to maintain it as the sole agent. There are no special contraindications to its use in the elderly, nor is it contraindicated in patients with renal or hepatic impairments, unless these are very severe.

Ketamine can produce the unique anaesthetic state of 'dissociative anaesthesia' in which there is analgesia and amnesia without marked hypnosis or muscle relaxation. Following a single intravenous dose, the onset of anaesthetic state is usually within 1 minute, lasts for 8 - 10 minutes, with analgesia persisting for 30 - 40 minutes. An intramuscular dose takes up to 5 minutes for full effect and the anaesthesia duration is 10 - 20 minutes. The emergence reactions constitute the principal limitation of ketamine anaesthesia. Incidence of these is less in children, making ketamine valuable in paediatric anaesthesia.¹⁵ Ketamine and lidocaine spray has been used to facilitate laryngeal mask airway insertion in children. It can be an alternative to propofol in this regard, avoiding the apnoea and airway obstruction possible with propofol.¹⁶

Ketamine, in combination with midazolam, has been used for total intravenous anaesthesia in prolonged surgeries such as abdominal operations. It may provide better surgical conditions and better recovery than halothane-nitrous oxide-oxygen anaesthesia.¹⁷

Ketamine reduces airway resistance and may improve lung compliance. It is thus an agent of choice for induction in asthmatic patients and is also effective in treating bronchospasm during anaesthesia. Ketamine infusion has helped to avoid mechanical ventilation. However, as reflexes are maintained, ketamine cannot be used as sole agent in operations on the pharynx, larynx and tracheobronchial tree. A muscle relaxant should be used.

Ketamine has been used safely in patients with a history of malignant hyperthermia and in those with acute intermittent porphyria.

Ketamine has been used for intravenous regional anaesthesia but consciousness may be lost following release of tourniquet. This limits its use in this technique. However, adding ketamine 0.1 mg/kg to lidocaine for intravenous regional anaesthesia delays the onset of severe tourniquet pain and decreases the associated need for analgesia. Ketamine may have a more potent effect than clonidine in this regard.¹⁸

Although ketamine is contraindicated in patients with raised intracranial pressure, it has been used safely in combination with midazolam, as sedative, maintaining intracranial pressure and cerebral perfusion in patients with severe head injury placed under controlled mechanical ventilation.¹⁹

The role of ketamine as an analgesic rather than anaesthetic is also being explored. It has been used satisfactorily as low-dose analgesic premedicant for laparoscopic

gynaecological operations,²⁰ intra-articular analgesic in arthroscopic knee surgery,²¹ low-dose intravenous premedicant for reduction of pain associated with propofol injection²² and reduction of withdrawal movements seen with the muscle relaxant rocuronium.²³

Combination of ketamine and midazolam can be very useful and safe for sedation and pain relief in intensive care patients, especially during ventilator management. Ketamine may be the drug of choice for painful procedures in intensive care units.²⁴

Low-dose ketamine is a safe and useful adjuvant to standard practice opioid-analgesia.²⁵ At sub-anaesthetic doses most of the adverse drug reactions, including psychotomimetic effects, are unlikely. In patients with pain due to cancer, however, the available evidence is not sufficient to conclude that ketamine improves the effectiveness of opioid treatment and further trials are needed.^{26,27} Ketamine is being explored by various other routes for chronic pain of other types such as fibromyalgia, phantom limb pain, postherpetic neuralgia, acute on chronic neuropathic pain and ischemic pain. In most of these situations the evidence is not conclusive and further controlled studies are necessary.^{28,29}

Recommendation

The unique pharmacological profile of ketamine makes it a safe and effective intravenous anaesthetic and postoperative analgesic in a wide variety of surgical situations. It is particularly important in the practice of paediatric anaesthesia. Ketamine should be retained in the WHO Model Essential List of Medicines. The abuse potential needs to be mentioned in the WHO Formulary, and its use as an analgesic needs to be highlighted.

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2.3 Ether (subsection 1.1.2) See single drug review

2.4 Halothane (subsection 1.1.2)

Introduction

Halothane is one of the two volatile inhalational general anaesthetic agents listed in the 2004 WHO Model Formulary for induction and maintenance of general anaesthesia¹. The other product listed in this category is ether. Unlike ether, halothane is a fluorinated general anaesthetic agent.

The product^{2,3}

Halothane is available as a clear, colourless, dense, non-flammable liquid with a characteristic non-irritant odour. The boiling point is 50.2 °C. Some decomposition occurs on exposure to light and to avoid this it is stabilised the addition of 0.01% thymol. Because thymol is not volatile it accumulates in vaporisers, imparting a yellow colour to the residual liquid. Halothane that is discoloured should be discarded.

Halothane is supplied in amber-coloured glass bottles that should be protected from light and heat. Rubber and plastics may deteriorate in contact with halothane liquid or vapour. It can also corrode metals in vaporisers and breathing systems in the presence of moisture.

Dosage

Halothane is administered through specially designed calibrated vaporisers that allow close control over the concentration of the inhaled vapour. It can be given in closed or semi-closed circuits incorporating soda lime for removal of carbon dioxide.

For induction of anaesthesia, ADULT 2 - 4% v/v and CHILD 1.5 - 2% v/v, in oxygen or oxygen-nitrous oxide mixture. Induction may also be started at 0.5% v/v and gradually titrated upwards to the required level.

For maintenance of anaesthesia, ADULT and CHILD, 0.5 - 2% v/v. Lower concentration is usually used in the elderly.

Because of the small but definite risk of fulminant hepatitis, anaesthetic history should be taken carefully and use of halothane avoided if there is a risk of hepatotoxicity. Once used, at least 3 months should be allowed to elapse before re-exposure.

Adverse drug reactions^{2,3}

- Hepatotoxicity: this may be either in the form of asymptomatic elevation of liver enzymes (relatively common) or as fulminant life-threatening hepatic failure (uncommon). The latter may be a hypersensitivity reaction. Repeated exposures within a short interval increases risk. Delayed jaundice is also possible.
- Cardiovascular effects: dose-dependent myocardial depression leading to bradycardia and hypotension. The sensitivity to catecholamines is increased and cardiac arrhythmias, usually ventricular ectopics and bigeminy, may occur. Cardiac arrest is unlikely. Use in phaeochromocytoma carries a high risk of arrhythmias. Concurrent use of epinephrine or other sympathomimetics, dopaminergics or theophylline also increases risk.

- Postoperative nausea, vomiting and shivering.
- Increase in intracranial pressure. This is undesirable in neurosurgical situations and may be countered by moderate hyperventilation.
- Transient reduction of renal blood flow and glomerular filtration rate due to renal vasoconstriction. There are few reports of acute renal failure.
- Malignant hyperthermia: may be precipitated by use of suxamethonium in presence of halothane. It occurs in genetically predisposed individuals and is potentially fatal.
- Abuse liability, by parenteral or inhalational route, has been reported.
- Intravenous injection may lead to death from pulmonary oedema.

Contraindications^{2,3}

- Compromised liver function, history of halothane-induced hepatitis or unexplained jaundice or pyrexia following an operation where halothane was used. These are absolute contraindications.
- Prior use of halothane within 3 months.
- Family history of malignant hyperthermia.
- Dental procedures below 18 years unless treated in hospital (risk of arrhythmias).
- Other situations where concurrent epinephrine is to be used.
- Poor cardiac function.
- Early pregnancy.
- Obstetrics. Although used,⁴ may not be preferable because of the possibility of increased postpartum bleeding and neonatal depression.
- Porphyria.

Evidence of value

Halothane is a potent inhalational anaesthetic. It is non-flammable and is not explosive in presence of oxygen. It is non-irritant to skin and mucous membranes and will not cause necrosis if spilt on tissues. It suppresses salivary, bronchial and gastric secretions and dilates the bronchioles.

Being a time-tested anaesthetic with known limitations, recent controlled studies on the efficacy of halothane are scarce. However, use in a few novel situations and comparisons with other inhalational or intravenous general anaesthetics, particularly sevoflurane, isoflurane and propofol, are being reported.

Placing an implantable cardioverter defibrillator involves the induction of ventricular fibrillation, whereupon the minimally effective defibrillation energy threshold (DFT) is determined. Halothane has been used in this situation, and like isoflurane, may increase the DFT values, whereas lidocaine plus intermittent small doses of propofol reduces these thresholds.⁵

Halothane has been used safely in neonates. Abnormal breathing patterns may be seen during general anaesthesia in neonates and episodes of apnoea may occur associated with substantial arterial oxygen desaturation. In this regard, caution is required during use of halothane which is a known respiratory depressant.⁶ Anaesthesia based on the short-acting opioid remifentanil may be a safer alternative to halothane in this situation.^{6,7}

Rapid induction of anaesthesia has been achieved safely in children with high concentration (5%) of halothane.⁸⁻¹⁰ When compared to 8% sevoflurane in this regard, there is no difference in induction time, quality of induction or the incidence of airway complications. However, the incidence of dysrhythmias is more with halothane and tachycardia more with sevoflurane. Induction may be perceived to be more pleasant with sevoflurane.¹⁰

Low concentration of halothane may suffice for laryngeal mask airway insertion, in comparison to endotracheal intubation, in children.^{11,12}

Induction and recovery characteristics of halothane anaesthesia have been compared to sevoflurane in a variety of surgical situations, including paediatric operations.^{13,14} In general the two are comparable. However, recovery is faster and haemodynamic tolerance is better with sevoflurane compared to halothane.¹⁵ This may be of particular advantage in some situations, such as squint surgery in children.¹⁶ On the other hand, emergence agitation with sevoflurane may make it less suitable in paediatric day case surgery.¹⁷⁻¹⁹ Sevoflurane has been seen to be superior to halothane for paediatric bronchoscopy and gastroscopy.²⁰

Halothane has also compared well with isoflurane. Induction is faster with isoflurane,²¹ but halothane may be a better choice in children with long QT interval²² (halothane shortens the QTc interval while isoflurane prolongs it). The incidence of postoperative nausea and vomiting may be less with isoflurane.²³

Comparisons with the intravenous anaesthetic propofol are also being undertaken in various surgical situations, including in children.^{24,25} Propofol may cause less postoperative vomiting and allow faster recovery.^{26,27} The use of nitrous oxide, may, however, attenuate the less emetic advantage of propofol.²⁸ In cardiopulmonary bypass surgery, propofol produced a more optimal relationship between the hepatosplanchnic blood flow and oxygen consumption.²⁹

It has been reported that the benzodiazepine antagonist flumazenil improves recovery of high cortical and neuromotor functions following halothane anaesthesia, reduces shivering and improves the overall quality of emergence.³⁰

Recommendation

Halothane is a time-tested inhalational anaesthetic. It is also the least expensive of the currently available fluorinated general anaesthetics. Its limitations are well established. It can be used safely if the cautions and contraindications to its use are respected. Halothane should be retained in the WHO Model List of Essential Medicines.

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2.5 Nitrous oxide (subsection 1.1.3)

Introduction

Nitrous oxide is an inhalational gas intended for the maintenance of general anaesthesia. It is used in conjunction with oxygen or air and is the only such agent listed in the 2004 WHO Model Formulary.¹

The anaesthetic potency of nitrous oxide is insufficient for it to be used alone. However, it permits other anaesthetic agents to be used at lower doses. It has good analgesic activity.

A 50:50 v/v mixture of nitrous oxide with oxygen is known as entonox. It is usually used for analgesia (e.g. in obstetric and dental practice) rather than for anaesthesia. This product is not separately listed in the WHO formulary, although the mixture is mentioned in the dosage section.

The product²

Nitrous oxide is a colourless non-irritant gas without appreciable odour or taste. One litre of the gas, at 0 °C and at 760 mmHg pressure, weighs 1.97 g. One volume dissolves in 1.4 volumes of water at 0 °C and 760 mmHg pressure. The anaesthetic property increases under hyperbaric conditions. The gas is stable and relatively inert at room temperature. It is non-flammable but supports combustion.

Nitrous oxide is supplied as a liquid, compressed in cylinders of various sizes. Filling of cylinders is by weight and weighing can indicate the amount of nitrous oxide remaining in partially filled cylinders. National standards exist regarding colouring schemes and other cylinder specifications and the purity of the gas. [The ISO standard (International Standard 32, Gas cylinders for medical use, 1977) specifies blue colour of both body and shoulder for cylinders containing nitrous oxide, and blue body with alternating blue and white quarters for shoulders of cylinders containing nitrous oxide-oxygen mixtures]. Strict limits (< 1 ppm) are applied to the presence of the toxic higher oxides of nitrogen. The gas flow can be affected by low ambient temperatures and cooling of cylinders.

Nitrous oxide may also be supplied through piped medical gas supply systems.

Dosage

Nitrous oxide for anaesthesia is administered through anaesthesia machines that allow flow and pressure to be regulated. Oxygen is administered simultaneously, with other induction and maintenance agents if needed.

In anaesthesia for surgery of various types, concentration used, in ADULT and CHILD, is usually 70-75%. Analgesia occurs at these concentrations but surgical anaesthesia cannot be assured and muscle relaxation will not occur. Therefore, nitrous oxide is usually used as a component of balanced anaesthesia techniques that include other agents for induction and maintenance of unconsciousness and for muscle relaxation.

Nitrous oxide-oxygen mixtures intended for analgesia are often administered through simple demand-supply valves. Self-administration may be permitted. It has been

used in this manner in dentistry, obstetric cases, casualty wards, during painful procedures such as dressing of burns and removal of drains, and also in 'psychotropic analgesia' for the alcohol withdrawal state.³

Adverse drug reactions

- Diffusion hypoxia. The discontinuation of nitrous oxide at the end of surgery leads to rapid back diffusion of the gas from blood to the pulmonary alveoli. This can result in transient, but potentially deleterious, hypoxia if oxygen is discontinued simultaneously.
- Nitrous oxide can diffuse across biological membranes and body cavities much faster than nitrogen. Thus it may cause expansion of air- or nitrogen-containing gas mixtures in closed cavities. The consequent pressure rise can be dangerous to the patient in situations like tension pneumothorax, pulmonary bullae or cysts, surgical emphysema, intestinal obstruction and air embolism. It can also be deleterious in the context of middle ear surgery or expansion of the anterior chamber by air in ophthalmic surgery. In patients with blocked eustachian tubes, nitrous oxide anaesthesia can cause transient deafness.
- Prolonged administration has been associated with disturbed bone marrow function (manifesting as megaloblastic anaemia, aplastic anaemia or granulocytopenia) and peripheral neuropathy owing to disturbed vitamin B₁₂ metabolism. Delayed deaths have been reported. The bone marrow toxicity is greater in more severely ill patients. Disturbed vitamin B₁₂ metabolism can occur with just 2 – 6 hours exposure. However, exposure for up to 6 hours is generally considered safe.⁴ Patients with pre-existing vitamin B₁₂ deficiency have developed subacute combined degeneration of the spinal cord following nitrous oxide anaesthesia.
- Myocardial depressant effect may be of significance in the presence of cardiac disease or in cardiac surgery.
- Nausea and vomiting. Nitrous oxide has an emetogenic effect and omission of the gas from anaesthetic regimes may reduce the incidence of postoperative nausea and vomiting (PONV).^{5,6} This is a distinct disadvantage compared to other inhalational anaesthetics. However, it must be remembered that omitting nitrous oxide cannot ensure complete control over PONV and, in the absence of potent inhalational agents, there is a chance of increased intraoperative awareness.⁷
- Repeated (occupational) exposure to nitrous oxide raises concerns regarding neuropathic illness, impaired fertility, increased abortions in early pregnancy and higher incidence of liver and kidney disease. Although, there is no conclusive evidence regarding these,⁴ unnecessary or heavy occupational exposure should be avoided.
- Nitrous oxide is a 'greenhouse' gas but emission of nitrous oxide from medical use is estimated to contribute less than 0.05% to total annual greenhouse gas emission.⁴

Contraindications²

- Intracavitary, intraluminal or intraparenchymal accumulation of air as in demonstrable collection of air in pleural, pericardial or peritoneal space; intestinal obstruction; occlusion of middle ear (blocked eustachian tube); arterial air embolism; chronic obstructive airway disease, emphysema, pulmonary bullae, etc.
- Tension pneumothorax.

- Decompression sickness.
- During latter stages of middle ear surgery – the nitrous oxide component of the anaesthesia is withdrawn 5 minutes before graft placement in tympanoplasty or myringoplasty to avoid displacement due to these volume effects.
- Surgical injection of air into the closed globe of the eye.
- Prolonged use, specially in the critically ill (e.g. intensive care unit patients).

Evidence of value

Nitrous oxide is a time-tested inhalational general anaesthetic with well-known limitations and adverse drug reactions. If recommendations are followed, it is safe to use in all age groups. Recent controlled trials on its efficacy are therefore lacking. Its ancillary uses are however being explored.

Safe and predictable analgesia is required for the potentially painful or uncomfortable procedures often undertaken in an emergency department. Despite increasing availability of newer anaesthetic agents, nitrous oxide continues to be used safely in these situations.⁸

In dental practice, inhalational sedation with nitrous oxide is being advocated as an alternative to general anaesthesia for children.⁹ It is particularly suitable for orthodontic treatment, for older children, and for children requiring no more than four extractions. Morbidity associated with inhalational sedation is minor and infrequent, and user satisfaction is high, or higher compared with general anaesthesia. The cost component may also be lower than general anaesthesia.

Recommendation

Nitrous oxide continues to be a widely used inhalational gas for the maintenance of general anaesthesia. It has to be used in conjunction with induction agents. It serves as a carrier gas and has a dose sparing effects for modern inhalation general anaesthetics. In addition to anaesthesia, its analgesic property is utilised widely. Nitrous oxide should be retained in the WHO Model List of Essential Medicines.

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2.6 Oxygen (subsection 1.1.3)

Introduction

Oxygen is listed in the 2004 WHO Model Formulary ¹ as an inhalational gas to maintain adequate tissue oxygenation in inhalational anaesthesia. It has other important medical uses, particularly in the management of acute or chronic hypoxaemic states.

There are many variants of oxygen therapy. It may be administered under normobaric or hyperbaric conditions. Application of hyperbaric oxygen will be briefly reviewed here. Oxygen in combination with nitrous oxide in equal parts by volume (entonox) is used for analgesia. Oxygen-helium mixture (heliox) has special applications. The use of oxygen in undersea, high altitude, aviation and space medicine is not considered in this review.

The product²

Medical grade oxygen is available either in compressed gas form in cylinders or in liquid form from liquid oxygen storage systems. It may also be generated at the point of consumption by oxygen concentrators.

Cylinder oxygen is bulky (hence inconvenient to handle, store and transport) but relatively inexpensive. In developing countries, it is probably the most common form in which oxygen for medical use is supplied. National standards are in operation regarding colour coding and other cylinder specifications and the purity of the gas. The ISO standard (International Standard 32, Gas cylinders for medical use, 1977) specifies black body and white shoulder for oxygen cylinders; blue body with alternating blue and white quarters for shoulders of entonox cylinders and black body with alternating white and brown shoulder quarters for heliox cylinders.³

Liquid oxygen supply systems are used in institutions and vacuum-insulated evaporators are considered the most economical way to store and supply oxygen in the institutional setting. Oxygen concentrators extract oxygen from air and deliver it at concentrations of around 95% by volume. The principal residual constituent is argon. Concentrators are built to various capacities and may be large enough to feed piped supply systems.

Dosage²

Oxygen is delivered in concentrations ranging from 21% (the normal concentration in air) to 100%. Low concentrations (up to 35%) are used when there is a chance of carbon dioxide (CO₂) retention. Flow rates are adjusted depending upon clinical need. Prolonged high concentration oxygen increases risk of oxygen toxicity. Ideally the arterial oxygen saturation should be monitored in anaesthetic practice and in hypoxic states.

There are various means of oxygen delivery, including nasal cannulae, face masks, oropharyngeal or nasopharyngeal airways, endotracheal tubes, endobronchial tubes, laryngeal mask airways, tracheostomy tubes, indwelling tracheal catheters, oxygen tents and hyperbaric chambers. Nasal cannulae are well tolerated by patients and are most widely used for home oxygen therapy but allow only low flow rates (up to 4 L/minute). Hypoxaemic patients at risk of CO₂ retention should receive low

concentration oxygen through nasal cannulae or specially designed masks that allow flow control.

Oxygen flow can cause drying and cooling of the respiratory tract which is unpleasant for the patient. A variety of humidification devices, both heated and cold, are used to overcome this problem.⁴

No special precautions are needed in administering oxygen to children, elderly, pregnant and breast-feeding women. In neonates, the lowest concentrations that will maintain adequate oxygenation should be used for as short a duration as possible because prolonged use in high concentrations can cause retrolental fibroplasia.

Adverse drug reactions

- Acute CO₂ retention (potentially fatal): oxygen therapy may raise arterial pCO₂ by removing the hypoxic respiratory drive. This can lead to acidosis and death. Hence, hypercapnic patients should be given only low concentration oxygen and facilities for assisted ventilation should be available.
- Pulmonary toxicity (potentially fatal): oxygen concentrations greater than 80% inhaled for long periods (over 12 hours) can lead to pulmonary congestion, exudation and hyaline membrane changes. There may be co-existent tracheobronchitis.
- Cerebral toxicity: this can occur with hyperbaric oxygen, manifesting as mood changes, nausea, dizziness and convulsions. Full recovery is possible but fits have been linked to death.
- Alcohol, by causing respiratory depression, may potentiate the ventilatory depression resulting from oxygen inhalation and indirectly aggravate CO₂ retention and acidosis.
- Smoking is dangerous in the presence of oxygen. Severe burns and deaths have been reported.
- Relapse of bleomycin-induced lung disease.
- Blindness, from retrolental fibroplasia, in preterm babies. There is also risk of chronic lung disease in this situation.⁵
- Genotoxicity of hyperbaric oxygen: oxygen toxicity and possible cancer-promoting effects of hyperbaric oxygen have been a matter of serious concern. Although a cancer-inducing effect of hyperbaric oxygen has not been found to date, recent studies clearly indicate an induction of oxidative DNA damage in blood cells of healthy subjects.⁶

Evidence of value

In addition to maintaining adequate oxygen saturation in anaesthetised patients, oxygen has several medical uses.

Treatment of acute hypoxia – oxygen is standard treatment. Frequent indications include pneumonia, acute severe asthma, acute exacerbations of chronic obstructive pulmonary disease (COPD), pulmonary embolism, pulmonary oedema, adult and neonatal respiratory distress syndrome, neuromuscular disorders that lead to inadequate ventilation, and shock. High concentrations (over 50%) are used initially, unless there is risk of CO₂ retention, as in chronic bronchitis-empysema states.

Treatment of chronic hypoxia – long-term oxygen therapy improves quality of life in COPD patients and confers a survival advantage in patients with resting hypoxia (paO₂ less than 60 mmHg). Domiciliary oxygen therapy should be maintained for as many hours as possible. Long-term home oxygen therapy can improve outcome in children with bronchopulmonary dysplasia.⁷

Management of low haemoglobin states – high-concentration oxygen can be life-saving in acute carbon monoxide poisoning. It is also used in severely anaemic patients. The value of hyperbaric oxygen in carbon monoxide poisoning, though practised if facilities are available, has been questioned in a recent review.⁸

Adjunctive management of local hypoperfusion – oxygen is routinely used in the acute stage management of myocardial infarction, cerebrovascular accidents and peripheral vaso-occlusive disease. The value of routine use in such situations is debatable. The question of optimal dosing is also not settled.⁹

Conditions in which hyperbaric oxygen is believed to be beneficial or is being actively researched include:

- Decompression sickness and air-gas embolism.¹⁰
- Delayed radiation injury.¹¹⁻¹²
- Promotion of wound healing at various sites.¹³⁻¹⁵

However, cost is currently a major limitation of hyperbaric oxygen therapy.¹⁶

Although practised, the benefits of oxygenation is controversial in the following situations and recent reviews have not recommended routine use:

- Hyperbaric oxygen treatment for multiple sclerosis.¹⁷
- Hyperbaric oxygen treatment for cerebral palsy.¹⁸
- Maternal oxygenation for foetal distress.¹⁹
- Maternal oxygenation for foetal growth retardation.²⁰

Finally, the utility of helium-oxygen mixtures is being explored.²¹ The density of helium is markedly lower than that of air or any of its components, leading to a substantial decrease in airway resistance to flow when it is inhaled. In mechanically ventilated patients with obstructive airway disease, replacing the usual air-oxygen mixture with helium-oxygen reduces dynamic hyperinflation and intrinsic positive end-expiratory pressure; decreases lung inflation pressures, respiratory acidosis, and work of breathing; and improves arterial blood gases. Aerosol delivery to distal airways is also enhanced with helium-oxygen. Preliminary data also suggest that the use of helium-oxygen could be a valuable approach to decrease postextubation respiratory distress. However, interference with ventilator function and added costs are two major disadvantages of helium-oxygen.

Recommendation

Oxygen should be retained in the WHO List of Essential Medicines. The uses and dosage sections of the Formulary should be expanded.

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2.7 Bupivacaine hydrochloride (subsection 1.2)

Introduction

Bupivacaine is a potent amide-type local anaesthetic. It is one of two representative local anaesthetics listed in the 2004 WHO Model Formulary, the other being lidocaine.¹ Bupivacaine is about four times as potent as lidocaine, has a slower onset but longer duration of action and shows greater variability in its activity duration.

Many other local anaesthetics are in clinical use. Levobupivacaine^{2,3} and ropivacaine,^{4,5} are two, relatively recently introduced, enantiomerically pure local anaesthetics which resemble bupivacaine in their nerve blockade profile but probably carry less risk of toxicity. They are currently not listed.

The product

Bupivacaine (as bupivacaine hydrochloride) is available, in the form of clear, colourless, sterile, buffered, aqueous solution in different strengths – 0.25% (2.5 mg/mL), 0.5% (5 mg/mL) or 0.75% (7.5 mg/mL) in single or multidose ampoules or vials. Other strengths may also be available. The solution may contain epinephrine (1 in 200,000) as a vasoconstrictor to prolong duration of local action and limit systemic absorption; these combination solutions may contain sodium metabisulfite as excipient.

Bupivacaine injection is isotonic with plasma. However, bupivacaine for spinal use is made hypertonic with addition of glucose e.g. bupivacaine 0.5% with dextrose monohydrate 8% in 4 mL ampoules.

Preparations are stable at room temperature.

Solutions containing preservatives should not be used for spinal, epidural, caudal or intravenous regional anaesthesia (Bier's block).

Dosage^{6,7}

The dose of bupivacaine used depends upon the procedure, the site of injection and the condition of the patient. The maximum cumulative dose for adults and children is 150 mg with or without epinephrine, followed if needed by additional doses of up to 50 mg every 2 hours. Lower doses should be used for elderly, epileptic, debilitated, or acutely ill patients. The recommendation is to avoid bupivacaine for Bier's block and for paracervical block in obstetrics. The 0.75% solution is contraindicated for epidural block in obstetric anaesthesia. A test dose of bupivacaine, preferably with epinephrine, should be administered before commencing an epidural block to avoid inadvertent intravascular or intrathecal injection and subsequent doses should be given in small aliquots. Epinephrine-containing preparations are usually not used for spinal anaesthesia.

Representative doses in ADULT are as follows:

- Infiltration anaesthesia, using 0.25% solution, with or without epinephrine, up to 150 mg (up to 60 mL)
- Dental anaesthesia, using 0.5% solution, with or without epinephrine, 9 - 18 mg (1.8 - 3.6 mL), initially. A total dose of 90 mg (18 mL) should not be exceeded in a single setting.

- Peripheral nerve block, using 0.25% solution, 12.5 mg (5 mL) or, using 0.5% solution, 25 mg (5 mL); maximum 150 mg.
- Sympathetic nerve block, using 0.25% solution, 50 - 125 mg (20 - 50 mL).
- Retrobulbar block in ophthalmic surgery, using 0.75% solution, 15 - 30 mg (2 - 4 mL).
- Lumbar epidural block, using 0.25% solution, 25 - 50 mg (10 - 20 mL) or, using 0.5% solution, 50 - 100 mg (10 - 20 mL); maximum 150 mg. Single doses of 75 - 100 mg using the 0.75% solution (10 - 20 mL) has also been used for lumbar epidural block in non-obstetric cases. Lower doses of 15 to 30 mg (6 - 12 mL of the 0.25% solution) or 30 - 60 mg (6 - 12 mL of the 0.5% solution) are used for analgesia during labour.
- Caudal block, using 0.25% solution, 37.5 - 75 mg (15 - 30 mL) or, using 0.5% solution, 75 - 100 mg (15 - 30 mL); maximum 150 mg.
- Spinal block, using a 0.5% 'spinal' (hyperbaric) solution, 10 - 20 mg (2 - 4 mL) or, using 0.75% 'spinal' (hyperbaric) solution, 7.5 - 11.25 mg (1 - 1.5 mL).

Bupivacaine is used safely in children. However, the doses need proportionate reduction in accordance with the age and weight of the child.

Adverse drug reactions⁷

- Bupivacaine is cardiotoxic. Large doses or accidental intravascular injection of high concentrations have caused cardiac arrhythmias that are potentially fatal.
- Inadvertent intravascular or intrathecal administration may cause respiratory depression and arrest. This has been reported following retrobulbar injection.
- Transient neuropathic symptoms like anxiety, tinnitus, circumoral numbness and metallic taste in mouth. Transient neurologic symptoms after spinal anaesthesia is less common with bupivacaine than lidocaine.⁸
- Persistent neuropathic symptoms, like paraesthesias, in the distribution of blocked nerves.
- Acute (systemic) overdose can cause light-headedness, dizziness, blurred vision, restlessness, tremors and, occasionally, convulsions rapidly followed by drowsiness, unconsciousness and respiratory failure; cardiovascular toxicity includes hypotension, heart block and cardiac arrest.
- Epidural anaesthesia is occasionally complicated by urinary retention, faecal incontinence, headache, backache or loss of perineal sensation; transient paraesthesia and paraplegia are rare. Transient shivering is relatively common and can be treated effectively with epidural morphine.
- Rare hypersensitivity and allergic reactions have been reported.

Contraindications

- Intravenous regional anaesthesia.
- Concentrations above 0.5% for obstetrical cases.
- Spinal or epidural anaesthesia in dehydrated or hypovolaemic patient.
- Local infection at infiltration site.
- Severe cardiac conduction disturbances.
- Known hypersensitivity to the drug.

Evidence of value

Bupivacaine is indicated for all forms of central and peripheral nerve blocks (except intravenous regional anaesthesia) whenever a long duration of action is required. The variety of applications can be inferred from the dosage section. However, in view of its potency and long duration of action, the risk of toxicity is greater and it has been recommended that bupivacaine should not be used by the non-anaesthetist except in the minimum of doses.⁷

Despite its toxicity, bupivacaine is used safely in children, even for caudal and spinal anaesthesia.^{9,10} Haemodynamic stability is well preserved in neonates.¹⁰ Since, catastrophic events can occur with neuraxial techniques,¹¹ care must be taken in evaluating the relative risks of different anaesthetic approaches before selecting spinal block with bupivacaine in children.

An interesting approach is to use small doses of bupivacaine to achieve unilateral spinal anaesthesia, controlling the spread of intrathecal drugs, thereby restricting the distribution of spinal block to the operated side.¹² The small amount of local anaesthetic injected, as well as the reduced extent of spinal block, can provide a favourable profile of resolution of the block, which can be useful in an ambulatory setting. The intraperitoneal application of bupivacaine for postoperative analgesia in abdominal surgery, whether by open or laparoscopic techniques, is under investigation.^{13,14}

Recommendation

Bupivacaine is a time-tested, potent, long-acting local anaesthetic used for almost all types of locoregional anaesthesia. If used with care, at recommended doses, it is unlikely to cause catastrophic events. It should be retained in the Model WHO List of Essential Medicines. The dosage section in the Formulary should be expanded.

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2.8 Lidocaine hydrochloride (subsection 1.2)

Introduction

Lidocaine (also called lignocaine) is an amide type local anaesthetic used for all types of locoregional anaesthesia. It is probably the most widely available and used local anaesthetic.

Lidocaine is listed in the 2004 WHO Model Formulary,¹ as one of two representative local anaesthetics, the other being bupivacaine. The pharmacological profile of lidocaine is different from that of bupivacaine.

Lidocaine is also a Class I-b antiarrhythmic agent, used to prevent ventricular arrhythmias, particularly following myocardial infarction or cardiac surgery, and to raise the threshold for ventricular fibrillation. This indication is not reviewed here.

The product^{2,3}

Lidocaine (as lidocaine hydrochloride), is available in a wide variety of preparations for topical or parenteral use. It is stable at room temperature but should be protected from light.

Topical preparations include (strength as lidocaine hydrochloride):

- Gels, containing 2% or 2.5%.
- Ointments, containing 2% or 5%.
- Sprays, containing 4% or 10%.
- Topical solutions, containing 4%.
- Topical oral solution, containing 2.5%.

Parenteral preparations include (strength as lidocaine hydrochloride):

- Injections, containing 0.5%, 1%, 1.5%, 2% or 4%.
- Intramuscular injections, containing 10%.
- Intravenous infusions, containing 0.1%, 0.2%, 0.4% or 0.8% in 5% dextrose (mainly for cardiac use).
- Intravenous solutions, for dilution before infusion, containing 4%, 10% or 20%.
- Hyperbaric injections for spinal anaesthesia, containing 1.5% or 5% in 7.5% dextrose.

Topical preparations may contain excipients such as parabens or propylene glycol. Injections may contain epinephrine 1 in 80,000 (12.5 microgram/mL), 1 in 100,000 (10 microgram/mL) or 1 in 200,000 (5 microgram/mL), as vasoconstrictor, to prolong duration of local activity and to limit systemic absorption. Dental cartridges containing lidocaine hydrochloride 2% plus epinephrine 1 in 80,000 are available in some countries.

The drug has also been incorporated into various mixed topical preparations including oral gels, topical rectal preparations (for piles and painful perianal conditions), ear drops, in eye drops in combination with fluorescein (for tonometry), transdermal patches (for post-herpetic neuralgia) and also occasionally in intramuscular injections of compatible drugs to reduce pain (e.g. depot corticosteroids, tetracyclines). A combination of lidocaine base 2.5% and prilocaine base 2.5% is available as a eutectic mixture of local anaesthetics (EMLA) cream for surface anaesthesia.

Dosage^{1,2,3}

The dose of lidocaine used depends upon the procedure, the site of injection and the condition of the patient. In general the lowest concentration and amount that achieves the desired effect should be used. The maximum cumulative dose for healthy adults and children is 200 mg (or 3 mg/kg) without epinephrine, and 500 mg (or 7 mg/kg) with epinephrine for peripheral nerve blocks. Lower doses should be used for epileptic, debilitated, or acutely ill patients. In neuraxial administration, dosing should be adjusted to the number of segments or area to be blocked. In obstetrics, the standard doses should be reduced by 30%. A test dose of lidocaine, preferably with adrenaline, should be administered before commencing an epidural block to avoid inadvertent intravascular or intrathecal injection and subsequent doses should be given in small increments. Epinephrine-containing preparations are not used for spinal and intravenous regional anaesthesia.

Representative doses in ADULT are as follows:

- Surface anaesthesia, using 5% ointment, to a maximum of 20 g.
- Topical anaesthesia of the urethra prior to catheterization or instrumentation, using 2% gel, up to 200 mg in females and up to 800 mg in males.
- Topical analgesia during gastrointestinal endoscopy, using 2% gel, up to 400 mg (some amount used for lubrication of the instrument as well).
- Bronchoscopy, laryngoscopy, endotracheal intubation; minor surgical procedures in the oral cavity or throat; minor ENT procedures; using 4% topical solution or 10% spray, up to 200 - 300 mg.
- Topical laryngotracheal anaesthesia, using 4% spray, up to 160 mg instilled directly.
- Infiltration anaesthesia, using 0.5% injection, up to 250 mg (50 ml) or using 1% injection, up to 250 mg (25 ml).
- Peripheral nerve blocks, using 1% or 2% injection, up to the maximum recommended doses at each site; for retrobulbar blocks, using 4% injection, 3 - 5 mL (120 - 200 mg).
- Sympathetic nerve blocks, using 1% injection, 50 mg (5 mL) for cervical block and 50 - 100 mg (5 - 10 mL) for lumbar block.
- Dental anaesthesia, using 2% injection with epinephrine, 20 - 100 mg (1 - 5 mL).
- Intravenous regional anaesthesia (Bier's block), using 0.5% injection, 50 - 300 mg (10 - 60 mL).
- Epidural anaesthesia, using 1%, 1.5% or 2% injection, up to 200 - 300 mg.
- Caudal anaesthesia, using 1% or 1.5% injection, up to 300 mg.
- Spinal anaesthesia, using 5% injection (with glucose 7.5%), 50 - 75 mg (1 - 1.5 mL).

In children, the doses need reduction proportionate to the indication and in accordance with the age and weight of the child.

Adverse drug reactions

Although adverse reactions to lidocaine are more likely after neuraxial or intravenous use, topical preparations are not entirely innocuous. The drug is readily absorbed from damaged skin and across mucous membrane, and serious toxicity has occurred following application in large doses to mucosal surfaces, including the urethra.

- Lidocaine is cardiotoxic. Large systemic doses or accidental intravascular injection of high concentrations have caused cardiac arrhythmias that are potentially fatal.
- Acute (systemic) overdose can cause central nervous stimulation followed by depression, manifesting as light-headedness, dizziness, tinnitus, nystagmus, fine muscle twitching and restlessness, and, occasionally, convulsions followed by drowsiness, unconsciousness and respiratory failure; cardiovascular toxicity includes hypotension, heart block and cardiac arrest.
- The risk of developing transient neurologic symptoms (mainly manifesting as pain in the lower extremities) after spinal anaesthesia with lidocaine is higher than with bupivacaine, prilocaine or procaine.⁴
- Epidural anaesthesia is occasionally complicated by urinary retention, faecal incontinence, headache, backache or loss of perineal sensation.
- Methaemoglobinaemia has been reported following use of lidocaine, but this is less severe than with prilocaine. EMLA cream can cause methaemoglobinaemia, particularly in neonates and infants.⁵
- Rare hypersensitivity and allergic reactions have been reported.

Contraindications

- Spinal or epidural anaesthesia in dehydrated or hypovolaemic patient.
- Local infection at infiltration site.
- Severe cardiac conduction disturbances.
- Severe hepatic impairment.
- Known hypersensitivity to the drug.
- Solutions containing epinephrine in anaesthesia ('ring' blocks) of digits and appendages, because of the risk of irreversible ischaemia.

Caution is also required in respiratory impairment, epilepsy, porphyria, myasthenia gravis, debilitated and acutely ill patients.

Evidence of value

Lidocaine is widely used in almost all types of locoregional anaesthesia, including infiltration anaesthesia, regional nerve blocks, peripheral nerve blocks, sympathetic nerve blocks, and Bier's block. There is no question regarding its efficacy, and it is quite safe at recommended doses. More dilute solutions have a greater safety margin.

The onset of action ranges from 5 minutes for infiltration anaesthesia to 20 minutes for intravenous regional anaesthesia. The duration of action of single doses is about 1 hour without epinephrine and 1.5 - 2 hours with epinephrine. This is sufficient for majority of procedures where local anaesthesia is sought.

The availability of EMLA cream has bridged the gap between topical and infiltration anaesthesia, enabling the comfortable accomplishment of procedures such as venepuncture, cannulations, wart removal, split skin grafting and other minor procedures, including circumcision.⁶

However, spinal lidocaine use has been associated with some neurotoxic symptoms⁸ – it is implicated in the syndrome of transient neurologic symptoms (previously referred to as transient radicular irritation), manifest through pain or paraesthesia in

the buttocks or legs after recovery from anaesthesia. Although the pain typically resolves within 1 week without lasting sequelae, it can be severe in up to one third of patients with the syndrome. For this indication, bupivacaine may thus be preferable.⁹

Lidocaine is also used to reduce the pain of propofol injection; 10 mg is added to the propofol preparation or administered into the same vein immediately prior to propofol.

Recommendation

Lidocaine is a time-tested, widely used, intermediate-acting local anaesthetic used for all types of locoregional anaesthesia. It has important non-anaesthetic uses too. If used with care, at recommended doses, it is unlikely to cause serious adverse events. Spinal use may be avoided if alternatives are available. Lidocaine should be retained in the WHO Model List of Essential Medicines. The section in the Formulary on dosage should be expanded.

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2.9 Ephedrine hydrochloride (subsection 1.2)

Introduction

Ephedrine is a naturally occurring alkaloid (now synthesised) with direct and indirect sympathomimetic properties. In its direct action it stimulates α , β_1 and β_2 -adrenergic receptors; it acts indirectly by stimulating release of catecholamine neurotransmitters from sympathetic nerve terminals. In general, most of its actions mimic those of epinephrine but are slower in onset, less potent and longer in duration.¹ Unlike epinephrine, tachyphylaxis occurs due to depletion of neurotransmitters from storage sites.

Ephedrine is listed in the 2004 WHO Model Formulary 2004 as a systemic vasoconstrictor agent intended to prevent hypotension during caesarean deliveries under spinal or epidural anaesthesia.² It is included as a complementary drug. Potential alternative vasoconstrictors to ephedrine, not currently listed, are phenylephrine³ and metaraminol.⁴

Ephedrine, owing to its nasal decongestant and bronchodilator properties, can be an ingredient of cough and cold preparations. It has also been used in the treatment of narcolepsy and nocturnal enuresis.¹ These uses are not reviewed here.

The product

Parenteral ephedrine is available as the hydrochloride or sulphate. The hydrochloride is used more widely and is usually supplied in 30 mg/mL concentration, in 1 mL ampoules.

*Dosage*¹

By slow intravenous injection, ADULT 3 - 6 mg (maximum single dose 9 mg), repeated if necessary every few minutes; maximum cumulative dose 30 mg.

Single intravenous slow bolus doses of 15, 20 and 30 mg have also been used.⁵⁻⁶

Intravenous infusion, ADULT 5 mg/minute initiated immediately after the spinal injection and then titrated to maintain systolic blood pressure, has also been reported to be effective in preventing maternal hypotension in deliveries under spinal anaesthesia.^{4,7,8}

Intramuscular ephedrine 45 mg has been used pre-emptively during elective caesarean section under spinal anaesthesia and found to reduce the severity of hypotension and subsequent intravenous rescue dose of ephedrine.⁹ However, this approach requires further investigation.

Adverse drug reactions

Haemodynamic and cardiovascular disturbances occur specially at larger doses. Reactive maternal hypertension can occur.⁶ Palpitations, angina and arrhythmias are possible. Foetal tachycardia has also been reported.

Other manifestations of sympathetic overactivity and central stimulation like anxiety, restlessness, tremor, hypersalivation, sweating, flushing; difficulty in passing urine;

changes in blood glucose; headache, dizziness, nausea. Acute overdose can lead to potentially life-threatening convulsions.

Although not relevant here, chronic or excessive use of ephedrine may predispose to insomnia and psychoses. Inappropriate use of ephedrine nasal drops can cause rebound congestion in the nose.

It is to be noted that ephedrine is a banned substance under international anti-doping regulations.

Contraindications and special precautions^{1,2}

- Ischemic heart disease.
- Uncontrolled hypertension.
- Thyrotoxicosis.
- Prostatic enlargement.
- Athletes and other sportspersons.
- Pregnancy (adjunctive use in caesarean deliveries under spinal or epidural accepted).
- Breast-feeding.

As far as possible, use in children and the elderly should be avoided as they are more sensitive to the effects of ephedrine. Caution is also needed in diabetes, angle-closure glaucoma and renal impairment.

Evidence of value

Maternal hypotension is the most frequent complication of spinal and epidural anaesthesia for caesarean section. It is often associated with nausea and vomiting and, if severe, poses serious risks to mother (unconsciousness, pulmonary aspiration) and baby (hypoxia, acidosis and neurological damage). Although various strategies have been used against this complication, few have established efficacy.¹⁰ Intravenous ephedrine is effective prophylactically.^{10,11} However, it does not improve neonatal outcome and, on the contrary, is associated with dose-related maternal hypertension and tachycardia and foetal acidosis of uncertain clinical significance.^{10,11}

Few other vasoconstrictors have been investigated for this indication. Phenylephrine has been used but it may suffer the same drawbacks as those of ephedrine.^{3,12}

Ephedrine has numerous interactions with drugs used in anaesthesia. It has been found to accelerate the onset of action of rocuronium^{13,14} and cis-atracurium,¹⁵ but not vecuronium¹⁶ or atracurium.¹⁴ Combination with rocuronium may serve as an alternative to suxamethonium for achieving rapid intubation.¹⁷ Clonidine premedication may augment the pressor and tachycardia response to ephedrine during propofol anaesthesia.¹⁸ Interestingly, small doses of ephedrine may reduce the pain of propofol injection without significantly affecting haemodynamics.¹⁹

Ephedrine may counteract propofol induced hypotension but not that due to sevoflurane.^{20,21} Spinal anaesthesia induced hypotension during transurethral prostatectomy may also be prevented.^{22,23} Ephedrine may be particularly valuable in situations where perioperative fluid loading is undesirable.²⁴ However, firm recommendations are yet to be made regarding these indications.

Recommendation

Ephedrine should be retained in the WHO List of essential Medicines. The WHO Formulary should note that the use of ephedrine should not detract from appropriate perioperative intravascular fluid volume maintenance, and that the product is more effective given prophylactically than as rescue medication.

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2.10 Epinephrine (subsection 1.2)

Introduction

Epinephrine (adrenaline) is the prototypical catecholamine sympathomimetic agent used clinically as a vasoconstrictor adjunct to local anaesthesia, in the treatment of anaphylactic shock and acute angioedema and in cardiopulmonary resuscitation. epinephrine is used to prolong the duration of action of local anaesthetics. . It is now seldom used in the management of asthma.

Apart from epinephrine, ephedrine is listed as a vasoconstrictor in the 2004 WHO Model Formulary.¹ However, ephedrine is intended to be used as a pressor agent in spinal anaesthesia and not for retarding systemic absorption of the anaesthetic in infiltration anaesthesia.

The product²

Epinephrine, as the acid tartrate, is available in the form of sterile clear colourless solution for subcutaneous, intramuscular or intravenous use. Usual strengths are 250 microgram/mL in 1 mL ampoules, 100 microgram/mL (1 in 10,000) in 10 mL ampoules and 1 mg/mL (1 in 1000) in 1 mL ampoules. In some countries it is marketed in pre-filled syringes for emergency use.

Epinephrine injection has to stored in a cool place. Solutions showing pink or brown discolouration are degraded and must be discarded.

For use in anaesthetic practice, epinephrine is usually incorporated in local anaesthetic injections e.g. lidocaine and bupivacaine. Such injections may contain epinephrine 1 in 80,000 (12.5 microgram/mL), 1 in 100,000 (10 microgram/mL) or 1 in 200,000 (5 microgram/mL), as vasoconstrictor. Convenient dental cartridges containing lidocaine hydrochloride 2% with epinephrine 1 in 80,000 are available in some countries.

Dosage²

In anaesthetic practice, the dose of epinephrine is not calculated separately. The volume of local anaesthetic to be injected is determined on the basis of the procedure, the site of injection and the condition of the patient. Epinephrine is used usually at a final concentration of 5 microgram/mL (1 in 200,000) or occasionally at 10 microgram/mL (1 in 100,000). Epinephrine containing solutions are usually not used in spinal anaesthesia.

In dental surgery, in which small volumes are injected, concentrations of up to 12.5 microgram/mL (1 in 80,000) are commonly used

In managing cardiac arrest, epinephrine 100 microgram/mL (1 in 10,000) is recommended in a dose of 10 mL by intravenous injection, preferably through a central line. If injected through a peripheral line, it must be flushed with at least 20 mL of 0.9% sodium chloride solution to aid entry into the central circulation. Doses can be repeated every 3 minutes.

In the management of anaphylactic shock and angioedema, epinephrine by the intramuscular route (preferably in the anterolateral thigh) is now considered more

suitable than subcutaneous administration. The dose varies depending on strength and, using the 1 mg/mL (1 in 1000) solution, ranges from 0.05 mL in INFANT under 6 months of age to 0.5 mL in ADULT. Alternatively 0.1 mL of this solution can be used for every 10 kg body weight, to a maximum of 0.5 mL. These doses may be repeated, several times at 5 minute intervals, depending on the response as judged by the effect on the underlying problem together with the patients pulse and respiratory rate, and blood pressure.

If the shocked patient is ill enough for absorption from intramuscular sites to be compromised, the drug may be given by slow intravenous injection – 500 microgram in ADULT at the rate of 100 microgram per minute; stopping when a response has been obtained. A CHILD can be given 10 microgram/kg by slow intravenous injection over several minutes. Great care must be taken to ensure the correct dose and it is always preferable not to waste time in securing intravenous access when an intramuscular injection might still succeed.

In emergency situations, epinephrine has also been given by the tracheal route, in doses of 2 to 3 mg diluted to a volume of 10 mL.³

Adverse drug reactions

- Tachycardia (palpitations), hypertension, arrhythmias.
- Anxiety, tremor, headache, nausea, vomiting, dizziness, sweating, cold extremities.
- Hyperglycaemia.
- Pulmonary oedema on overdose.
- Acute overdose or too rapid intravenous injection can be fatal.

Clinically important drug interactions

- Volatile inhalational anaesthetics: Risk of arrhythmias with halothane.
- Antidepressants: Hypertension and arrhythmias can occur in subjects receiving tricyclic antidepressants.
- Beta-blockers: Adequate response may not be obtained in subjects on non-selective beta-blockers. There may also be severe hypertension in these subjects.

However, epinephrine in local anaesthetic preparations, because of the low concentrations present, is unlikely to interact significantly with the above drugs.

Contraindications

- Injection solutions containing epinephrine in ring block of digits, penis or other appendages where there is risk of local ischaemia.
- Cardiovascular disease e.g. hypertension, arrhythmias, heart blocks, atherosclerotic heart disease, cerebrovascular insufficiency.
- Thyrotoxicosis.
- Diabetes mellitus.

Majority of the contraindications in systemic disorders are relative and epinephrine may be used with care.

Evidence of value

Of the various vasoconstrictors currently used in anaesthetic practice (epinephrine, ephedrine, phenylephrine, mephentermine, metaraminol, dopamine, dobutamine, vasopressin analogues), epinephrine has the best pharmacological profile suited to its role as a vasoconstrictor adjunct to local anaesthesia. The very low concentrations at which it can serve the purpose is unlikely to cause major systemic reactions. On the contrary it permits a larger dose of the local anaesthetic to be used safely.

The prohibition against the use of local anaesthetics with epinephrine for digital blocks or infiltration is an established surgical tradition. However, a recent systematic review⁴ has found scant evidence for this prohibition; indeed there have been no case reports of digital gangrene using commercial lidocaine with epinephrine, introduced in 1948. The authors recommend that instead of being an absolute contraindication, this technique may be used with caution.

Intrathecal epinephrine has been used to advantage in epidural analgesia in various studies.⁵⁻⁶ Used at low doses, it reduces the risk of toxicity from systemic absorption of epidural local anaesthetics without causing haemodynamic disturbances and may potentiate the analgesic action.⁷ Further, intrathecal epinephrine can prolong the duration of spinal anaesthesia by reducing vascular absorption of the local anaesthetic and also influence its local spread and hence the level of blockade.^{8,9}

In arthroscopic surgery of the knee, epinephrine in combination with local anaesthetics has been used to facilitate better haemostatic control and may help to potentiate the post-arthroscopy analgesia.¹⁰⁻¹¹ However, more trials are needed for this indication.

Epinephrine is the cornerstone of anaphylaxis management and delay in administration may be fatal.¹²⁻¹⁴ The most important recent finding in this regard is that the intramuscular route of administration is the route of choice, and the lateral aspect of the thigh is the site of choice.^{12,15} Intravenous administration necessitates electrocardiographic monitoring, and subcutaneous epinephrine takes too long to act. In addition, recent research reveals that it is grossly underused in the management of anaphylaxis.¹⁵ There is therefore the urgent need for education of both physician and patient in this regard. It has been recommended that patients with known anaphylactic reactivity should be prescribed an epinephrine auto-injector to be carried at all times for treatment of potential recurrences.¹⁴

As a resuscitative drug in cardiac arrest, the benefits and outcome with epinephrine are now being subjected to close scrutiny and there is ongoing debate concerning the optimal dose of epinephrine.¹⁶ Vasopressin seems to be more effective than epinephrine in animal studies for treatment of cardiac arrest due to resistant ventricular fibrillation; however, this is yet to be proven conclusively in clinical trials.^{17,18} A recent randomised controlled trial¹⁹ assigned adults who had had an out-of-hospital cardiac arrest to receive two injections of either 40 IU of vasopressin or 1 mg of epinephrine, followed by additional treatment with epinephrine if needed. The conclusion was that the effects of vasopressin were similar to those of epinephrine in the management of ventricular fibrillation and pulseless electrical activity, but was superior to epinephrine in patients with asystole. Vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest.¹⁹

Epinephrine has long been used as a local haemostatic agent, for example in epistaxis. Bismuth subgallate-epinephrine paste has a modest haemostatic effect in

adenotonsillectomies, in which epinephrine is probably the active ingredient.²⁰ However, proven effective variant of this use is in endoscopic management of bleeding peptic ulcer²¹⁻²³ and Mallory-Weiss syndrome.²⁴ Additional endoscopic treatment after initial epinephrine injection, for instance by thermal probe, reduces further bleeding, need for emergency surgery, and mortality in patients with bleeding peptic ulcer.

Cisplatin/epinephrine injectable gel is a preparation for intratumoural injection containing cisplatin 4 mg/mL, epinephrine 100 microgram/mL and bovine collagen as a protein carrier matrix. It has been evaluated for the palliative treatment of accessible inoperable metastatic or recurrent solid tumours. The vasoconstrictor action of epinephrine limits the diffusion of cisplatin into the systemic circulation. Intratumoural injection of cisplatin/epinephrine injectable gel achieves high concentrations of cisplatin in the tumour with very low concentrations in plasma and other tissues. In double-blind randomised trials, cisplatin/epinephrine injectable gel has been more effective than placebo in the palliative treatment of recurrent and resistant head and neck squamous cell carcinoma.²⁵⁻²⁶ It has also shown palliative benefits in metastatic breast cancer, metastatic malignant melanoma, oesophageal carcinoma and hepatic tumours in a number of noncomparative clinical trials.²⁷ Adverse events with the use of this preparation are mainly limited to the local site of injection. No systemic adverse events, such as nephrotoxicity, neurotoxicity or ototoxicity, have been reported.

Other situations in which epinephrine has been used without conclusive evidence of its benefit so far include:

- As a bronchodilator in acute bronchiolitis in infants.^{28,29} Epinephrine may be favourable compared to placebo and salbutamol for short-term benefits among outpatients. There is insufficient evidence to support the use of epinephrine among inpatients.
- Nebulized racemic epinephrine for facilitating extubation of newborn infants following a period of mechanical ventilation, especially after prolonged, traumatic or multiple intubations.³⁰
- Parenteral epinephrine for the resuscitation of apparently stillborn or extremely bradycardic newborn infants.³¹
- Epinephrine infusion for inotropic support in preterm infants with clinical cardiovascular compromise.³²

Recommendation

There is currently no alternative to epinephrine as a vasoconstrictor adjunct to local anaesthesia, in terms of both efficacy and cost. It can be life saving in anaphylaxis, acute angioedema and cardiac arrest. Epinephrine (adrenaline) should be retained in the WHO List of Essential Medicines.

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2.11 Atropine sulfate (subsection 1.3)

Introduction

Atropine is a non-selective competitive antagonist of acetylcholine at muscarinic cholinergic receptors. In anaesthetic practice, atropine is used to inhibit excessive salivation and respiratory secretions, to prevent arrhythmias resulting from vagal stimulation and to counteract muscarinic effects during anticholinesterase reversal of peripheral neuromuscular blockade. Atropine injection is listed in the WHO Model Formulary 2004¹ in the section on preanaesthetic medication. There are other uses for the antimuscarinic property of atropine, notably in ophthalmic practice as a mydriatic-cyclopegic agent, and in the treatment of poisoning by organophosphorus insecticides and other acetylcholinesterase inhibitors. The local use of atropine is not considered here.

The natural alkaloid scopolamine and the synthetic compound glycopyrrolate, both non-selective antimuscarinic drugs, are the other agents in this category currently used in anaesthetic practice. They are not listed in the 2004 WHO Model Formulary.

The product²

Atropine, as atropine sulfate, is supplied as sterile solution for injection. Ampoules commonly contain 600 microgram/mL in 1 mL for intravenous, intramuscular or subcutaneous use. Other strengths (e.g. 50, 100, 300, 400, 500 or 1000 microgram/mL) may also be available. In some markets, pre-filled syringe preparations are available for use in cardiopulmonary resuscitation and to counteract bradycardia following myocardial infarction.

Atropine may also be available in tablet form, containing 400 or 600 microgram of atropine sulfate per tablet.

All preparations of atropine should be protected from light. Tablets should be stored in airtight containers.

Atropine is available in some countries in fixed dose combination products e.g. with diphenoxylate hydrochloride in tablet form (Lomotil), with morphine in injection form, and with hyoscine and various other agents for oral use as intestinal antispasmodic.

Dosage²

Anaesthetic premedication, by intramuscular injection 30 - 60 minutes before induction, ADULT and CHILD 20 microgram/kg; by intravenous injection immediately before induction, ADULT up to 500 microgram maximum; by mouth 2 hours before induction, CHILD 20 microgram/kg.

Inhibition of bradycardia in perianaesthetic period, by intravenous injection, ADULT 400 - 1000 microgram, CHILD 10 - 30 microgram/kg.

Reversal of depolarising neuromuscular block, by intravenous injection 2 - 3 minutes before anticholinesterase, ADULT 600 - 1200 microgram, CHILD 20 microgram/kg

Treatment of organophosphorus, nerve gas, mushroom or other poisonings where acetylcholinesterase is inhibited, ADULT initially 2 mg and CHILD 20 microgram/kg

by intravenous or intramuscular injection, and then repeated as often as every 5 - 10 minutes till muscarinic effects of toxicity resolve and tachycardia develops with the skin dry and flushed (resolution of miosis may be delayed and it should not be used as an index to adequate atropinisation). Doses in excess of 100 mg may be required in the first 24 hours and smaller oral doses should be continued thereafter to prevent reappearance of symptoms until full recovery occurs.

To counteract bradycardia (e.g. following myocardial infarction, particularly if hypotension also present) by intravenous injection ADULT 300 - 1200 microgram, repeated if necessary up to maximum 3000 microgram.

In advanced cardiac life support (cardiopulmonary resuscitation), if spontaneous circulation fails to return after epinephrine injection, by intravenous route 3000 microgram or doses as per accepted advanced cardiac life support algorithms.

No particular problems are associated with use of atropine in neonates, children, pregnant and breast-feeding women if dosage recommendations are followed. The elderly are particularly at risk from the adverse central nervous system (CNS) and anticholinergic effects, including constipation, paralytic ileus, retention of urine and precipitation of acute glaucoma.

Adverse drug reactions

- Anticholinergic effects of dry mouth, thirst and blurring of vision are common above 1 mg and are dose-dependent. Constipation, paralytic ileus, retention of urine and precipitation of acute glaucoma may occur readily in the predisposed.
- CNS effects like confusion, drowsiness, restlessness, ataxia, hallucinations, delirium, convulsions, along with hot dry flushed skin, blurred vision, photophobia and disturbed speech can occur with large or cumulative doses.
- Heat prostration and convulsions in febrile children.
- Cardiac toxicity can be life-threatening. In addition to tachycardia, there may be atrial arrhythmias, atrioventricular dissociation and ventricular ectopics. Thus inappropriate dosing in the setting of myocardial infarction may further compromise the myocardial ischaemia.
- Drying and inspissation of bronchial secretions may lead to worsening of chronic lung diseases in case of continued use of atropine.
- Reduction of lower oesophageal sphincter tone and delayed gastric emptying may worsen symptoms of gastro-oesophageal reflux disease.

Acute overdose of atropine can be fatal though deaths have been rarely reported.

Contraindications

- Unstable cardiac rhythm e.g. sick sinus syndrome.
- Tachycardias (e.g. thyrotoxicosis, heart failure with tachycardia) and tachyarrhythmias.
- Chronic lung disease.
- Gastro-oesophageal reflux disease.
- Glaucoma.
- Prostatic enlargement.
- Severe constipation.
- The elderly (who are often predisposed to some of the above problems).

Evidence of value

In anaesthetic practice atropine is used primarily for three indications:

- As anaesthetic premedication for inhibition of secretions.
- As anaesthetic premedication for inhibition of vagal cardiac reflexes.
- During reversal of depolarising neuromuscular blockade to counteract the muscarinic effects of the anticholinesterase.

Atropine can reduce salivary and tracheobronchial secretions that tend to be induced by irritant inhalational anaesthetics like ether. The action is less potent than scopolamine and glycopyrrolate but is also less prolonged. The need for atropine has declined in recent times because the newer inhalational anaesthetics are less irritant and use of non-inhalational anaesthetics is increasing. However, atropine can still be of particular value in children in whom salivation is often more profuse and airway complications are more likely.³ It may also be valuable in dental surgery where excessive salivation can hamper clear access to the operative field.⁴

Atropine is also the traditional premedicant for the prevention of vagal reflex bradycardia that may occur during procedures like laryngoscopy, tracheal intubation, intra-abdominal manipulation, and in preventing the oculocardiac reflex during ophthalmic surgery. The last is particularly important during ocular surgery in children. Although the incidence of bradycardia is effectively reduced, there may be no reduction in the overall incidence of ventricular arrhythmias that may occur during halothane use.⁵

Both intravenous and intramuscular atropine can counteract the bradycardia during spinal anaesthesia, although the intravenous route is more effective.⁶

The use of suxamethonium can be associated with profound sinus bradycardia in children, particularly infants. Nodal rhythm and ventricular ectopics may occur. Dysrhythmias appear to occur only with intravenous, rather than intramuscular dosing, and atropine has protective effect. However, the routine use of atropine in older children has been questioned and the use before a single dose of suxamethonium in children deserves to be reconsidered.^{7,8}

Atropine premedication has been used prior to bronchoscopy, with the rationale that it will dry secretions, allow a better view of the bronchial tree, counteract vasovagal episodes and protect against bronchospasm. However, controlled studies have failed to reveal substantial benefits.^{9,10}

Intramuscular meperidine (pethidine), promethazine, and chlorpromazine combinations have been traditionally used for conscious sedation in children undergoing repair of lacerations and other emergency department procedures. However, newer agents like intramuscular ketamine may be superior in this regard.¹¹ Atropine is given along with the ketamine to reduce salivation. Interestingly, atropine has been reported to prevent midazolam-induced core hypothermia in elderly patients.¹²

Atropine is the drug of choice to prevent or counteract bradycardia and hypotension that may occur as a result of vagal stimulation associated with a hyperactive carotid sinus reflex (vasovagal syndrome) or during invasive cardiac investigations. It is also used in second degree atrioventricular block following myocardial infarction. With careful use, the block may improve without dangerous tachyarrhythmias developing. Atropine is also included in advanced cardiac life support algorithms as mentioned above.

Dobutamine-atropine stress echocardiography is an established test for the diagnosis and risk stratification of patients with coronary artery disease. The use of atropine permits attainment of target heart rate earlier and shortens test time.^{13,14}

Atropine can be life saving in cases of poisoning by organophosphorus insecticides, nerve gases and other agents that have acetylcholinesterase inhibiting activity. As mentioned earlier, very large initial parenteral doses are required, followed by prolonged oral dosing till full recovery. Along with atropine, the timely use of oximes (e.g. pralidoxime) as cholinesterase reactivators and anticonvulsants (e.g. diazepam) improves prognosis.²

Atropine can also be useful in counteracting the muscarinic side effects of anticholinesterases used in the treatment of myasthenia gravis.²

Atropine has been used by inhalational route for the treatment of acute asthma and by oral route in chronic asthma. The benefits are questionable and atropine cannot be recommended as antiasthmatic drug.¹⁵

Recommendation

Atropine is a relatively inexpensive traditional drug used in anaesthetic practice for its antimuscarinic action. Its importance as a premedication agent has declined with increasing use of non-irritant inhalational and non-inhalational agents. Nevertheless, there are many situations, particularly in children, where use of atropine would be required, and in some of its non-anaesthetic uses too atropine continues to be indispensable. Atropine should be retained on the WHO List of Essential Medicines.

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2.12 Diazepam (subsection 1.3)

Introduction

Diazepam is the prototype benzodiazepine that is very widely used for its anxiolytic, sedative, hypnotic, amnesic, anticonvulsant and myorelaxant properties. It is listed in the 2004 WHO Model Formulary in the section on pre-anaesthetic medication and sedatives.¹ Among the benzodiazepines, diazepam has a relatively long duration of action. Midazolam, the short-acting benzodiazepine that is increasingly being used in anaesthetic practice, is currently not listed.

Owing to its dependence potential and abuse liability, diazepam, like other benzodiazepines, is subject to international control under the Convention on Psychotropic Substances (1971).

The product^{1,2}

Diazepam is available, in the following dosage forms:

- As tablets, containing 2, 5, or 10 mg of diazepam.
- As oral solution (syrup), containing 2 mg per 5 mL.
- As rectal suppositories, containing 10 mg.
- As rectal solution, containing 2 mg/mL or 4 mg/mL diazepam in 2.5 mL rectal squeeze tubes.
- As injection, containing sterile diazepam solution or emulsion 5 mg/mL in 2 mL ampoules or 10 mL vials. The injection is intended for intramuscular or slow intravenous use. Because of the non-aqueous nature of the solvent, diazepam injection should not normally be diluted, except when given slowly in large volume intravenous infusion of 5% or 10% dextrose or normal saline (for instance in the treatment of tetanus or status epilepticus). Not more than 20 mg should be added to not less than 250 mL of the infusion fluid. The drug may be adsorbed by plastic infusion equipment.

Preparations may be stored at room temperature but should be protected from light. Injections should not be frozen.

Diazepam may also be available in fixed dose combination with various drugs such as imipramine, dicyclomine, metoclopramide, conjugated oestrogens, and others. The composition of many such products is of dubious value.

Dosage

Premedication, by mouth 1 - 2 hours before induction of anaesthesia or before procedure, ADULT and CHILD over 12 years, 5 - 10 mg; CHILD up to 12 years 100 - 200 microgram/kg.

Sedation, by slow intravenous injection immediately before procedure, ADULT and CHILD over 12 years, 100 - 300 microgram/kg.

Absorption following intramuscular injection is slow and erratic; this route should only be used if oral or intravenous administration is not possible. Intravenous injection must be slow and into a large vein to reduce the risk of thrombophlebitis. For intravenous use, resuscitation equipment should be at hand. Patients must be

warned not to perform skilled tasks, for example drive or operate moving machinery, for 24 hours.

Diazepam may be administered by oral, intramuscular and intravenous routes in children at doses proportionate to their body weight. Intravenous administration requires special attention to ensure that the airway is clear.

Elderly individuals are at greater risk of the central nervous system (CNS) depressant and adverse behavioural effects of benzodiazepines. Dosing must be done carefully and limited to the minimum effective quantities.

Benzodiazepines should not be used during pregnancy and lactation in general. Concerns have been raised over possibility of foetal malformations but the teratogenic risk is uncertain.^{3,4} In most studies involving first trimester use of benzodiazepines, the majority of infants were normal at birth and had normal postnatal development. Late third trimester use and exposure during labour seems to be associated with much greater risks to the neonate. Some infants exposed at this time, exhibit either the floppy infant syndrome, or marked neonatal withdrawal symptoms. Symptoms vary from mild sedation, hypotonia, and reluctance to suck, to apnoeic spells, cyanosis, and impaired metabolic responses to cold stress. These symptoms reportedly persist for hours to months after birth.

Occasional or short-term treatment with benzodiazepines could be considered as compatible with breastfeeding, although maternal diazepam treatment has caused sedation in suckling infants even after short-term use.⁵ Continued use can cause lethargy, sedation, and weight loss in infants.⁴

Diazepam, like other benzodiazepines, should be used very carefully in depressed, psychiatric and emotionally labile patients. Depressed patients with suicidal ideation are especially at risk. Psychotic patients may show paradoxical reactions and it may be prudent to avoid diazepam in ambulatory subjects showing psychotic tendencies. Risk of abuse is greater in emotionally and psychologically disturbed patients.

Adverse drug reactions

- CNS effects are common and dose-dependent, and include drowsiness, somnolence and fatigue. Confusion, dizziness, vertigo, and ataxia may occur, particularly in the elderly or severely ill patients. This increases the risk of hip fractures in the elderly.⁶
- Occasional paradoxical reactions, including irritability, excitability, hallucinations, sleep disturbances and increased muscle tone have been reported.
- Behavioural effects. These can be easily overlooked, particularly in individuals with pre-existing psychiatric illnesses or in those with mental retardation.⁷
- Impairment of cognitive performance and skilled psychomotor tasks.⁸
- Bradycardia and hypotension.
- Rapid intravenous administration can cause potentially fatal respiratory or cardiac arrest.
- Dependence and abuse liability.⁹ Both psychological and physical dependence have been widely reported as also have rebound phenomenon after repeated or prolonged use. The withdrawal syndrome manifests with anxiety, insomnia, trembling, anorexia and dizziness. To be successful, a withdrawal strategy should combine gradual dosage reduction and psychological support.^{10,11}
- Rare adverse events include hypersensitivity, exfoliative dermatitis, exacerbation of seizures in epileptic patients on withdrawal, and hepatotoxicity.

- Intramuscular injection can be painful. Local irritation and thrombophlebitis may occur upon intravenous use. Small peripheral veins should not be used and care must be taken to avoid extravasation and inadvertent intra-arterial administration.

Contraindications

- Coma, stupor or CNS depression.
- Shock or profound hypotension.
- Respiratory depression, chronic pulmonary insufficiency or sleep apnoea.
- Myasthenia gravis or other neuromuscular disorders that can cause muscle weakness.
- Patients requiring to drive, operate moving machinery or perform skilled psychomotor tasks.
- Infants below 6 months age, particularly preterm infants.
- Pregnancy.
- Breast-feeding.
- Subjects dependent on alcohol or other sedative-hypnotic drugs.

Evidence of value

Premedication

Diazepam is widely used as premedicant prior to a variety of surgical and other interventional procedures. A recent meta-analysis has shown that, in adult day case surgery, diazepam premedication, although impairing psychomotor performance in the postoperative period, does not delay discharge.¹² Oral diazepam has compared well with oral midazolam as sedative premedication for paediatric gastrointestinal endoscopy procedures, with diazepam being cheaper.¹³ The same applies to gastrointestinal endoscopy in adults.¹⁴ However diazepam is not routinely recommended prior to bronchoscopy because of concerns over respiratory safety.² It has been successfully used as intravenous sedative prior to physician-led direct current cardioversion and here again compares well with midazolam.¹⁵

Interestingly, low doses of diazepam (e.g. 100 microgram/kg orally) can reduce the incidence and severity of emergence reactions associated with ketamine anaesthesia.^{16,17}

Sedation and hypnosis

Diazepam has been a traditionally used sedative-hypnotic drug that has had a profound effect on the treatment of insomnia and the management of agitated psychiatric patients. The risk of use beyond the short-term in community dwelling patients is well-known.¹⁸ Many alternative benzodiazepines and benzodiazepine-like drugs have been introduced. Yet diazepam, being cheap and most widely available, continues to be used and abused.

The abuse liability becomes less important in institutionalised settings. Benzodiazepines are among the most widely used drugs in intensive care units.¹⁹ Prolonged continuous infusion is not desirable because of the risk of over-sedation and respiratory depression. However, otherwise they are acceptably safe under supervision. Since benzodiazepines are not analgesics, the combined use of an opioid and a benzodiazepine is often necessary. Many different benzodiazepines are available, but the agents most commonly used in the critically ill are diazepam, lorazepam and midazolam.²⁰

Diazepam has proven useful in postoperative acute agitation and in psychiatric cases. In postoperative states, benzodiazepines have to be used with adequate analgesia.²¹ In psychiatric emergency care, antipsychotic medication is particularly indicated for the treatment of schizophrenia, mania, drug-induced psychoses and delirium whereas benzodiazepines are favourable for the treatment of acute anxiety, restlessness and agitation due to neurotic or reactive circumstances.²²

Acute alcohol withdrawal may result in nausea, vomiting, diarrhoea, weakness, sweating, tremors, tachycardia, hypertension, agitation, delirium, hallucinations, seizures, and, even, death in alcoholics. Benzodiazepines are cross-tolerant with ethanol and are considered first-line therapy for treating alcohol withdrawal syndrome.²³ Patients with significant symptoms, patients with complications such as seizures or delirium tremens, or patients at higher risk for complications of alcohol withdrawal should receive benzodiazepines. Diazepam is effective in preventing and treating the serious complications of alcohol withdrawal.²⁴

Anticonvulsant

Diazepam is widely used for the management of acute convulsions including refractory status epilepticus in adults and children.^{25,26} It has even been used safely in out-of-hospital emergency management by paramedical personnel.^{27,28} However, it may be less effective than midazolam in refractory generalised tonic-clonic seizures in children.^{29,30} Also, unlike midazolam, diazepam will not be effective by the intramuscular route.³¹ Nevertheless, diazepam can still be regarded as a first choice drug for treating acute tonic-clonic convulsions and convulsive status epilepticus in children.³²

Diazepam has been used by the rectal route in convulsive disorders in children, including status epilepticus.³³ A rectal gel formulation has also been investigated in adults and found to be satisfactory.³⁴ The gel formulation has advantages over intravenous diazepam administration, notably a very low incidence of respiratory depression, low potential for abuse and the opportunity for out-of-hospital use by non-professional caregivers. Studies have shown that rectal diazepam used in such settings can reduce the number of emergency room visits, costs associated with emergency care and stress on the patient and family. Also overdose of the rectal gel has less serious consequences.³⁵ There is some evidence that rectal lorazepam can be a better alternative to rectal diazepam in this regard.^{28,32}

Diazepam has been used in the management of febrile convulsions in children. However, preventive treatment for recurrences has not been recommended because of the lack of documented efficacy and the risk of oversedation.³⁶

Diazepam has also been widely used for the management of eclamptic convulsions. The current consensus, however, is that magnesium sulphate is substantially more effective than diazepam and therefore should be the treatment of choice for eclampsia.³⁷

Other situations where diazepam has been used as anticonvulsant include falciparum malaria³⁸ and tetanus.^{39,40} It has been estimated that about a third of acute seizures in children with cerebral malaria, do not manifest as convulsions, but as changes in eye deviation and salivation. Whatever the manifestation, prolonged convulsions are associated with neurological deficits in survivors. Initial management should include putting the child in the recovery position, checking the blood glucose and administering oxygen if hypoxic. Diazepam is then used to control the convulsive episode. In tetanus, preliminary evidence is available but more studies are needed to make firm recommendations.⁴¹

Muscle relaxation

Diazepam is effective in decreasing excessive muscle tone in patients with multiple sclerosis, cerebrovascular lesions, or other types of spasticity.⁴² The action is centrally mediated. Unlike botulinum toxin and intrathecal baclofen, diazepam is non-invasive, and also more economical.⁴³ Oral diazepam is as effective as oral baclofen but carries a greater risk of causing drowsiness.⁴⁴ The other effective oral agent, tizanidine, affects the muscle strength less and its tolerability is possibly better than diazepam.⁴⁵

Diazepam has also been used in spasticity associated with spinal cord injury. However, the documented evidence so far does not suggest a clinically useful effect.⁴⁶

Other indications for which diazepam has been studied include:

- Adjunctive management of convulsant poisonings. In organophosphorus pesticide toxicity diazepam reduces the incidence and severity of convulsions and can also have a beneficial effect on the muscle fasciculations, that can be otherwise quite unpleasant.⁴⁷
- Drug-induced delirium. Diazepam, lorazepam and midazolam are the first choice benzodiazepines in managing iatrogenic delirium. Use in such cases should not be routine but when indicated by aggression, risk of harm to self or others, hallucinations, excessive distress, and where compliance with therapy or procedures is essential.⁴⁸
- Focal dystonias. Diazepam can be an alternative to high dose oral anticholinergics and locally infiltrated botulinum toxin. It may also be used in conjunction.⁴⁹
- Acute vertigo. Parenteral diazepam has been tried in terminating attacks of acute vertigo, occurring spontaneously or as a manifestation of disorders like Meniere's disease.⁵⁰
- Smoking cessation. The evidence currently is incomplete and does not suggest a role for anxiolytics in helping smokers to quit and abstain.⁵¹
- Tardive dyskinesias associated with prolonged use of neuroleptic medication. Diazepam is ineffective.⁵²

Recommendation

Diazepam is a widely used benzodiazepine with a broad spectrum of application in all age groups. It is listed in the 2004 WHO model formulary, as a representative benzodiazepine. Lorazepam and midazolam can serve as alternatives to diazepam for its anxiolytic, sedative-hypnotic and premedicant uses. However, the cost advantage still rests with diazepam, which should be retained in the WHO Model List of Essential Medicines

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2.13 Promethazine hydrochloride (subsection 1.3)

Introduction

Promethazine is a selective competitive H₁-receptor antagonist drug with sedative property. Chemically it is a phenothiazine. In addition to its H₁-antihistaminic property, promethazine is also antiemetic, antimuscarinic, local anaesthetic and antitussive, as well as being a weak α -adrenoceptor antagonist. Its sedative, antisialagogue and antiemetic effects are utilised in anaesthetic practice. It is the only antihistamine listed in the preoperative medication section of the 2004 WHO Model Formulary.¹ Chlorphenamine (chlorpheniramine) maleate is another sedative antihistamine listed in the antiallergic section. However, this is seldom used in anaesthetic practice.

The product²

Promethazine is available, as promethazine hydrochloride, in the following dosage forms:

- As tablets, containing 10, 12.5, 25 or 50 mg promethazine hydrochloride.
- As oral solution (elixir or syrup), containing 5, 6.25 or 25 mg promethazine hydrochloride per 5 mL.
- As rectal suppositories, containing 12.5, 25 or 50 mg promethazine hydrochloride.
- As injection, containing clear colourless sterile promethazine hydrochloride solution 25 mg/mL in 1 mL or 2 mL ampoules. Strength of 50 mg/mL is also available in 1 mL ampoules or prefilled cartridges. The injection is intended primarily for intramuscular use. For intravenous use, the concentration of 25 mg/mL may be given via a running infusion or the injection may be diluted to 2.5 mg/mL with sterile water for injection and given slowly. Injectable solutions may contain sodium metabisulfite as excipient.

Promethazine preparations should be protected from light. Tablets should be stored in airtight containers. Suppositories should be stored at 2 - 8 °C.

Promethazine hydrochloride is also a constituent of various cough, cold, decongestant and antiallergic preparations for symptomatic use. The composition of many such products is of dubious value. It has also been marketed in topical formulations for symptomatic treatment of cutaneous allergy. Promethazine theoclate is available in tablet form, primarily for use as antiemetic.

Dosage^{2,3}

For anaesthesia premedication, by mouth 1 hour before surgery, CHILD over 1 year 0.5 - 1 mg/kg; by deep intramuscular injection 1 hour before surgery, ADULT 25 mg.

As adjunct to epinephrine in acute anaphylaxis, by slow intravenous injection (observing precautions as mentioned above) 25 - 50 mg; maximum 100 mg. In other acute allergic reactions it may be given in similar doses by deep intramuscular injection.

For symptomatic treatment in other allergic or non-allergic pruritic conditions, by mouth, ADULT 25 - 50 mg daily in 1 - 2 divided doses; CHILD of age 2 - 5 years 5 -

15 mg daily in 1 - 2 divided doses and age 6 - 10 years 10 - 25 mg daily in 1 - 2 divided doses.

As sedative-hypnotic, by mouth at bedtime, ADULT 25 - 50 mg; CHILD of age 2 - 5 years up to 15 mg and 6 - 10 years up to 25 mg.

Promethazine is not recommended for use in neonates, infants and children below 2 years of age because, being poorly metabolised in this age group, there is greater risk of profound central nervous system (CNS) and respiratory depression. An association with sleep apnoea and sudden infant death syndrome has also been reported.^{4,5} Although most manufacturers recommend that promethazine should not be used in pregnancy, it has been extensively used as antiemetic in obstetric practice without reports of teratogenicity or other problems. Cautious use must be made in the elderly as they are likely to be predisposed to the anticholinergic adverse effects.

Adverse drug reactions²

- Sedation is the principal dose-limiting adverse effect of promethazine. The CNS depression is dose-dependent and ranges from mild drowsiness to deep sleep. Psychomotor performance is definitely impaired.⁶ A feeling of fatigue is common. On occasions there may be confusion, incoordination and, rarely, psychotic behaviour. Co-administration of promethazine with alcohol or other CNS depressant drugs can be dangerous.
- Paradoxical CNS excitation, manifesting as nervousness, insomnia and hallucinations has been reported and is more likely in children.
- Anticholinergic effects include dry mouth, blurring of vision, constipation, retention of urine and precipitation of acute glaucoma.
- Use during labour can impair platelet aggregation in the newborn and predispose to bleeding.
- Rapid intravenous administration can cause symptomatic hypotension.
- Inadvertent subcutaneous injection or extravasation of promethazine injection can cause severe tissue irritation leading to necrosis and ulceration. Intra-arterial administration can cause severe arterial spasm and even gangrene.
- Other uncommon or rarely reported adverse effects include extrapyramidal reactions (on parenteral use), reversible bone marrow depression, seizures, obstructive jaundice and hepatotoxicity. Topical formulations can cause dermal sensitisation with risk of subsequent acute allergic reactions.

Contraindications

- Hypersensitivity to phenothiazines.
- Respiratory depression.
- Patients requiring to drive, operate moving machinery or perform skilled psychomotor tasks.
- Predisposition to anticholinergic effects e.g. constipation, prostatic enlargement, glaucoma.
- Epilepsy.
- Severe liver disease.
- Concomitant use of alcohol and other sedative-hypnotic drugs.

Evidence of value

The sedative, antisalivation and antiemetic effects of promethazine make it useful as preanaesthetic medication. It has been used in a variety of operative situations, including orthopaedic surgery,⁷ middle ear surgery,⁸ oocyte retrieval,⁹ and diagnostic laparoscopy.¹⁰ Reduction in the incidence and severity of postoperative nausea and vomiting is a particular advantage, although the newer serotonin receptor antagonist antiemetics (e.g. ondansetron, granisetron, tropisetron, dolasetron) are better in the sense that they lack the CNS depressant and anticholinergic effects of phenothiazines.¹¹ Premedication with promethazine has been used successfully to combat postoperative nausea and vomiting in orthopaedic surgery using intrathecal morphine.¹²

Promethazine has also been used in conscious sedation, for instance in paediatric dentistry.¹³ However, oral midazolam may be a better choice.¹⁴ Intramuscular meperidine (pethidine), promethazine, and chlorpromazine combination has been a traditionally used anxiolytic-sedative for children undergoing cardiac catheterisation, repair of lacerations and other emergency department procedures. Here again, newer agents like oral midazolam,¹⁵ intramuscular ketamine¹⁶ and buccal fentanyl¹⁷ may be superior in this regard. Midazolam is also superior to haloperidol-promethazine combination for rapid tranquillisation of agitated patients in psychiatric emergency situations.¹⁸

As an antiemetic, promethazine has been widely used for the prevention of nausea and vomiting associated with motion sickness, either alone or in combination with ephedrine or other agents. Indeed, both intramuscular and oral promethazine has been successful pharmacologic management strategy for motion sickness affecting space flight crews.^{19,20} It has also been a commonly used antiemetic for pregnancy nausea and vomiting.²¹ However, as a general antiemetic, prochlorperazine,²² metoclopramide or the serotonin receptor antagonists may be preferred because of their greater efficacy and less sedation.

Intravenous promethazine has been used as an adjunct to epinephrine in the management of anaphylactic shock. Oral promethazine has been widely used for symptomatic treatment of allergic disorders like hay fever, perennial allergic rhinitis, acute urticarial rashes as well as non-allergic conditions associated with histamine release, such as chronic urticaria, dermographism and itchy insect bites. Sedation is the principal dose-limiting adverse effect in such situations and the newer non-sedating antihistamines are increasingly preferred.²³

Other uses of promethazine reported in the literature include:

- As an anticholinergic medication in Parkinson's disease and in the management of drug-induced Parkinsonism. However, there are also reports of occasional dystonic reactions to promethazine.
- Combating itching associated with intrathecal use of morphine. Intramuscular promethazine has been effective.²⁴
- Combating chloroquine-induced pruritus in malaria. Oral promethazine has been used. However, oral prednisolone may give better results.²⁵
- Ambulatory treatment of acute migraine headache by intramuscular promethazine in combination with meperidine (pethidine).^{26,27}

Recommendation

Promethazine is an effective H₁ antihistamine with a well-known adverse event profile. However, a well-equipped modern day anaesthetic unit is likely to have access to drugs that can supplant promethazine for most of its pre-anaesthetic and peri-anaesthetic uses. These include the short-acting benzodiazepine, midazolam and the analgesic-anaesthetic, ketamine. However, because of its ready availability and economy in usage, its non-anaesthetic uses and its safety in children over 2 years of age, and the familiarity that prescribers will have with this product (the 'familiarity dividend'), promethazine should be retained in the WHO Model List of Essential Medicines.

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2.14 Alcuronium chloride (subsection 1.4)

Introduction

Alcuronium is a non-depolarising peripheral neuromuscular blocking agent that provides muscle relaxation during surgery. It is listed as a representative non-depolarising muscle relaxant in the 2004 WHO Model Formulary.¹

In addition to being used as an adjunct to general anaesthesia to relax skeletal muscles during surgery, alcuronium has been used to facilitate endotracheal intubation where subsequent neuromuscular blockade is required and to facilitate controlled pulmonary ventilation. Its action starts in 2 to 4 minutes after a single intravenous injection and lasts about 20 to 40 minutes.

Vecuronium is the other agent in this therapeutic category, listed as a complementary non-depolarising muscle relaxant.

The product

Alcuronium, as alcuronium dichloride, is marketed as a sterile solution for intravenous injection. The usual strength is 5 mg/mL supplied in 2 mL ampoules. The solution may be diluted with water for injection prior to use. Alcuronium should be protected from heat and light.

Dosage^{1,2}

As with all neuromuscular blockers, alcuronium should be administered only by personnel trained in their use and facilities for maintenance of an adequate airway and ventilatory support must be available.

By intravenous injection, ADULT initially 200 - 250 microgram/kg, then 30 - 50 microgram/kg as required for maintenance; CHILD initially 125 - 200 microgram/kg, then 30 - 50 microgram/kg for maintenance.

Specific data on the use of alcuronium in the elderly is not available but no particular problem is anticipated unless renal failure is present.²

Adverse drug reactions

- Histamine release, causing allergic reactions, such as wheal and flare effects at the site of injection, flushing and bronchospasm. Anaphylactoid reactions have been reported.
- Autonomic ganglion blockade; a full neuromuscular paralysing dose causes significant vagal blockade. Transient hypotension is usual. There may be significant increase in heart rate.
- Prolonged paralysis is expected in individuals with renal impairment given large or repeated doses.

Contraindications

- As with other neuromuscular blockers, respiratory insufficiency or pulmonary disease; dehydration or severe illness; myasthenia gravis or other neuromuscular disorders.

- Patients known to be hypersensitive to the drug.
- Large or repeated doses in pregnancy and renal insufficiency.

Evidence of value

Alcuronium has limited availability and there is hardly any current literature exploring the use of this drug. In 1995, it was reported to be in use in 26 countries worldwide.³ Even in countries where it is still available its use has declined with the availability of newer agents. Germany is an example.^{4,5}

Economic considerations may still prompt acceptance of alcuronium.⁶ However, it is no longer considered acceptable for rapid sequence induction.⁶ Its intermediate duration of action has also been called into question in view of its long plasma half-life and slow excretion.³ Alcuronium has been used in cardiopulmonary bypass surgery but its plasma concentration decreases with onset of the bypass.⁷

The drug offers no advantage compared to vecuronium. On the other hand, the propensity for causing adverse drug reactions typical of peripheral neuromuscular blockers, such as histamine release, autonomic blockade and adverse cardiovascular effects is greater. Although duration of satisfactory muscle relaxation for surgery is comparable to vecuronium, full recovery is slow with a relative sparing effect on respiration.

Anaphylactoid reactions have been reported with alcuronium. Although alcuronium has more potent histamine releasing action than vecuronium,⁸ the incidence of anaphylactoid or anaphylactic reactions may be comparatively less.⁹

Recommendation

In view of the limited use and drawbacks of alcuronium vis-à-vis vecuronium, it is recommended that the Committee asks for alcuronium to be deleted from the WHO Model List of Essential Medicines. Were it to be deleted, its place as a representative neuromuscular blocker should be taken by vecuronium.

If retained, errors in the dosing section of the 2004 WHO Model Formulary (mg/kg to be replaced by microgram/kg) need correction (N.B. from WHO Secretariat: this has been noted and measured taken to correct it.) .

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2.15 Vecuronium bromide (subsection 1.4)

Introduction

Vecuronium is a non-depolarising peripheral neuromuscular blocking agent used for obtaining muscle relaxation during surgery. It is listed as a complementary non-depolarising muscle relaxant in the 2004 WHO Model Formulary.¹

Alcuronium is the other agent in this therapeutic category.

Vecuronium is a potent competitive neuromuscular blocker with a high degree of selectivity for the nicotinic cholinergic receptors at the myoneural junction. Following a single intravenous injection, action starts in about 1.5 to 2 minutes and lasts for about 30 min. It causes little or no histamine release, ganglion blockade or unwanted cardiovascular effects. Spontaneous recovery from vecuronium blockade is predictable and rapid. Placental transfer is limited. These properties make vecuronium a versatile muscle relaxant for surgery, including caesarean section. It has also been used to facilitate pulmonary ventilation in the intensive care unit.

The product²

Vecuronium, as vecuronium bromide, is marketed in the form of sterile lyophilised powder to be reconstituted prior to administration, with the diluent supplied by the manufacturer or with sterile water for injection. The reconstituted solution is administered by the intravenous route, either as such, or as an infusion after further dilution with a compatible intravenous fluid (e.g. 5% dextrose, 0.9% sodium chloride, lactated Ringer's solution).

Vials are available in different strengths. They should be protected from heat and light. Reconstituted solutions and dilutions are stable for 24 hours at room temperature.

*Dosage*¹⁻³

As with all neuromuscular blockers, vecuronium should be administered only by personnel trained in their use and facilities for maintenance of an adequate airway and ventilatory support must be available. Compared to adults, the duration of effect is less in children but more in neonates and infants who are more sensitive to vecuronium's effects. The action may be intensified and its duration prolonged to some extent when used in the presence of potent inhalational anaesthetic agents, including halothane and isoflurane.

Intubation, by intravenous injection, ADULT and CHILD over 5 months, 80 - 100 microgram/kg, reduced for maintenance to 20 - 30 microgram/kg or lower; CHILD under 5 months, initially 10 - 20 microgram/kg as test dose, followed by increments according to response.

By intravenous infusion, ADULT, initial bolus 40 - 100 microgram/kg, then 0.8-1.4 microgram/kg/minute

Adverse drug reactions

- Bradycardia. Especially with concurrent use of opioids or halothane. May be more pronounced in patients receiving beta-adrenergic antagonists. Anticholinergic premedication reduces risk.
- Respiratory paralysis. If apnoea develops, artificial ventilation should be continued till spontaneous recovery occurs.
- Hypersensitivity reactions, including urticaria and bronchospasm. These are uncommon but have been reported.

Contraindications and special precautions

Apart from a history of severe allergic reactions to vecuronium, there are no absolute contraindications to the use of this drug. Extra caution is necessary in the following situations as the recovery time may be prolonged:

- Neonates and infants. Both pharmacokinetic and pharmacodynamic factors prolong the effect. Vecuronium behaves as a long-acting agent in this age group and therefore dose requirements are reduced.⁴
- Elderly. Pharmacokinetic factors may lead to a longer onset and recovery time compared to young adults. Moreover there may be significant variability in offset time.⁵
- Pregnant women.
- Respiratory insufficiency or pulmonary disease. Duration and recovery times of vecuronium are prolonged in respiratory acidosis and shortened in respiratory alkalosis.⁶ Care is needed in bronchial asthma because of the small risk of bronchospasm.
- Dehydration or severe illness.
- Neuromuscular disorders e.g. myasthenia gravis, poliomyelitis, myopathies, muscular dystrophies.
- Patients known to be hypersensitive to the drug.
- Renal failure. Ideally the neuromuscular blockade should be monitored.⁷
- Severe hepatic disease. In cirrhotic patients, however, onset time may be slower but recovery more rapid.

Evidence of value

The clinical efficacy of vecuronium is well established. It can be used safely in all age groups and various situations. It has been used safely in intracranial aneurysm clipping surgery. Unlike atracurium, there is no penetration into the cerebrospinal fluid and central nervous system effects are therefore unlikely.

In intensive care, vecuronium intravenous infusion provides a very convenient method of muscle relaxation. The short duration of action, lack of accumulation, virtual absence of histamine release and cardiovascular stability are great advantages in this situation. Intensive care patients are frequently in haemodynamic instability, and for them vecuronium can be a muscle relaxant of choice.²

Vecuronium is being compared with the relatively newer depolarising neuromuscular blockers in various studies. It has compared well with atracurium in laparatomies.⁹ In patients undergoing coronary artery surgery, rocuronium may be a better agent than vecuronium in terms of lower requirement for vasopressors, faster onset of neuromuscular blockade, and better conditions for mask ventilation and tracheal intubation.¹⁰

Neuromuscular blockers are prone to potentially significant drug-drug interactions. Sevoflurane anaesthesia can potentiate (accelerate onset and prolong duration of) vecuronium blockade.¹¹⁻¹² The propensity for interaction with gentamicin is minimal at the usual doses of this antibiotic.¹³ In the context of use of suxamethonium, rocuronium pretreatment has been found to be more effective in reducing fasciculations than vecuronium pretreatment, but both have been equally effective in preventing postoperative myalgia.¹⁴

Rapid sequence induction of anaesthesia and intubation is required in patients with 'full stomach' to avoid regurgitation and aspiration. Suxamethonium, rocuronium, rapacuronium, and vecuronium are currently the neuromuscular blocking agents being used in children who require rapid sequence induction in emergency settings. Suxamethonium is the only agent with rapid onset and ultra-short duration of action; however, it has many adverse drug reactions, including some that are potentially fatal. Rocuronium has a good safety profile and a rapid onset of action similar to suxamethonium. Despite a longer duration of action, it is the preferred agent for rapid sequence induction in children in many units. For those units that do not have access to rocuronium, vecuronium is frequently the alternative used.¹⁵ It has longer onset of action and recovery, but its side effects are minimal when compared to suxamethonium.

Various treatment protocols have been tried in managing diverse manifestations of severe tetanus. High dose diazepam and vecuronium with mechanical ventilation has been used successfully in the control of spasms in neonatal tetanus.¹⁶ However, more studies are needed in this situation.

Recommendation

Among the non-depolarising neuromuscular blocking agents with rapid onset and intermediate duration of action, vecuronium is relatively inexpensive and has a safe and predictable course of action. It should be retained in the WHO Model List of Essential Medicines and should be listed as the representative drug in its class, replacing alcuronium.

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2.16 Atracurium besilate

Introduction

Atracurium is a non-depolarising peripheral neuromuscular blocking agent indicated for obtaining muscle relaxation during surgery, facilitating endotracheal intubation and, in intensive care units, facilitating controlled pulmonary ventilation. It is not listed in the 2004 WHO Model Formulary.¹ Alcuronium and vecuronium are the listed agents in this category.

Atracurium has the unique property of spontaneous and extensive degradation. It is also subject to degradation by non-specific plasma esterases unrelated to cholinesterase.² Clearance of atracurium is thus unaffected by hepatic and renal function. Following a single intravenous injection the onset of action is in 2 to 2.5 minutes and full spontaneous recovery occurs in 35 minutes.

The product^{3,4}

Atracurium, as atracurium besilate, is marketed in the form of a sterile clear aqueous solution intended for intravenous injection or infusion in compatible intravenous fluids (usually 5% dextrose, 0.9% sodium chloride and Ringer's solution). The usual strength is 10 mg/mL. Ampoules and vials of different capacities are marketed; 2.5 mL and 5 mL are convenient. The marketed product is a mixture of 10 optical and geometric isomers.

Preparations must be stored at 2 - 8 °C, but not frozen. Once removed from refrigeration, the manufacturer's recommendations regarding shelf-life must be followed.

Dosage³

As with all neuromuscular blockers, atracurium should be administered only by personnel trained in their use and facilities for maintenance of an adequate airway and ventilatory support must be available. Duration of neuromuscular blockade may be prolonged in the elderly because of a longer elimination half-life. The dose requirements in children over 1 month age are essentially similar to that for adults on body weight basis and no special precautions are required. Neonates may be more sensitive to atracurium with greater patient to patient variability.

By intravenous injection, ADULT and CHILD 0.3 - 0.6 mg/kg; endotracheal intubation can be done within 1.5 minutes of a 0.5 - 0.6 mg/kg dose. Supplementary doses of 0.1 - 0.2 mg/kg may be used to prolong blockade as necessary.

By intravenous infusion, to maintain muscle relaxation during long surgical procedures, ADULT and CHILD 0.2 to 0.6 mg/kg/hour following an initial intravenous bolus dose of 0.3 to 0.6 mg/kg.

In cardiopulmonary bypass surgery, with induced hypothermia to 25 - 26 °C, full neuromuscular blockade with atracurium has been maintained at infusion rates approximately half of those required under normothermic condition.⁵

Adverse drug reactions

- Histamine releasing activity is present, manifest as local cutaneous reactions, bronchospasm and flushing. These changes are more likely if large doses are administered rapidly and may be blocked by premedication with H₁ plus H₂ antihistamines.⁶ Potentially life-threatening anaphylactic or anaphylactoid reactions have been reported with atracurium though there is no evidence that the risk is greater than with other neuromuscular blockers.
- Hypotension and alteration of heart rate have been occasionally reported with atracurium. These effects are transient and the hypotension may be related to the histamine releasing activity.
- Cerebrospinal fluid penetration has been reported,⁷ though the clinical significance of this is unknown.

*Contraindications*³

The following are relative contraindications to use of atracurium

- Respiratory insufficiency or pulmonary disease.
- Dehydrated or severely ill patients.
- Myasthenia gravis or other neuromuscular disorders.
- Severe electrolyte imbalance.
- Cardiovascular disease predisposing the patient to hypotension.
- History of allergic reactions to prior use of atracurium.

Evidence of value

The prime advantage of atracurium is the ability to use it in the presence of hepatic or renal insufficiency without risking prolongation of the blockade. Indeed, randomised controlled trials in renal failure have reported predictable action in terms of onset and duration.⁸ Consistency of recovery after repeated supplemental doses indicates absence of a cumulative effect and is of great advantage when prolonged surgical procedures require repeated doses or sustained intravenous infusion.

Dosing is essentially similar in adults and children, except neonates. The pharmacokinetics and pharmacodynamics are not significantly altered in the elderly.⁹ Allergic reactions are a problem but may be blocked by adequate premedication.⁶

A comparison of direct costs incurred in the use of various neuromuscular blocking agents suggest that atracurium is a cost-effective option in the modern operating room.¹⁰ In this respect it may be comparable to vecuronium.¹¹

Recommendation

Atracurium is a neuromuscular blocking agent with similar efficacy to vecuronium, in terms of adequate muscle relaxation, but different pharmacokinetics. It has the unique advantage that its metabolism is independent of renal or hepatic function. The adverse drug reaction profile is acceptable and the cost reasonable. It can serve as an alternative to vecuronium in settings where refrigeration facilities are available. It is recommended that the Committee asks for atracurium to be added to the WHO Model List of Essential Medicines, as a complementary agent in its category.

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2.17 Suxamethonium chloride (subsection 1.4)

Introduction

Suxamethonium (also called succinylcholine) is the only depolarising muscle relaxant currently in clinical use. It produces very rapid and short duration paralysis in most patients and is thus widely used for laryngoscopy and intubation. It has also been used to reduce the intensity of muscle contractions during electroconvulsive therapy. Should paralysis be prolonged, ventilation must be assisted till muscle power is fully restored.

Suxamethonium normally produces depolarising neuromuscular block. With large doses or prolonged use there may be dual blockade, with the addition of non-depolarising features. This carries the risk of prolonged paralysis and apnoea.

No other depolarising neuromuscular blocker is listed in the 2004 WHO Model Formulary.¹ Alcuronium and vecuronium are listed as non-depolarising muscle relaxants.

The product

Suxamethonium, as suxamethonium chloride, is available as a clear colourless solution intended for intramuscular or intravenous use or as a sterile powder to be reconstituted prior to administration, with a suitable intravenous fluid (usually 5% dextrose or 0.9% sodium chloride), to a concentration of 0.1 to 0.2%. It is marketed in ampoules or multidose vials.

Suxamethonium preparations should be protected from light and solutions should preferably be refrigerated. Dilutions for infusion should be used within 24 hours.

Suxamethonium should not be given prior to induction of general anaesthesia because paralysis is usually preceded by painful muscle fasciculation. Prior administration of a non-depolarising blocker may reduce the intensity of this problem. Premedication with an antimuscarinic agent like atropine may be of value in reducing bradycardia and excessive salivation. Assisted respiration is essential. Muscle relaxation starts within 1 minute of injection, and single-dose effects persist for less than 8 minutes.

Dosage^{2,3}

By intramuscular injection, INFANT up to 4 - 5 mg/kg; ADULT and CHILD up to 4 mg/kg; maximum 150 mg.

By intravenous injection, ADULT and CHILD 0.3 - 1 mg/kg, followed if necessary by supplements of 300 microgram/kg; INFANT 2 mg/kg.

By intravenous infusion, ADULT 35 - 100 microgram/kg/minute of solution containing 1 - 2 mg/mL.

Total dose administered by repeated intravenous injection or infusion should not exceed 500 mg/hour.

In general, suxamethonium doses need to be carefully titrated for individual patients according to the patient's response. Prolonged neuromuscular blockade is uncommon but may be the result of dual block or reduced plasma cholinesterase activity.

The dosing of suxamethonium is currently being reviewed. Some studies suggest that lower than conventional doses may suffice with less chance of postoperative myalgia.^{4,5} Low-dose suxamethonium can facilitate laryngeal mask airway insertion.⁶ In modified electroconvulsive therapy, however, a dose of 1 mg/kg may be needed rather than 0.5 mg/kg.⁷

Adverse drug reactions^{2,3}

- Muscle fasciculations and postoperative myalgia are both very common. Myalgia may last for several days and be severe in intensity. Pain may not correlate with the degree of fasciculation. Precurarisation (administration of a small subclinical dose of a nondepolarising muscle relaxant prior to suxamethonium) may abolish the fasciculations and prevent myalgia from developing. Vecuronium, rocuronium and mivacurium are effective in this regard but cisatracurium may be unsuitable.⁸⁻¹⁰
- Prolonged neuromuscular blockade and apnoea. This occurs in patients deficient in plasma pseudocholinesterase or possessing atypical variants of the enzyme. It may also occur in patients who develop dual block following large or repeated doses of suxamethonium. Ventilatory support would be necessary.
- Dysrhythmias. The drug can cause profound sinus bradycardia in infants and young children. Nodal rhythm and ventricular ectopics may occur. Dysrhythmias appear to occur only with intravenous, rather than intramuscular dosing, and atropine has a protective effect.
- Tachycardia and increase in blood pressure may occur due to stimulation of sympathetic ganglia. These may be preceded by bradycardia and hypotension.
- Increased salivary, bronchial and gastric secretions.
- Hyperkalemia. Elevation of plasma potassium levels by 0.3 - 0.5 mmol/L is usual, and dangerous levels may be attained in the setting of massive tissue destruction (e.g. severe burns) and central nervous system injury with muscle wasting. Hyperkalemia may lead to dysrhythmias and cardiac arrest.
- Myoglobinaemia and increase in creatine phosphokinase plasma levels can develop and this is more likely to occur in children. These do not appear to be related to muscle fasciculations, and are probably of little clinical significance.
- Raised intraocular pressure is particularly undesirable in the presence of glaucoma and is harmful in the context of penetrating eye wounds and ocular surgery requiring incision of the globe.
- Masseter muscle spasm can occur during the onset of blockade. Tracheal intubation is greatly hindered in the affected subject. Spasm may signal the onset of malignant hyperthermia.
- Malignant hyperthermia: Occurs in genetically predisposed individuals and is potentially fatal. Use in the presence of halothane adds to the risk.
- Hypersensitivity. Although anaphylaxis is rare, suxamethonium is a frequently implicated neuromuscular blocker in allergic reactions. Flushing, rash, urticaria, bronchospasm and shock have been reported.

Contraindications

- Anticipated inability in securing an airway.
- Hypersensitivity to suxamethonium.
- Deficiency or genetically determined atypicality of plasma pseudocholinesterase.
- Personal or family history of malignant hyperthermia.
- Open eye injuries.
- Hyperkalemia.
- Severe burns, massive trauma, spinal-cord lesions, stroke, or other neurological injury with muscle wasting.
- Myopathies associated with elevated creatine phosphokinase levels.
- Duchenne muscular dystrophy, congenital myotonia or myotonic dystrophy.

The presence of advanced myasthenia gravis, Guillain-Barre syndrome, cerebral palsy, tetanus, cardiac dysrhythmias, cardiac pacemaker, recent digitalisation, glaucoma, and severe liver disease are relative contraindications to use of suxamethonium.

Evidence of value

The activity time course of suxamethonium is unmatched even 50 years after its introduction into anaesthetic practice. This is probably why the drug, despite its multiple and occasionally life-threatening adverse reactions, is still considered indispensable by many anaesthetists and emergency doctors.^{11,12} Suxamethonium also enjoys the economic advantage.¹³ However, the routine use of suxamethonium as a relaxant for intubation is undesirable, particularly in children, and in settings where new anaesthetic equipment (e.g. laryngeal mask airway) or new drugs (e.g. sevoflurane^{13,14}) provide alternatives to using suxamethonium.

There are two areas where suxamethonium still is the first-choice agent – for the treatment of laryngospasm or for rapid sequence induction in patients with 'full stomach'. Suxamethonium produces more intense block in a shorter time at the laryngeal muscles, in contrast to the adductor pollicis muscle, compared with vecuronium, rocuronium, rapacuronium, and mivacurium.

Patients requiring emergency endotracheal intubation often require a rapid sequence induction intubation (RSI) technique to protect against gastric aspiration or raised intracranial pressure. Suxamethonium has been the most common muscle relaxant used for RSI because of its very fast onset and short duration of action. Rocuronium and rapacuronium have been suggested to create intubating conditions similar to suxamethonium. However, in recent meta-analyses,^{15,16} suxamethonium created superior conditions to rocuronium when comparing excellent intubation conditions. Using a less stringent outcome, namely clinically acceptable intubation conditions, the two agents are comparable. Further, intubation conditions were not statistically different between suxamethonium and rocuronium when propofol was used.

Comparisons with the other new rapidly acting nondepolarising muscle relaxant, rapacuronium, have also not produced sufficient evidence to supplant suxamethonium.¹⁷⁻¹⁹

Recommendation

The role of suxamethonium in anaesthetic units with access to new equipment and new drugs has become restricted to facilitation of intubation, particularly in rapid sequence induction intubation scenarios. It is no longer being used in maintenance of muscle relaxation and there are alternatives for planned intubation. However, the rapid and spontaneous recovery from suxamethonium blockade in the majority of cases still makes it the preferred muscle relaxant for a suspected difficult intubation where use of a longer-acting relaxant can be life-threatening if intubation cannot be achieved and adequate ventilation cannot be maintained with an oral airway alone. Suxamethonium should be retained in the WHO Model List of Essential Medicines.

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2.18 Neostigmine metisulfate (subsection 1.4)

Introduction

Neostigmine, a reversible inhibitor of acetylcholinesterase, is used to counteract the effect of non-depolarising muscle relaxants administered during surgery. Its anticholinesterase property is also used to relieve postoperative non-obstructive urinary retention, paralytic ileus, and muscle weakness in myasthenia gravis. This review concentrates on the anaesthetic use of neostigmine.

Neostigmine is the only cholinesterase inhibitor listed in the anaesthesia section of the 2004 WHO Model Formulary.¹ Pyridostigmine is listed as a complementary cholinesterase inhibitor for the treatment of myasthenia gravis.

The product

Neostigmine, as neostigmine metilsulfate, is marketed for subcutaneous, intramuscular and intravenous injection. The usual strengths are 500 microgram/mL in 1 mL ampoule; 1 mg/mL in 10 mL multidose vial and 2.5 mg/mL in 1 mL ampoule. In some countries the injection may be available in combination with the antimuscarinic agent atropine or glycopyrrolate.²

Preparations are stored at room temperature but need protection from light.

Neostigmine bromide is available as 15 mg tablets for oral use in myasthenia gravis.

*Dosage*¹

Reversal of non-depolarising block, by intravenous injection over 1 minute, ADULT 2.5 mg, followed if necessary by supplements of 500 microgram to maximum total dose of 5 mg; CHILD 40 - 50 microgram/kg.

To reduce muscarinic effects of neostigmine, atropine sulfate is commonly administered by intravenous injection (ADULT 0.6 - 1.2 mg, CHILD 20 microgram/kg) with or before neostigmine. Indeed, neostigmine should not be used by intravenous route unless atropine (or an alternative anticholinergic agent) is available to counteract severe cholinergic reactions.

Post-operative urinary retention, by subcutaneous or intramuscular injection, ADULT 500 microgram. Catheterization is required if urine is not passed within 1 hour.

Adverse drug reactions

- The majority of adverse reactions to neostigmine are predictable from the excessive muscarinic stimulation by acetylcholine that fails to be degraded owing to inhibition of cholinesterase activity. These include increased salivary, tracheobronchial and gastrointestinal secretions; abdominal cramps, diarrhoea, nausea and vomiting; and bradycardia with a resultant fall in cardiac output.
- In larger doses, neostigmine may have direct depolarising effects on the motor end plate, leading to decreased muscle activity and paralysis. In overdose, this may precipitate a state of profound muscle weakness accompanied by muscarinic stimulation, referred to as a cholinergic crisis. This is a potentially life-threatening state.

- Increased incidence of postoperative nausea and vomiting, particularly when doses over 1.5 mg are used.³

*Precautions and contraindications*²

Extra caution is needed in the use of neostigmine in the following situations, and depending upon clinical severity, use may be contraindicated.

- Bronchial asthma.
- Cardiovascular disease, including arrhythmias (especially bradycardia or atrioventricular block) and hypotension.
- Epilepsy.
- Parkinsonism.
- Peptic ulcer.
- Renal impairment.
- Urinary tract infections.

Evidence of value

Neostigmine is the most widely used cholinesterase inhibitor in anaesthetic practice. After injection, it takes at least 2 minutes for the action to start but recovery from neuromuscular blockade is maximally enhanced by 5 - 7 minutes. No special problems have been reported during use in children, the elderly, pregnancy and breast-feeding.² However, use must always be in conjunction with an anticholinergic agent to avoid muscarinic overstimulation.

An emerging indication for neostigmine is its potential to provide analgesia when given through the neuraxial route. For instance, neostigmine by caudal route provides postoperative analgesia in children undergoing genitourinary surgery.⁴⁻⁷ Similar benefits have been reported in gynaecological operations⁸⁻⁹ and orthopaedic procedures.¹⁰⁻¹¹ Dose-dependent nausea can be a limitation in this regard.^{7,12}

Neostigmine is also being added as a potentiating agent to local anaesthetics for central and peripheral nerve blocks and in intravenous regional anaesthesia.¹³⁻¹⁵ However, there are conflicting reports in this regard¹⁶ and further studies are required before recommendations can be made.¹⁷

Recommendation

Neostigmine is the only anticholinesterase agent currently available to facilitate early recovery from neuromuscular blockade during surgery. It should be retained in the WHO Model List of Essential Medicines.

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Part 3: Search Strategy

The medical literature was searched to identify systematic reviews, meta-analyses, practice guidelines, randomised controlled trials and other major clinical studies related to individual anaesthetic agents and related drugs listed in sections 1.1 to 1.4 of the 2004 WHO Model Formulary.

The **Medline database** accessed online through the PubMed portal [<http://www.ncbi.nlm.nih.gov/PubMed/>] served as the major reference point for all agents. The search was restricted to last 10 years i.e. July, 1994 to August, 2004. The name of the agent was used as the keyword and in most cases the following three filters were used:

- human
- with abstract only
- keyword in title-abstract

All abstracts downloaded have been saved and hardcopies or softcopies can be forwarded if necessary.

Other online or offline databases that were searched (Search period: Last 10 years unless otherwise mentioned) were included. The searching was done in multiple sessions, mostly between July 20 to Aug 15, 2004.

Cochrane Library (Cochrane Reviews Issue 1 2004) Accessed on the E-Talc CD-ROM (Issue 6) published by TALC, UK.

Anesthesia & Analgesia <http://www.anesthesia-analgesia.org>

Anaesthesia and Intensive Care <http://www.aaic.net.au/>
Search period: 1996 - 2004.

Anesthesiology www.anesthesiology.org/

European Journal of Anesthesia [http://www.eja-online.org/](http://www.eja-online.org)

Journal of Paediatric Anaesthesia
Search of the Blackwell Science website (<http://www.blackwell-synergy.com/>) with individual agents as the search term.

Acta Anaesthesiologica Scandinavica
Search of the Blackwell Science website (<http://www.blackwell-synergy.com/>) with individual agents as the search term.

World Anaesthesia
Search of World Anaesthesia webpage through <http://search.ox.ac.uk/web/medsci/clinmed/anaes/>

BMJ Clinical Evidence website <http://www.clinicalevidence.com/>

International Anesthesiology Clinics <http://www.anesthesiaclinics.com>

Current Opinion in Anesthesiology www.currentopinion.com

The print version of the following texts and references were scanned:

1. Mehta DK, Ryan RSM, Hogerzeil HV, editors. **WHO model formulary 2004**. Geneva: World Health Organization, 2004.
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In most cases the 2004 WHO Model Formulary provided the starting point for the section on dosage, and Martindale and Dollery as the starting point for product descriptions and adverse event listings.

Issues in the last 3 year of the following journals (which were readily accessible to the authors) were also hand-searched:

- British Journal of Anaesthesia
- British Medical Journal
- Drug and Therapeutics Bulletin
- Indian Journal of Anaesthesia
- New England Journal of Medicine
- Prescrire International
- The Lancet

Texts, meta-analyses, reviews and other articles that have been used to prepare individual monographs have been listed in the respective reference sections.
