Proposal for update of the anaesthesia and muscle relaxant sections of the WHO EML

April 2010

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Introduction

 Provision of anaesthesia is an essential component of health services throughout the world. Access to safe anaesthesia is considered a basic human right and there are international standards for its safe practice (Bosenberg, 2007). Therefore it is important for health systems to be able to provide safe and effective anaesthesia for a wide range of surgical procedures in children and adults. However, there are many challenges facing the provision of anaesthesia, particularly in the developing world where facilities, equipment, and staff training are often inadequate (Cherian et al., 2007). As a result, rates of morbidity and mortality related to anaesthesia vary dramatically from developed countries, where mortality rates as low as 1 in over 70 000 cases have been reported, to developing countries where mortality rates as high as 1 in 150 cases have been reported (Cherian et al., 2007). This burden affects patients with many indications for surgery, but falls most heavily on pregnant women and children who make up a large proportion of surgical cases (Ouro-Bang’na Maman et al., 2009). In recent years the World Health Organization has begun to attempt to improve this situation with initiatives such as the "Safe Surgery Saves Lives" challenge.

Case mix in developing world

 The World Health Organization estimated that 536,000 maternal deaths occurred worldwide in 2005 (World Health Organization, 2009). Of these deaths, 99% were in developing countries, and more than half were in sub-Saharan Africa. The probability that a 15 year old female will eventually die of a maternal cause was estimated to be 1 in 26 in Africa (1 in 7 in Niger), in contrast to 1 in 7300 in developed regions (World Health Organization, 2009). Emergency caesarean section is the most common major surgical procedure in Africa, despite many sub-Saharan countries having caesarean section rates of less than 1% (rates of between 5 and 10% are recommended) (Clyburn et al., 2007). For patients who do have a caesarean section, mortality rates in some reports from Africa are as high as 1-2% (Clyburn et al., 2007). A survey of 87 hospitals in Zambia in 2006 listed obstetric surgery (including caesarean), laparotomy, gynaecologic surgery, herniorraphy, and incision and drainage of abscesses as the five most common surgical interventions in that country (Jochberger et al., 2008). Many developing countries have young populations, with children (under 18 years of age) accounting for greater than 50% of the population. Surgical requirements for the paediatric population are high, with some estimates that 85% of children require some surgical intervention by 15 years of age (Hodges et al., 2007b). The common indications for surgery in this group are trauma, abdominal emergencies, congenital abnormalities (such as inguinal hernias and anorectal malformations), infections (such as abscesses and osteomyelitis) (Hodges et al., 2007b).

Goals of anaesthesia

 In broad terms, anaesthesia aims to allow surgery to be conducted in a safe manner, under the most favorable operating conditions and with the patient experiencing little pain, anxiety or other discomfort. It is favorable, both for the patient and the efficient use of staff and other hospital resources, for the anaesthetic to rapidly induce suitable operating conditions, and then to allow rapid recovery with few side effects or adverse events. Anaesthesia can be achieved using regional anaesthesia (including spinal and epidural anaesthesia, as well as peripheral nerve blocks) or general anaesthesia. In regional anaesthesia, the patient is
generally fully awake and aware, but is unable to feel pain in the anaesthetised area. Although regional anaesthesia is of great utility and importance, this review focuses on general anaesthesia. In general anaesthesia, the patient is unconscious and unaware of their surroundings but in practice, general anaesthesia is more than simply a state of unawareness. Analgesia, amnesia, muscle relaxation and reduction of autonomic reflexes are also important components (Tonner, 2005).

No single medicine used for general anaesthesia today provides all the elements of a general anaesthetic that are listed above. Anaesthetists therefore use a combination of medicines including the volatile inhalationals, intra-venous hypnotics and sedatives, muscle relaxants and opiates in order to achieve these goals. This is often referred to as "balanced anaesthesia" and aims to have synergism of desired effects without synergism of side effects (Tonner, 2005). The optimal medications used to provide balanced anaesthesia depend on a number of variables including the operation to be performed, the setting (e.g. emergency/elective) patient factors such as co-morbidities and anxiety, and the experience of the anaesthetist. In a laparotomy, for example, a high degree of muscle relaxation facilitates surgical access to the abdomen, while muscle relaxation may not be as important for debridement and closure of a limb wound. A patient with coronary artery disease may tolerate certain anaesthetics better than others depending on the medicines direct and indirect effects on the cardiovascular system. Safety could also be compromised if an anaesthetist is using medicines with which they are unfamiliar. The availability of a number of different agents to produce each of the desired components of general anaesthesia is recommended in WHO guidelines on anaesthetic infrastructure (Clinical Procedures Unit World Health Organization).

Problems related to anaesthesia

Many of the medications that are used in anaesthesia have common physiologic effects such as hypnosis, anxiolysis, analgesia, apnoea, vasodilation, cardiac depression and loss of autonomic reflexes. These effects are desired or undesired in different circumstances or degrees of severity. These effects are well described (although patients’ responses to the medications varies), often dose dependent and vary between and within drug classes. These effects therefore dictate the therapeutic uses of each of the drug classes, and each medication within a class, as well as some of the problems associated with that use. Dosage is therefore a trade off between desired clinical effect (e.g. hypnosis, and/or analgesia) and undesired side effect (e.g. apnoea or hypotension). Poor results can be seen when this titration is at either end of the spectrum: depression of physiological homeostasis with over treatment (potentially resulting in dire consequences; e.g. hypotension and/or hypoxia leading to cardiac arrest); and awareness and pain with under treatment (a particular problem when muscle relaxants are also used because patients are unable to move or communicate).

As with medications used elsewhere in medicine, some of the drugs used in anaesthesia are toxic to certain end organs. Many of the volatile inhalationals, most notably halothane, can cause a range of liver impairment (Reichle and Conzen, 2003b). In rare cases (1 in 35,000 with halothane) (Stachnik and Bonk, 2006) this can be of a fulminant nature, and result in death. Compound A is a nephrotoxic product of the breakdown of sevoflurane (another volatile inhalational) by CO2 absorbents (which are used in anaesthetic breathing circuits to allow rebreathing without hypercarbia). Although compound A has been shown to result in renal damage in animal studies, this has never been shown in human studies (Reichle and Conzen,
2003b). All of the volatile anaesthetics and suxamethonium, a depolarising muscle relaxant, can trigger malignant hyperthermia, a rare, severe syndrome that is triggered by some medications and can be fatal (Australian Medicines Handbook, 2006). Allergy and anaphylaxis are also potential problems in anaesthesia, particularly due to the muscle relaxants (Nathan and Odin, 2007).

Further common adverse effects associated with anaesthetic agents include: tachy/bradyarrhythmias, hyper/hypotension, pain with injection (often seen with propofol), laryngospasm, bronchospasm, post-operative nausea and vomiting (PONV) - a common problem that occurs more frequently after the use of volatile inhalational anaesthetics, post-operative confusion or delirium (noted to be more common in children after use of sevoflurane), and vivid dreams or hallucinations (commonly seen with ketamine) (Australian Medicines Handbook, 2006). These adverse effects need to be considered, taking into account the risk profile of the patient and the nature of the surgery (emergency/elective, major/minor) when deciding on an appropriate anaesthetic plan.

**Anaesthesia process**

General anaesthesia has three phases which are important to consider when using anaesthetic medications. These are induction, maintenance and recovery. Induction is an unstable time as medications are administered which can result in haemodynamic instability, apnoea and loss of airway tone. Overdose or choice of an unsuitable induction medication (for the given situation and patient) is one of the most common causes of anaesthesia related death (Nathan and Odin, 2007). Induction can be achieved using either the intra-venous (IV) route (most common), or via inhalation of an anaesthetic gas (commonly used in paediatric practice where it is advantageous to gain IV access after induction). IV induction often involves the administration of other medications with a similar rationale to that for balanced anaesthesia outlined above. Some inhalational agents (in particular, desflurane) are considered inappropriate for use at induction due to high rates of airway irritation which makes their use difficult (Australian Medicines Handbook, 2006). Muscle relaxants are frequently used to facilitate endotracheal intubation which is carried out to protect the patient’s airway and allow mechanical ventilation. One induction technique worth specific note is rapid sequence induction (RSI). RSI is used most commonly when the patient is considered to be at high risk for aspiration. The technique involves IV administration of rapidly acting anaesthetic agents and muscle relaxants (Nathan and Odin, 2007). Pressure is then applied to the cricoid cartilage to occlude the oesophagus in order to prevent the regurgitation of stomach contents until the trachea is intubated (Australian Medicines Handbook, 2006).

Maintenance of anaesthesia is the continuation of general anaesthesia during the operation and can be achieved via the use of IV or inhalational agents, regardless of the mode of induction. Once again multiple agents can be used to result in optimal conditions. Drugs administered during the induction phase may continue to exert effects during the maintenance phase. Both the induction and maintenance agents also effect the recovery phase. The recovery phase, or emergence, is a crucial time due to autonomic hyper-responsiveness that can occur as the patient is returning to full consciousness (Falk and Fleisher). Patient recovery profiles after induction and maintenance with different agents have been investigated in clinical trials (Gupta et al., 2004). These trials have investigated
outcomes such as time to discharge and incidence of post-operative nausea and vomiting. A systematic review of this topic in patients undergoing ambulatory surgery concluded the choice of specific agent for maintenance appeared to play only a minor role in the outcome after surgery (Gupta et al., 2004). This review did, however, show some differences between agents, notably a reduction in PONV after propofol compared to inhalational anaesthetics, and also various small differences in recovery times that were probably of little clinical significance (Gupta et al., 2004).

**Challenges in developing world**

Many developing countries face significant difficulties in providing resources for health care such as war, famine, geographical isolation and HIV/AIDS (Ouro-Bang’na Maman et al., 2008). More than half the governments in Africa spend less than 10 dollars per person per year on health and there are problems with corruption, procurement, storage and supply that lead to a lack of essential equipment and medications (Nambiar et al., 2007). Anaesthesia is resource intensive with high requirements for equipment, disposables and medications. Equipment used in the developed world may need regular servicing which is often unavailable in the setting of developing countries, resulting in many machines being rendered unusable. A survey of anaesthetists in Uganda found that only 13% had the essential equipment for providing anaesthesia to children under 5 years of age (Hodges et al., 2007a). These challenges facing health care in the developing world contribute to poor underlying health state and late presentation of disease that further complicate the provision of anaesthesia.

In many developed countries, anaesthetic services are provided by anaesthetists who are medical doctors that have undergone many years of post-graduate training to become qualified in the field. This high level of training provides the anaesthetist with practical skills and an intimate knowledge of physiology and pharmacology that enable them to provide safe and effective anaesthesia. In contrast most anaesthetics in developing countries are delivered by non-physicians, nurses or unqualified personnel (Nambiar et al., 2007). There are large differences in anaesthesia staffing levels between and within these countries (Ouro-Bang’na Maman et al., 2008). In Zambia, one survey found the presence of a physician anaesthetist markedly increased the rate of endotracheal intubation for general anaesthesia (Jochberger et al., 2008). In this survey 80% of anaesthetics were carried out by non-physicians and greater than half of all anaesthetics were carried out using ketamine. This high rate of ketamine anaesthesia without airway protection was thought to have contributed to the high incidence of respiratory complications (Jochberger et al., 2008).
Anaesthetic section update: objectives

The objectives of this proposal are:

1. To review the literature regarding anaesthesia in the developing world to appreciate the common operations performed, common anaesthesia techniques and agents in use, level of training of anaesthetic staff and challenges facing the provision of anaesthesia services in this setting.

2. To identify good quality treatment guidelines, or reviews (systematic or otherwise) of the literature, regarding the use of anaesthetic agents and muscle relaxants.

3. To review this evidence to determine the benefits and hazards concerning the use of each agent in both children and adults, with special attention to the developing world.

4. To indentify the prices of the medicines in use.

5. To generate tables of comparative information that could be used to select appropriate medications for the WHO essential medicines list.

6. To propose a list of medicines as suitable for inclusion in the WHO essential medicines list. These medicines will be used in a variety of settings, for both children and adults and need to allow the provider of anaesthesia to:
   a. provide pre-op medications as indicated
   b. induce anaesthesia for a variety of procedures via IV and inhalational routes in children and adults
   c. induce muscle relaxation required for intubation and to improve surgical conditions as required in children and adults
   d. provide maintenance of general anaesthesia via inhalational and alternative routes

Anaesthetic section update: methods

1. Literature regarding the context, setting, conduct, purpose and other information related to anaesthesia practice in the developing world was found by searching the MEDLINE database with the relevant terms including: "anaesthesia", "anaesthetic", "developing world", "developing countries", "paediatric anaesthesia", "non-doctor anaesthesia".

2. Lists of the medicines on the 16th edition of the WHO model list of essential medicines (2009) and the 2nd edition of the WHO model list of essential medicines for children (2009) were extracted from the WHO publications, available at:

Essential medicines lists (some in draft format) from nine countries on file at the World Health Organization were reviewed.
3. WHO databases were searched for treatment guidelines or other documents relevant to choice of anaesthetic medicines at health system level, single hospital level or the individual patient level. Four documents were identified:
   - Pocket book of hospital care for children: Guidelines for the management of common illnesses with limited resources, 2005
   - Surgical care at the district hospital, 2003
     i. WHO "Guide to anaesthetic infrastructure and supplies at various levels of health care facilities" was compiled from this document
   - Managing complications in pregnancy and childbirth: A guide for midwives and doctors, 2000

4. The National Guidelines Clearinghouse database was searched using terms "anaesthesia" and "anesthesia".
   - www.guideline.gov

Further searches of relevant professional association websites were also conducted.
   - Australian and New Zealand College of Anaesthetists
     i. www.anzca.edu.au
   - American Society of Anesthesiologists
     i. www.asahq.org
   - Anaesthetics Association of Great Britain and Ireland
     i. www.aagbi.org

These searches found many guidelines addressing the practice of anaesthesia. However, no guidelines that attempted to summarize available evidence and recommend individual pharmaceutical agents were found, with the exception of guidelines addressing highly specialized patient groups that were not considered appropriate for inclusion as the basis for selections in this proposal.

A small number of guidelines were included because they contained useful data on specific issues, such as comparisons of the utility of different agents in breastfeeding mothers.

5. The Cochrane database of systematic reviews was searched using the terms "anaesthesia" and "anesthesia". The website of the Cochrane Anaesthesia group was also examined. These searches did not find any reviews that attempted to summarize available evidence and recommend particular agents in a general setting.
   - www.cochrane.org/reviews/index.htm

Data from a small number of systematic reviews from the Cochrane database were included in this review.

6. The databases MEDLINE and EMBASE were searched for review literature regarding drug analysis, drug comparisons, or adverse events using the following terms: "anaesthesia", "anesthesia", "anaesthetic", "anesthetic", "propofol", "ketamine", "etomidate", "thiopentone", "thiopental", "halothane", "isoflurane", "enflurane", "

- http://www.embase.com/search/drug

Titles, and then abstracts were reviewed with the most recent and comprehensive review literature on relevant topics obtained. Pertinent evidence found referenced in results from the above searches was included.

Further specific searches were carried out in order to fill specific gaps in data.

7. Further information was obtained about medications from the following publications:
   - Australian Medicines Handbook 2006
   - BNF for children 2006
   - WHO model formulary 2004
   - WHO model prescribing information: Drugs used in anaesthesia (1989)

8. Pricing information was obtained from the BNF for children 2006 or the International drug price indicator guide (where South Africa was chosen as the index nation because, firstly, information on pricing from South Africa was available for most of the medications reviewed, and secondly, it was felt to be as good an index country as other alternatives given its geographical, political and economic profile).
   - http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=DMP&language=English

9. From the literature obtained, data relevant to a number of key points for decisions on the suitability of medicines for the WHO model essential medicines list was extracted and tabulated. These tables and the articles themselves were used to compare anaesthetic and muscle relaxant medicines, with due consideration of contextual factors relevant to the developing world, in order to select a number of medicines to be included in a proposed update to the relevant sections of the WHO essential medicines list.

Comparisons were made within the following classifications:
   - inhalational anaesthetic agents
   - intravenous anaesthetic agents (for induction and/or maintenance of anaesthesia)
   - muscle relaxants
   - pre-op medications and sedation for short procedures

**Anaesthetic section update: results**

1. **Proposed medicines for the WHO essential medicines list**

A list of medications considered by this review to be suitable for proposal to constitute the relevant sections of the WHO essential medicines list is presented and compared to the current list in table 1.
2. **Background information**

Information from the literature review regarding the context, setting, conduct, purpose and other information related to anaesthesia practice in the developing world was included in the Introduction of this proposal.

3. **Essential medicines lists**

Anaesthetic agents and muscle relaxants currently included in the WHO model list of essential medicines, WHO model list of essential medicines for children and the essential medicines lists of nine selected countries, are displayed in table 2.

4. **World Health Organization documents**

The anaesthetic agents and muscle relaxants included in the four relevant WHO documents are shown in table 3.

5. **Literature and other information describing relevant medicines**

The data extracted from guidelines, systematic reviews, product information documents and national/WHO formulary documents are summarized in tables 4a, 4b, 5, 6 and 7.

The rationale for selections made is given below, by medication type, with emphasis on medicines on the existing WHO essential medicines lists, and medicines proposed as suitable for inclusion by this review.

6. **Inhalational Anaesthetic Agents** (tables 4a and 4b)

The inhalational anaesthetics reviewed are listed and compared in tables 4a and 4b. The most important differences are discussed below in order to present the rationale for the selection of particular medicines to be recommended for inclusion on the WHO model essential medicines list.

Halothane is widely used in developing countries. It is used for induction and maintenance of general anaesthesia in children and adults. It is a particularly good agent for induction because it is does not irritate the airway (Fenton). However, a number of factors have seen halothane replaced in developed countries in recent years. Firstly, fulminant hepatic failure, which can occur after exposure to any of the volatile anaesthetic agents (with the exception of sevoflurane), is seen most commonly after halothane (1 in 35,000) (Stachnik and Bonk, 2006). This has been shown to occur more commonly after a previous hepatic impairment following volatile anaesthesia. This hepatic impairment is very common after halothane and it is recommended to avoid repeated exposures within 3 months (*BNFc*, 2006). Secondly, halothane can sensitize the myocardium to adrenaline and predispose to arrhythmias, and has more cardiovascular side effects than other volatile agents (Stachnik and Bonk, 2006). Thirdly, recovery from halothane is accepted to be slower than with newer volatile anaesthetic agents such as sevoflurane and isoflurane. This
is due to the different pharmacokinetic properties of the drugs that allow easier titration of the depth of anaesthesia, and a more rapid, and therefore efficient, recovery with the newer agents than with halothane.

Isoflurane, enflurane, desflurane and sevoflurane are the newer anaesthetic agents that have replaced halothane in many developed countries. However, like halothane, all the agents have weaknesses. This means that no agent is considered the best for all circumstances, but rather each agent is more or less suitable for a given patient/operation. Ideally this is overcome by having access to a number of agents and anaesthetic staff that are skilled in deciding which agent should be used for a given case. However, there are many barriers to achieving this situation, particularly in resource poor environments (Enright et al., 2007). In particular, each of the inhalational agents is given using an agent specific vaporizer, thus the use of multiple agents increases equipment and maintenance costs.

Isoflurane causes only 1 case of hepatic failure per 1,000,000 cases (Stachnik and Bonk, 2006). It is considered too irritant to the airway to allow it to be used for inhalational induction. Most inductions are done using IV drugs; however, inhalational induction of anaesthesia is a useful technique, particularly in paediatrics. Enflurane can be used for induction, and is less likely to cause hepatic failure (1 in 800,000 cases), arrhythmias or other cardiovascular side effects than halothane (Stachnik and Bonk, 2006). However, it can lead to EEG abnormalities and is avoided in patients with epilepsy. The risk of causing a seizure has lead to enflurane not being widely used in some countries (Stachnik and Bonk, 2006). Isoflurane and enflurane have more rapid onset and recovery than halothane.

Sevoflurane and desflurane have the most rapid onset and offset of action with few adverse effects (Stachnik and Bonk, 2006) (Gupta et al., 2004). Both agents are used widely in developed countries, but are more expensive than the other agents, potentially limiting their use in the developing world. Desflurane also requires a more sophisticated vaporizer than the other volatile inhalational agents, further increasing costs decreasing ease of use in resource poor settings (Myatt). Desflurane is more likely to irritate the airway than isoflurane and its use is not recommended for induction.

Sevoflurane does not cause respiratory irritation and is used for induction as well as maintenance in developed nations. Sevoflurane causes minimal arrhythmias and cardiovascular depression, and does not produce the metabolites that are responsible for fulminant hepatic failure associated with halothane and the other volatile agents (Stachnik and Bonk, 2006). Sevoflurane does, however, react with CO2 absorbents used in anaesthesia to produce Compound A. Compound A has been associated with renal toxicity in animal studies but this has not been shown to be the case in humans (Reichle and Conzen, 2003a). However, it is recommended that sevoflurane is not used with low fresh gas flow in order to limit exposure to compound A. Higher fresh gas flows means more anaesthetic agent used, resulting in decreased cost effectiveness. Fluoride ions are also produced with sevoflurane use, but again this has not lead to renal damage in human studies (Reichle and Conzen, 2003a).
Sevoflurane has been associated with an increased risk of agitation during recovery in children (Kuratani and Oi, 2008).

Thus, only halothane, enflurane and sevoflurane are suited to provide inhalational induction and maintenance of anaesthesia. Of these sevoflurane has fewer adverse effects, is more cardiovasculary stable and has faster onset and recovery. However, it is the most expensive agent. Compared to halothane, enflurane causes substantially less severe hepatic failure and is more cardiovasculary stable; however, enflurane does cause seizures. Which of these agents should be included on national essential medicine lists would depend partly on available resources. In settings where selection of two volatile anaesthetic agents is possible, isoflurane could be added to one of the three agents listed above. Isoflurane is cheaper than sevoflurane, causes less hepatic failure than halothane and it does not cause seizures.

Nitrous oxide is useful as an analgesic to allow procedures which do not require a general anaesthetic. Nitrous oxide has been used in anaesthesia for many years; however, it is not potent enough to provide a general anaesthetic without co-administration of another anaesthetic without, commonly one of the volatile inhalational anaesthetics. When nitrous oxide is used in this manner intraoperative awareness is reduced, and the required dose of volatile inhalational anaesthetic can be greatly reduced, minimizing cardiorespiratory side effects and potentially providing a cost saving (Hopkins, 2005). However, there are a number of adverse effects that result from nitrous oxide including neurodegeneration, megaloblastic anaemia and an increase in rates of post operative nausea and vomiting (Jahn and Berendes, 2005). This nausea and vomiting is not only unpleasant for patients, but is also potentially dangerous after some operations (for example, reduction/fixation of fractured mandible), and can negate a cost saving made via reduction in usage of volatile anaesthetic agent. Furthermore, supply of nitrous can be difficult and expensive in developing nations (Fenton). Therefore, nitrous oxide may be more useful and cost effective in some settings than others, and its inclusion on national essential medicine lists should reflect the local situation.

Other inhalational anaesthetics (including ether and trichloroethylene, which have been removed from the WHO essential medicines list and shown in the results table for comparison) have not been considered in this review because of decline in their use due to a variety of concerns.

7. Intravenous Anaesthetic Agents (table 5)

The intravenous anaesthetic agents that were considered by this review are compared in table 5. The discussion below addresses the important differences in terms of clinical use and presents the rationale for recommendations on whether or not to include particular medicines on the WHO model essential medicines list.

Intravenous anaesthetic agents are used to induce anaesthesia, provide maintenance anaesthesia, and provide sedation for short procedures. Ketamine is currently on the WHO essential medicines list and used extensively throughout the developing world (Jochberger et al., 2008). As well as being relatively cardiovasculary stable, airway
reflexes are preserved with ketamine and respiratory depression does not occur (although there may be a period of apnoea after injection) (Lupton and Pratt). For these reasons ketamine is often used for anaesthesia where the anaesthetic provider is not skilled in endotracheal intubation or when the surgeon is administering the anaesthetic. Ketamine is associated with hallucinations during recovery (Strayer and Nelson, 2008). However, ketamine is an essential anaesthetic tool in resource poor settings.

Thiopentone, propofol and etomidate have all been shown to be safe and effective induction agents (Nathan and Odin, 2007). Thiopentone is currently listed on the WHO essential medicines list (as a representative of the barbiturate class). It has a "hangover" effect and with repeated dosing can cause prolonged somnolence (Lupton and Pratt). Thiopentone administration results in dose dependant cardio respiratory depression, although this is less than that associated with propofol. Etomidate does not exhibit this cardiovascular depression and is the agent of choice in the shocked patient (Nathan and Odin, 2007). However, etomidate is associated with adrenal suppression (potentially after a single dose), a problem that has limited its use. Both etomidate and propofol are used for sedation for short procedures (Godwin et al., 2005). Propofol is also widely used for maintenance of general anaesthesia using both manually controlled infusions (i.e. doses manually administered) and target controlled infusions (i.e. delivered by a machine which uses software to calculate the plasma concentration of the drug, and adjusts the infusion to reach a certain target concentration) (Leslie et al., 2008).

While all of these medications have advantages and disadvantages over the others, propofol can be used for the greatest number of indications. Propofol's major short coming is its cardiovascular depression in the unstable patient. Ketamine is also a versatile drug, with properties that are favourable in resource poor environments. Ketamine and propofol would be suitable IV anaesthetic agents for the WHO essential medicines list.

8. **Pre-operative medications and sedation for short procedures**

These medicines were not extensively reviewed. However, discussion with experts in the field, as well as research used for other sections of this review allows some recommendations to be made. The rationale for these recommendations is outlined below.

The use of pre-operative medications to alleviate patient anxiety and reduce recall during induction is common. While promethazine is listed on the WHO essential medicines list it is no longer widely used for this purpose. The benzodiazepines are used more widely. Diazepam which is also listed on the WHO essential medicines list is used for this purpose, notably in resource poor settings where it may be more readily available than midazolam (Lupton and Pratt). Midazolam is well suited to pre-operative sedation because of its short duration of action and amnesic properties (Lupton and Pratt). For these reasons midazolam is generally considered the agent of choice for pre-operative sedation.
The ideal sedation agent for short procedures will vary depending on the type of procedure. While benzodiazepines and promethazine are sedating, deeper levels of sedation are obtainable with the IV anaesthetics listed above (including ketamine and propofol).

9. **Muscle Relaxants** (tables 6 and 7)

The muscle relaxants are compared in tables 6 and 7. The discussion below addresses the major differences between the medicines in terms of suitability for inclusion in the WHO model essential medicines list.

Three muscle relaxants are listed on the current WHO essential medicines list: suxamethonium (a depolarising neuromuscular blocker); alcuronium (a benzylisoquinolinium, non-depolarising neuromuscular blocker) listed with a box signalling that it is the representative of a class, and; vecuronium (an aminosteroidal non-depolarising neuromuscular blocker) listed for use in children and also listed with a square box.

Suxamethonium differs from all other available neuromuscular blockers in its mode of action, time from administration to effect (fast acting) and duration of action (short). It also has more common and serious adverse effects than many of the other agents (Claudius et al., 2009). However, its rapid onset and short duration make it the agent of choice for rapid sequence induction (it has also been found to produce better intubation conditions during rapid sequence induction compared to the only drug with similarly rapid onset: rocuronium) (Perry et al., 2008).

Alcuronium has a slow onset, long duration of action and has more side effects than more modern non-depolarising muscle relaxants (Hunter, 1995). It is no longer widely used: despite being listed on the WHO essential medicines list, alcuronium was found on only one of eight national essential medicine lists reviewed (it was included on Iraq’s essential medicines list, however, Iraq also listed six other neuromuscular blockers). Pricing data was not found for alcuronium. Alcuronium is no longer an appropriate representative agent to be listed on the WHO essential medicine list.

Comparative information on the neuromuscular blockers in common use is given in the results table. These agents differ in a number of clinically significant ways, primarily: time to induce optimal intubation conditions, duration of effect, metabolism and side effects (histamine release and autonomic effects are important common side effects). Once again an ideal situation would involve availability of a number of agents and staff with expertise in selecting the most appropriate agent. Supply and training are significant barriers to this in the developing world.

Atracurium and cisatracurium are both metabolised by Hofmann degradation, which means that, unlike other neuromuscular blockers, their elimination is not effected by renal or hepatic impairment. (O’Connor and Gwinnutt.). Cisatracurium does not cause histamine release, while atracurium does. As mentioned above, rocuronium has a rapid onset of action. Vecuronium is slower in onset and less likely to cause tachycardia than rocuronium, but the two agents are otherwise similar. Pancuronium
is related to vecuronium and rocuronium. It has a longer duration of action and sympatomimetic features. The survey of eight national essential medicine lists revealed that, with the exception of suxamethonium which is on all eight lists, atracurium (which was on seven of the lists) and vecuronium (on five of the lists) were the most commonly listed agents. Any of the agents presented would be more suitable than alcuronium as the class representative listed on the WHO model essential medicines list. Atracurium may have small advantages in terms of price, use in hepatic and renal impairment, as well as current availability and familiarity with the drug, despite being associated with histamine release.

**Summary of findings**

A summary of the medicines recommended by this review to constitute the anaesthetic and muscle relaxant sections of the WHO essential medicines list is provided in table one. Table one also lists the medicines currently (2009) on the WHO essential medicines list.

Four medicines (isoflurane, propofol, midazolam, atracurium) are recommended for addition:

- Isoflurane is a cost effective alternative to halothane for maintenance of anaesthesia. It has some safety advantages over halothane, but is not suitable for induction of anaesthesia. Thus, in settings where only one inhalational anaesthetic agent can be provided, halothane remains an appropriate choice.
- Propofol is an intravenous anaesthetic widely used for induction and maintenance of anaesthesia, and for sedation for short procedures. It is more versatile than thiopentone, and is safe and effective.
- Midazolam is used as a pre-operative medication to alleviate anxiety and for its amnesic properties. Its short duration of action and amnesic properties make it the agent of choice for pre-operative sedation.
- Atracurium is a neuromuscular blocker that is widely used in both the developed and developing worlds. It is safer in hepatic and renal failure than a number of other neuromuscular blockers.

Four medicines (Thiopentone, diazepam, promethazine and alcuronium) are recommended for deletion:

- Thiopentone is primarily used as an intravenous induction agent. In many developed countries its use has decreased in favour of propofol. Thiopentone is also less suitable for continuing anaesthesia or sedation.
- Diazepam is listed for pre-operative sedation. In many settings midazolam is preferred because of its short action and amnesic properties. Midazolam is a more appropriate medicine to be listed as a representative of the benzodiazepines.
- Promethazine is no longer widely used as a sedative in relation to anaesthesia.
- Alcuronium has a slow onset, long duration of action and has more side effects than more modern non-depolarising muscle relaxants. It is no longer widely used and is not an appropriate representative of this class.
References


### Table 1: Summary of proposed revisions to the WHO essential medicines list

<table>
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<th>Class</th>
<th>WHO model essential medicines list 2009</th>
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<tr>
<td>General anaesthetics and oxygen</td>
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<td>(Inhalational agents)</td>
<td>Halothane ☐</td>
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<td></td>
<td>Nitrous</td>
<td>Isoflurane ☐*</td>
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<td>(Intravenous agents)</td>
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<td>Propofol</td>
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<td>Pre-operative medication and sedation for short procedures</td>
<td>Atropine</td>
<td>Atropine</td>
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<td>Diazepam ☐</td>
<td>Midazolam ☐</td>
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<td>Alcuronium ☐</td>
<td>Atracurium ☐</td>
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<td>Vecuronium ☐</td>
<td>Vecuronium ☐*</td>
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<td>☐Representative of class</td>
<td>*possible additions as second agent</td>
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### Table 2: Comparison of the inclusion of anaesthetic medicines in National Essential Medicines Lists to the WHO Model List 2009

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**Table 3: Anaesthetic Medicines listed in International Guidelines**

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### Table 4a: Comparison of inhalational anaesthetic agents

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<th>Drug</th>
<th>Induction</th>
<th>Maintenance</th>
<th>Recovery</th>
<th>Cardiovascular/ Respiratory effects</th>
<th>PONV</th>
<th>Adverse effects</th>
<th>Pregnancy category</th>
<th>Limitations on use</th>
<th>Equipment needed</th>
<th>MAU</th>
<th>Citi (South African data from IDPI unless indicated)</th>
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<tr>
<td>Halothane</td>
<td>Non-irritant, smooth induction</td>
<td>good</td>
<td>Slow</td>
<td>See separate table</td>
<td>yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1. Most likely to cause arrhythmias. 2. Raised hepatic enzymes. 3. Raised ICP. 4. Malignant hyperthermia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 in 36,000</td>
<td>1.3 months between exposures. 2. Limit epinephrine use&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Halothane Vaporizer, ventilator&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.77&lt;sup&gt;e&lt;/sup&gt;</td>
<td>$46/250ml&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>Isoflurane</td>
<td>Licensed but considered too irritant for induction</td>
<td>good</td>
<td>Intermediate</td>
<td>year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1. Malignant hyperthermia</td>
<td>&lt;1 in 1,000,000</td>
<td>§3&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Not good agent for induction</td>
<td>Isoflurane Vaporizer, ventilator&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.15&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>Non-irritant, smooth induction</td>
<td>good</td>
<td>Intermediate</td>
<td>year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1. 2nd most likely to cause arrhythmias 2. Raised ICP. 3. Malignant hyperthermia</td>
<td>1 in 800,000</td>
<td>§9&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Epilepsy</td>
<td>Enflurane Vaporizer, ventilator&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.88&lt;sup&gt;e&lt;/sup&gt;</td>
<td>$62/250ml&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>Sevoflurane</td>
<td>Non-irritant, smooth induction</td>
<td>good</td>
<td>Rapid</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1. Malignant hyperthermia 2. Potential renal toxicity from compound A 3. Emergency agitation in children&lt;sup&gt;i&lt;/sup&gt;</td>
<td>None&lt;sup&gt;i&lt;/sup&gt;</td>
<td>§2&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1-2L fresh gas flow required</td>
<td>Sevoflurane Vaporizer, ventilator&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.05&lt;sup&gt;e&lt;/sup&gt;</td>
<td>$176/250ml&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>Desflurane</td>
<td>Highly irritant, considered very poor</td>
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<td>Rapid (marginally faster than sevo)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>year&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1. Malignant hyperthermia 2. Headache 3. Hypersensitivity, dizziness</td>
<td>&lt;1 in 10,000,000</td>
<td>§3&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Not suitable for induction or use in non-intubated children</td>
<td>Desflurane MODIFIED HEAT Vaporizer, ventilator&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6&lt;sup&gt;l&lt;/sup&gt;</td>
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<td>Trichlor-ethylene</td>
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<td>Adjunct</td>
<td>Can have prolonged sedative effects&lt;sup&gt;i&lt;/sup&gt;</td>
<td>yes&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1. Cardiac arrhythmias 2. Headache</td>
<td>Consider risks to mother and fetus&lt;sup&gt;i&lt;/sup&gt;</td>
<td>§1&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Not for co-administration of epinephrine 2. Adjunctivity</td>
<td>Trichlor-ethylene Vaporizer&lt;sup&gt;j&lt;/sup&gt;</td>
<td>0.17&lt;sup&gt;j&lt;/sup&gt;</td>
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<td>Used, Slow</td>
<td>Used</td>
<td>Slow</td>
<td>Yes ++&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Pneumothorax, convulsions in febrile patients&lt;sup&gt;i&lt;/sup&gt;</td>
<td>3rd trimester depressed respiratory function&lt;sup&gt;i&lt;/sup&gt;</td>
<td>§3&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Flammable, Can’t be used with diathermy</td>
<td>Ether Vaporizer&lt;sup&gt;j&lt;/sup&gt;</td>
<td>1.92&lt;sup&gt;j&lt;/sup&gt;</td>
<td>$3.78/500ml&lt;sup&gt;j&lt;/sup&gt;</td>
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<td>Nitrous oxide</td>
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<td>Adjunct</td>
<td>Rapid elimination&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Yes, possibly increases incidence of PONV when used with other inhalational&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Megaloblastic anaemia, leukopenia, agranulocytosis, neuropathy&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Category A1</td>
<td>1. Air filled nappies 2. Use Oxygen supply</td>
<td>Supply cylinders&lt;sup&gt;j&lt;/sup&gt;</td>
<td>104&lt;sup&gt;l&lt;/sup&gt;</td>
<td>Can be expensive and hard to transport in developing countries&lt;sup&gt;j&lt;/sup&gt;</td>
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**KEY:**
- *Incidence of PONV thought to be similar amongst halothane and modern inhalation<sup>i</sup>.
- PONV = Postoperative nausea and vomiting
- MAC = Minimum Alveolar Concentration
- IDPI = International drug price indicator guide
- ICP = Intracranial pressure

**Notes:**
- A = poentially fatal convulsions in febrile patients
- B = Air filled nappies
- C = Can’t be used with diathermy
- D = Flammable
- E = Need Oxygen supply
- F = Category A1
- G = Rapid elimination
- H = Consider risk to mother and fetus
- I = Hypersensitivity, dizziness
- J = Epilepsy
- K = Headache
- L = Flammable
- M = Cardiac arrhythmias
- N = Not suitable for induction or use in non-intubated children
- O = Flammable
- P = Megaloblastic anaemia
- Q = Leukopenia
- R = Agranulocytosis
- S = Megaloblastic anaemia
- T = Neuropathy
- U = Category A1
- V = Air filled nappies
- W = Need Oxygen supply
- X = Can’t be used with diathermy
- Y = Flammable
- Z = Cardiac arrhythmias
References for table 4a: comparison of inhalational anaesthetic agents


D. International drug price indicator guide: http://erc.msh.org/dmpguide/


F. Sevoflurane product information


H. Enflurane product information


K. WHO model prescribing information: drugs used in anaesthesia

### Table 4b: Effects of inhaled anaesthetics

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<td>↓</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Coronary steal</td>
<td>no</td>
<td>possibly</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Splanchnic blood flow</td>
<td>↓</td>
<td>unchanged</td>
<td>↓</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Sensitization to catecholamines</td>
<td>↑↑↑</td>
<td>nil</td>
<td>↑</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td><strong>Respiratory effects:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓↓</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>PaCO2</td>
<td>unchanged</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Other effects:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cerebral O2 requirement</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>EEG</td>
<td>burst suppression</td>
<td>burst suppression</td>
<td>epileptiform activity</td>
<td>burst suppression</td>
<td>burst suppression</td>
</tr>
<tr>
<td>Effect on uterus</td>
<td>some relaxation</td>
<td>some relaxation</td>
<td>some relaxation</td>
<td>some relaxation</td>
<td>some relaxation</td>
</tr>
<tr>
<td>Potentiation of muscle relaxation</td>
<td>some</td>
<td>significant</td>
<td>significant</td>
<td>significant</td>
<td>significant</td>
</tr>
<tr>
<td>Analgesia</td>
<td>some</td>
<td>some</td>
<td>some</td>
<td>some</td>
<td>some</td>
</tr>
</tbody>
</table>

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## Table 5: Comparison of intravenous anaesthetic medicines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sedation for short procedures</th>
<th>Induction</th>
<th>Maintenance</th>
<th>Recovery</th>
<th>Physiological effects</th>
<th>PONV</th>
<th>Adverse outcomes/effects</th>
<th>Pregnancy category</th>
<th>Limitations/contrindications</th>
<th>Dose (Induction)</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>Safe (Level A recommendation)¹</td>
<td>Used - IV or IM</td>
<td>Widely used in developing nations. Often used without endotracheal intubation, and for sole operator</td>
<td>10-20% of adults experience hallucination or other emergence phenomena²</td>
<td>Particularly useful in shock/ impaired cardiovascular function, can raise BP (although these effects are dependant on endogenous noradrenaline). Airway reflexes and spontaneous ventilation</td>
<td>Infrequent⁴</td>
<td>Emergence hallucinations, hypertension, pain on injection, rarely laryngospasm, arrhythmias⁵</td>
<td>category A⁴</td>
<td>Not suitable if raised blood pressure or intraocular pressure. Contraindicated in stroke/ myocardial infarction/ valvular heart disease⁶</td>
<td>IV 1-4.5mg/kg</td>
<td>GBP 4.22/200mg⁷</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>Not commonly used - causes hangover, prolonged somnolence</td>
<td>Used</td>
<td>Not commonly used - causes hangover, prolonged somnolence</td>
<td>Rapid after single dose, becomes prolonged after multiple doses, some hangover effect⁴</td>
<td>Decreases blood pressure (but less than propofol). Respiratory depression²</td>
<td>Uncommon</td>
<td>Prolonged somnolence with repeated doses, cardiorespiratory depression, infrequently laryngospasm, bronchospasm⁴</td>
<td>category A⁴</td>
<td>Not suited for use with LMA.⁶ Porphyria⁴</td>
<td>IV 3-5mg/kg</td>
<td>GBP 3.06/500mg⁷</td>
</tr>
<tr>
<td>Propofol</td>
<td>Safe (Level B recommendation)¹</td>
<td>Used</td>
<td>Widely used in developed nations (TCI/MCI)</td>
<td>Rapid, smooth recovery from general anaesthesia⁴</td>
<td>Peripheral vasodilation, hypotension. Respiratory depression²</td>
<td>Least often of anaesthetic agents</td>
<td>Pain on injection, bradycardia, hypotension, apnoea, infrequently arrhythmias, thrombosis/ phlebitis at injection site, rarely seizure, pancreatitis, superficial infection</td>
<td>category C⁴</td>
<td>Allergy to soya oil, egg lecithin⁴</td>
<td>IV 2-2.5mg/kg</td>
<td>GBP 2.33/200mg⁷</td>
</tr>
<tr>
<td>Etomidate</td>
<td>Safe (Level C recommendation)¹</td>
<td>Used</td>
<td>Not commonly used²</td>
<td>Frequently unpleasant due to nausea and vomiting⁴</td>
<td>Particularly useful in shock/ impaired cardiovascular function. Respiratory depression²</td>
<td>Frequent¹</td>
<td>1. Adrenal suppression, pain on injection⁷ thrombophlebitis at injection site⁸</td>
<td>Depresses neonatal resp in 3rd trimester⁷</td>
<td>Not suited for use with LMA ⁶</td>
<td>IV 0.3mg/kg</td>
<td>GBP 1.50/20mg⁷</td>
</tr>
</tbody>
</table>

### KEY:
- **PONV** = Post operative nausea and vomiting
- **IV** = Intravenous
- **IM** = Intramuscular
- **LMA** = Laryngeal mask airway
- **GBP** = Great Brittish Pound
- **TCI** = Target controlled infusion
- **MCI** = Manually controlled infusion
References for table 5: comparison of intravenous anaesthetic medicines:


### Table 6: Comparison of non-depolarizing neuromuscular blockers (AMH table)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (minutes)¹,²</th>
<th>Duration of action (minutes)¹</th>
<th>Histamine release³</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>initial dose</td>
<td>maintenance dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| atracurium | 1.5               | 30–40                         | 15–25             | yes                       | • no effect on heart rate⁴  
• can be used in renal or hepatic impairment |
| cisatracurium | 2                  | 30–40                         | 20                | no                        | • no effect on heart rate⁴  
• can be used in renal or hepatic impairment |
| mivacurium | 2–2.5             | 15–30                         | 15                | yes                       | • no effect on heart rate⁴  
• metabolised by plasma cholinesterase; prolonged action in severe renal or hepatic impairment |
| pancuronium | 1.5–2.5         | 60–120                        | 25–60             | no                        | • vagolytic and sympathomimetic effects (tachycardia, hypertension)  
• prolonged action in severe renal or hepatic impairment |
| rocuronium | 1                 | 30–40                         | 15–20             | no                        | • may cause tachycardia at high doses  
• prolonged action in severe renal or hepatic impairment |
| vecuronium | 2–3               | 20–40                         | 20–40             | no                        | • no effect on heart rate⁴  
• prolonged action in severe renal or hepatic impairment |

¹onset and duration of action are dose-related; times given are for recommended doses
²time to satisfactory intubating conditions
³can cause flushing, hypotension, tachycardia, bronchospasm and rarely anaphylactoid reactions
⁴will not counteract bradycardia produced by many anaesthetics or by vagal stimulation during surgery; bradycardia may be more common with these drugs
### Table 7: Comparison of medicines for neuromuscular blockade

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose: mg/kg</th>
<th>Time maximal blockade: minutes</th>
<th>Recovery: minutes (25% baseline)</th>
<th>Recovery: minutes (75% baseline)</th>
<th>Comments</th>
<th>Cost (GBP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>0.2</td>
<td>7.1</td>
<td>47 (20% recovery)</td>
<td>90 (70% recovery)</td>
<td>1. Slow onset and very slow recovery</td>
<td>£0.70/100mg (2ml)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>£1.66/25mg (2.5ml)</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>£2.04/5mg (2.5ml)</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>£2.79/10mg (5ml)</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>£0.65/4mg (2ml)</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>£3.95/10mg (vial)</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>See AMH table</td>
<td>£3.01/50mg (5ml)</td>
</tr>
</tbody>
</table>