Proposal for the Re-inclusion of the drug Ether in the Anaesthetics section of the WHO Model List of Essential Medicines (EML)

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Summary

Ether was deleted from the WHO Model List of Essential Medicines in 2005. The WHO Expert Committee cited Ether’s cumbersome transport and storage requirements, its declining use and the availability of the preferred alternative fluorinated inhalational agent Halothane. Both the ISDB (International Society of Drug Bulletins) and the WFSA (World Federation of Societies of Anaesthesiologists) had suggested that Ether be retained on the WHO Model List because of its low cost and relative safety when used by inexperienced staff and especially in the absence of oxygen.

Ether remains the safest, cheapest and often the only available volatile anaesthetic agent for many millions of people requiring surgical procedures.

Ether should be re-instated to the WHO Model List of Essential Medicines to ensure its ongoing availability for life saving surgery, especially Caesarean Section in the low income countries of East Africa.

Background

It is estimated that surgical conditions account for around 11% of the Global Burden of Disease (GBD). This may well be an underestimate as it does not account for acute abdominal emergencies and surgical infections.

Anaesthesia and surgery are not without their risks. A central hospital in Malawi reported in 2000 an avoidable anaesthesia-mortality-rate of one death per 504 anaesthetics, in 2005 a district hospital in Zimbabwe reported one death per 482 anaesthetics, and also in 2005 a teaching hospital in Togo reported one death per 133 anaesthetics. In a Sub Saharan African series in 2005, nearly 50% of anaesthetic deaths were in mothers undergoing caesarean section. A Nigerian teaching hospital reported an avoidable anaesthesia-mortality-rate for caesarean section of one per 387 anaesthetics in a study published in 2006.

WHO is undertaking a number of global and regional initiatives to address surgical safety. The Global Initiative for Emergency and Essential Surgical Care (GIEESC) which commenced in 2005 focuses on access and quality. As part of this Global Initiative an Integrated Management for Emergency and Essential Surgical Care (IMEESC) toolkit was developed. This includes a prescriptive list of equipment required at referral, district and smaller hospitals or health centres. The reality of the situation in many low income countries is far from this ideal.

A 2001 study from Tanzania found that the major obstacle to safe anaesthesia was a lack of oxygen and suitable anaesthetic equipment to deliver anaesthetic agents.

A 2007 survey of Ugandan anaesthetists showed that only 23% of anaesthetists had the facilities to deliver safe anaesthesia to an adult having major surgery, 13% to deliver safe anaesthesia to a child, and 6% had the facilities to deliver safe anaesthesia to a mother undergoing caesarean section. Furthermore, ten anaesthetists were working without oxygen supplies.

Another study in 2007 of 550 Sub Saharan health facilities that were expected to offer basic emergency obstetric care showed that few had running water, electricity, a functional operating theatre, or midwives.
A 2009 study in Uganda found that none of the hospitals surveyed consistently met the standards for a WHO level 2 hospital in the previous three months and only seven out of twenty eight hospitals met this standard “sometimes”\(^{13}\).

Notwithstanding the lack of training and trained anaesthetists, the consistent finding of these studies is that safe anaesthesia requires a minimum of equipment and an assured supply of drugs. Many hospitals in the low income countries of Africa cannot afford to invest in newer anaesthesia health technologies. But fortunately the older technologies have a proven performance record.

**Ether anaesthesia in Sub Saharan Africa and elsewhere**

Draw over Ether anaesthesia has been widely practiced for many years in the countries of East Africa. The practice remains widespread in Uganda and Tanzania. In 2007 Hodges et Al found that in Uganda, Ether is the “most widely used volatile agent and always available to 68% of the respondents”\(^{11}\). More precise data for other countries is difficult to obtain. However Ether is probably only used in a handful of other countries including Malawi, some missionary hospitals in West Africa (Niger, Cameroon), West Timor, remote rural hospitals in Nepal and possibly missionary hospitals in India. Ether use in rural hospitals in Java, Indonesia was only abandoned in the last ten years only because of difficulties with supply (personal communication Professor Eddy Rahardjo).

Ether anaesthesia is a simple and safe technique for the administration of general anaesthesia. It requires minimal equipment for its delivery and is not dependant on the expensive and logistically challenging supply of oxygen cylinders\(^{14}\) as it can be used with low pressure oxygen from oxygen concentrators. Ether draw over anaesthesia is given by a draw over vaporiser (Epstein Mackintosh Oxford EMO or Portable Anaesthesia Complete PAC). Ether is still listed as an essential drug on the IMEESC toolkit list of essential anaesthetic supplies in WHO level 2 hospitals\(^{9}\).

The general anaesthetic drug Halothane can also be administered by a variety of draw over vaporisers (Oxford Miniature Vaporiser OMV, Portable Anaesthesia Complete PAC and the Diamedica Drawover Vaporiser DDV). In contrast to Ether, Halothane is a vasodilating and myocardial depressant drug which lowers the blood pressure and to be given safely needs a well trained anaesthetist, reliable apparatus and monitoring equipment. The sympathomimetic effects of Ether allow Ether anaesthesia to be more safely administered with the limited human, equipment and supply resources available in many low income countries.

The price of Ether compares favourably with the cost of Halothane: $3.78 / 500 mls of Ether and $20 / 250 mls Halothane\(^{15}\). There is certainly an increase in consumption of Ether in regard to the relative solubility and potency (MAC) of the drugs but not a 10.5 fold increase.

Halothane continuous flow anaesthesia machines (Boyles type) are relatively complex and need high pressure oxygen from cylinders or bulk liquid oxygen supplies. The monitoring and maintenance requirements for safe provision of anaesthesia with these systems are significantly increased. Reliable Halothane continuous flow anaesthesia remains an unobtainable dream for many hospitals in developing countries.

However in spite these considerations, the real issue is not what is the best agent or technique for general anaesthesia but rather what apparatus is available currently and will continue to be available for the foreseeable future in many low income country hospitals. This is especially germane in the rural areas of Sub Saharan East Africa where a large number of emergency life saving general surgical and obstetric interventions take place\(^{16}\). Aspirational changes to standards will not by themselves improve health care in low income countries.
The procurement of Ether and administration of Ether anaesthesia has not been made any easier by the removal of Ether from the WHO Essential Medicines List. Dr Ray Towey in the St Mary’s hospital in Lacor, Gulu, Uganda now sources his Ether from a factory in Norway and Ernestina Kimaro from the Buganda Medical Centre in Mwanza, Tanzania sources her supply from India (personal communication Dr Ray Towey and Ernestina Kimaro).

**Conclusion**

Ether should be re-instated in the Anaesthetics section of the Essential Medicines WHO Model List, in subsection 1.1 General anaesthetics and oxygen.

Ether should be included as an “individual medicine” and Halothane should retain the “square box” symbol unless Isoflurane is added to the EML.
Summary

1 Summary: This is a proposal for the re-instatement of Ether as a general anaesthetic agent.

2 WHO focal point:

3 Organisations consulted and supporting this application: World Federation of Societies of Anaesthesiologists

4 International Nonproprietary Name: Ether

5 Formulation: 500 ml bottles

6 International availability:

a) Eterfabrikk
   Etereveien 12
   0690 Oslo
   Norway
   Email post@eter.no Telephone +47 22 78 26 00
b) Mandkrishna Chemicals Pvt Ltd
   Mumbai Agra Road
   Nardana 425404 Dhule, Maharashtra
   India

7 Listing: as an individual medicine

8 Public Health relevance:

Surgery and anaesthesia in Low Income Countries.

It is estimated that surgical conditions account for around 11% of the Global Burden of Disease (GBD). This may well be an underestimate as it does not account for acute abdominal emergencies and surgical infections^2.

Anaesthesia and surgery are not without their risks^3. A central hospital in Malawi reported in 2000 an avoidable anaesthesia-mortality-rate of one death per 504 anaesthetics^4, in 2005 a district hospital in Zimbabwe reported one death per 482 anaesthetics^5, and also in 2005 a teaching hospital in Togo reported one death per 133 anaesthetics^6. In a Sub Saharan African series in 2005, nearly 50% of anaesthetic deaths were in mothers undergoing caesarean section^6. A Nigerian teaching hospital reported an avoidable anaesthesia-mortality-rate for caesarean section of one per 387 anaesthetics in a study published in 2006^7.

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A 2001 study from Tanzania found that the major obstacle to safe anaesthesia was a lack of oxygen and suitable anaesthetic equipment to deliver anaesthetic agents^10.
A 2007 survey of Ugandan anaesthetists showed that only 23% of anaesthetists had the facilities to deliver safe anaesthesia to an adult having major surgery, 13% to deliver safe anaesthesia to a child, and 6% had the facilities to deliver safe anaesthesia to a mother undergoing caesarean section. Furthermore, ten anaesthetists were working without oxygen supplies\textsuperscript{11}.

Another study in 2007 of 550 Sub Saharan health facilities that were expected to offer basic emergency obstetric care showed that few had running water, electricity, a functional operating theatre, or midwives\textsuperscript{12}.

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9 Treatment details

Ether is a volatile anaesthetic agent used to induce and maintain general anaesthesia. It is a vapour which is administered from a device (vaporiser) which produces a known concentration of the vapour from the liquid Ether. Ether vapour is mixed with air and oxygen and delivered to a patient by means of the breathing system or circuit (wide bore anaesthetic tubing, a ventilating device and a one way valve). It is used in a dose range between 2% and 15% (inspired percentages). Patients breathing spontaneously require between 6%-8% for surgery whilst ventilated patients usually need between 2% and 4%. Because of its sympathomimetic effects it is useful for shocked or haemorrhaging (especially obstetric) patients as it supports the circulatory system. Ether is pharmacodynamically a safer drug than the newer volatile agents (Halothane, Enflurane, Isoflurane and Sevoflurane) when administered by personnel with limited training or supervision. Ether has the added benefit of providing post operative analgesia for a period after surgery.

10 Summary of comparative effectiveness

There is no literature directly comparing Ether with the newer volatile anaesthetic agents introduced over the last fifty years. Ether was first used in 1846 and continued to be used in developed countries until the 1970s. This one hundred and twenty years of use is a testament to the safety and effectiveness of Ether.

Halothane use increased and Ether use decreased in developed countries because Halothane offered three advantages: 1 Halothane is less soluble in the blood and hence changing the depth of anaesthesia is more quickly achieved. 2 Halothane is a more potent anaesthetic drug and this also helps rapid titration of the depth of anaesthesia. 3 Halothane is neither flammable nor explosive. (Ether is safe when used with scavenging tubing and adherence to a few basic electrical safety rules.)

It is important to note that none of these reasons directly relate to an increased effectiveness of the Halothane. In the hands of trained physician anaesthetists Halothane was much easier to use because its effects could be so rapidly adjusted. In many ways however Halothane is a more dangerous drug requiring accurate measurement of blood pressure, oxygen saturation and inspired concentrations of volatile agent in order to safely give an anaesthetic. The equipment required to measure oxygen saturations and inspired concentration of volatile agents are rarely available in resource poor settings.
Unlike the newer volatile agents, Ether provides sufficient muscular relaxation to permit abdominal operations to be undertaken without the use of long acting muscle relaxant drugs (e.g. vecuronium, alcuronium).

Ether is one tenth the price of Halothane and one twentieth the price of Isoflurane. Although there is a difference in the amounts of agent used because of the difference in solubilities, there is not a ten or twenty fold difference.

### 11 Summary of comparative evidence on safety

There have been no clinical trials comparing the safety of Ether to the newer volatile agents. The long history of its clinical use is presumptive evidence of the safety of Ether. The continued use of Ether in resource poor low income countries reflects the safety and its suitability in these settings.

The pharmacokinetic properties of the drug enhance its safety profile. The high solubility of ether and its relatively high MAC (minimum alveolar concentration to achieve surgical anaesthesia) make it difficult to administer an over dosage compared to the newer volatile agents where over dosage can be relatively easily given. Ether does not cause an immunological hepatitis after repeat exposures (Halothane hepatitis although uncommon, is a serious complication with a mortality rate between 30% and 70%). Unlike Halothane, Ether does not sensitise the heart to catecholamines.

Ether is a safer drug to use with sick, dehydrated or hypovolaemic patients. These conditions are more commonly encountered in low income countries where patients present late in the course of their illness.

Halothane is a potent myocardial depressant and must be used with great caution in the presence of cardiac failure. In contrast Ether is a cardiac stimulant which leads to an increase in cardiac output and blood pressure. Ether is a respiratory stimulant whereas Halothane depresses respiratory function.

The avoidance of neuromuscular blocking drugs with Ether is an additional safety factor. At the completion of surgery, patients who have received non depolarising neuromuscular blocking drugs (necessary when Halothane is used for intra abdominal operations) who are inadequately “reversed” or remain partially paralysed are at great risk of hypoxia. This risk is increased with a lack of training of anaesthesia providers and insufficiently resourced post operative care areas (Recovery rooms).

### 12 Summary of available data on comparative cost and cost-effectiveness: Ether $3.50-$3.78/500mls, Halothane $20-$40.79/250mls

### 13 Summary of Regulatory status


Australia: S4 drug.

### 14 Availability of pharmacopoeial standards. A listing for anaesthetic Ether is to be found in the British Pharmacopoeia
Ether (diethyl ether)

Inhalation

Volatile liquid

Ether is a volatile anaesthetic with a very strong and characteristic smell. It is a flammable liquid and is explosive in oxygen in concentrations above 1.5%.

Uses: Maintenance of anaesthesia. Inhalational induction of anaesthesia is slow due to the solubility of Ether.

Contra-indications: There are no absolute contra-indications for Ether.

Precautions: Use a specifically calibrated Ether vaporiser. Avoid naked flames in the presence of Ether vapour. Avoid using diathermy in the presence of Ether/oxygen mixtures. Where possible scavenge exhaled Ether/air mixtures to avoid contact between Ether vapour and diathermy apparatus or other electrical devices. No potential source of combustion or sparking should be allowed within 30cm of an expiratory valve or scavenging tubing emitting Ether vapour. Minimise the risk of static discharge from operating theatre equipment especially in hot and dry climates. It is recommended to mount oxygen concentrators one meter above the floor to reduce the chance of electrical sparks from coming into contact with Ether vapour.

Dose: Administration of Atropine is useful to reduce salivary and bronchial secretions. Inhalational induction: slowly increase the concentrations of inspired Ether vapour by 1% every 4-6 breaths. Increments of 2.5% may be used after 10%. Maintenance: spontaneously breathing patients require 6-8% Ether. Light anaesthesia can be obtained with 3-5% and deep anaesthesia with concentrations up to 10%. Patients receiving muscle relaxants may only require 2-4% Ether.

Adverse effects: post operative nausea and vomiting associated with increased doses of Ether; less frequent incidence with muscle relaxant techniques.
Appendix 1


9 http://www.who.int/entity/surgery/publications/GuideAnestheticInfrastFormatted06.pdf


14 Cardio-pulmonary function during ether/air/relaxant anaesthesia. Roberts JG, Prys-Roberts C, Moore MA, Frazer ANL. Anaesthesia 1974; 29: 4-16


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