National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Anaesthesia

Date: March 5th 2015

Medication: Sevoflurane

Current EML Status: Not included

Indication:

1. Inhalational induction of anaesthesia.
2. Maintenance of anaesthesia for short cases where rapid theatre turnover times required

Introduction:
Sevoflurane is a volatile liquid that can be used for both inhalational induction and maintenance of general anaesthesia.

Properties that make it suitable for inhalational induction include being non-irritant to airways, low blood solubility (so rapid onset and emergence from anaesthesia) and cardiovascular stability. These properties also make it an excellent agent for maintenance of anaesthesia in haemodynamically unstable patients and if rapid emergence is required.

The only alternative for inhalational induction of anaesthesia is halothane.
The alternatives for maintenance of anaesthesia are isoflurane and halothane.

Problems associated with halothane:

1. Cardiovascular depression (may be lethal)
2. Cardiac dysrhythmias (may be lethal)
3. Halothane hepatitis (may be lethal)
4. Slow onset and emergence times.
5. Postoperative nausea and vomiting
6. Lack of familiarity with its use
7. Many anaesthetic machines currently not compatible with halothane vapourisers
8. Many institutions do not have halothane vapourisers
9. Halothane becoming obsolete internationally

Evidence for above problems with halothane:

1. **Cardiovascular (CVS) depression**

   Morray JP et al[1]. Described causes of perioperative cardiac arrests related to anaesthesia from 1994-1997 as reported voluntarily from 63 institutions in USA and Canada (mostly University based Children's Hospitals) and recorded in the Pediatric Perioperative Cardiac Arrest (POCA) Registry. Here, 150 (52%) cardiac arrests were judged due to anaesthesia, of which 26 (17.3%) were solely due to

CVS depression from halothane and 11 (7.3%) due to CVS depression from halothane plus an intravenous medication (fentanyl, bupivacaine, lignocaine, propranolol, sufentanil).The median age for the 37 cardiac arrests due to halothane was 6 months and 23 (62%) were ASA physical status 1-2 ie otherwise healthy children. Mortality was 3/37 (8%) and 2 (5.4%) had permanent disability. The 3 children who died were found at post-mortem to have acquired cardiomyopathies. Sevoflurane induced CVS depression resulted in 2 (1.3%) cardiac arrests; both occurred during induction of sick children (ASA physical status 3) and both were successfully resuscitated with no sequelae.

Discussion concerning the halothane related deaths noted that 50% of children were <6 months old and 50% arrested whilst being given conventional doses of halothane (2% or less). Sensitivity to the CVS depressant effect of halothane in young babies and those with heart disease, which may not be diagnosed preoperatively, were considered contributory factors.

This article has been followed up by another, Bhananker et al 2007[2], reporting on the results of the POCA from 1998-2004. A total of 193 (49%) cardiac arrests were due to anaesthesia. There were fewer medication related cardiac arrests compared to 1994-1997 (18% vs 37%; P<0.05). Halothane induced CVS depression caused 9 cardiac arrest (5%) and sevoflurane induced CVS depression caused 6 (3%) of cardiac arrests. The discussion contributes the lower number of cardiac arrests in healthy children and infants under 1y old to the declining use of halothane.

POCA Registry Time Period	Anaesthesia related cardiac arrests (% of total cardiac arrests (CA's))	Medication related cardiac arrests (% of total anaesthesia CA's)	Halothane related cardiac arrests (% of total anaesthesia CA's)	Sevoflurane related cardiac arrests (% of total anaesthesia CA's)
1994-1997	150 (52%)	55 (37%)	37 (24%)	2 (1%)
1998-2004	193 (49%)	35 (18%)	9 (5%)	6 (3%)

Table 1. Results of the POCA Registry 1994-2004.

The conclusion from the POCA registry of anaesthesia related deaths is that due to the declining use of halothane in USA and Canada, the rate of medication related anaesthesia deaths has fallen, particularly in otherwise healthy children and infants <1y old.

2. Cardiac dysrhythmias

Pubmed Literature search using terms "halothane and dysrhythmias and anaesthesia". Filters: Human, English language, Clinical trials.

Yielded 74 articles, of which those from 1985 which compared halothane to sevoflurane or isoflurane, or investigated halothane induced dysrhythmias in otherwise healthy children were included.

Author	Study Description	Patient Inclusion criteria	Intervention	Primary Outcome	Results	Comment
asson 1985[3]	Prospective randomised trial. 60 patients.	Healthy adults having dental extractions	Halothane, enflurane or isoflurane GA.	Incidence of cardiac dysrhythmias	Higher with Halothane than isoflurane or enflurane (43% vs 5% vs 0%, P<0.05 both)	36% of patients had ventricular dysrhythmias with halothane.
Rodrigo MRC 1986[4]	Prospective randomised trial. 76 patients.	Healthy Chinese adults aged 15-30 having 3rd molar extractions	Halothane or isoflurane GA	Incidence of cardiac dysrhythmias	Incidence higher with halothane than isoflurane (60% vs 5.7%, P<0.001)	Halothane dysrhythmias mostly ventricular, especially ventricular bigeminy. No ventricular Dysrhythmias with isoflurane
Cattermole RW 1986[5]	Prospective single blind randomised study.	Healthy children 2-14y for dental surgery.	Halothane or isoflurane induction and maintenance	Incidence of induction complications and ECG abnormalities during anaesthesia.	Isoflurane more induction complications (P<0.005). More dysrhythmias with halothane (52% vs 7%, P<0.005)	Isoflurane not recommended for induction of anaesthesia.
Cripps TP 1987[6]	Prospective randomised single-blind trial. 100 patients.	Dental outpatients in dental chair.	Halothane or isoflurane.	Incidence of cardiac dysrhythmias	Incidence of ventricular dysrhythmias higher with halothane than isoflurane (18% vs 0%, P<0.0013)	Induction time longer with isoflurane and more difficult due to airway problems.
Hutchison GL 1989[7]	Prospective randomised cross-over study. 50 patients.	Healthy young adults for bilateral 3rd molar extractions	After IV induction and intubation, either halothane or isoflurane for surgery to one side and then other agent for ther side	Incidence of cardiac dysrhythmias	Incidence of ventricular dysrhythmias higher with halothane than isoflurane (3.1(mean 10.4)/min vs 0.09(mean 0.21)/min, P<0.025	More halothane ventricular dysrhythmias when used for side 1 first.
Johannesson GP 1995[8]	Prospective randomised trial. 40 patients.	Healthy children, ENT surgery, aged 1.1-7.3y.	Halothane or sevoflurane for induction and maintenance.	Incidence of cardiac dysrhythmias, anaesthesia times, CVS parameters, recovery problems	Incidence of dysrhythmias higher with halothane than sevoflurane (61% vs 5%) (9 nodal and 2 VE's vs 1 nodal rhythm)	PONV higher with halothane. (25% vs 9%). More postoperative excitement with sevoflurane unless paracetamol given pre-induction, then similar results. More rapid awakening with sevoflurane.
Meretoja OA 1996[9]	Prospective randomised trial. 120 patients.	Infants and children having bronchosco	Halothane or sevoflurane for induction and maintenance.	Induction, emergence times, cardiac Dysrhythmias,	Incidence of ventricular dysrhythmias higher with halothane than	Halothane group also more nodal rhythm,.

		py +/- gastroscopy.		patient satisfaction.	sevoflurane (33% vs 0%, P<0.0287)	Sevoflurane greater patient/parental satisfaction, faster induction and recovery.
Kataria B. 1996[10]	Phase III open label multi centre randomised comparative trial. 428 patients.	Healthy Children 0-18y, surgery > I hour. No GA < 2 weeks ago	Halothane or sevoflurane for induction and maintenance.	Anaesthetic times, complications, serum fluoride	Bradycardia more with halothane (2% vs 11%; P<0.001). Halothane dysrhythmias resulted in 2 patients removed from study.	1 patient in halothane group developed malignant hyperthermia. No significant increases in fluoride levels with sevoflurane.
Paris ST 1997[11]	Randomiseddouble blind study. 100 patients.	Outpatient dental anaesthesia children 2-12y.	Sevoflurane or halothane induction and maintenance	Incidence of cardiac dysrhythmias	Cardiac dysrhythmias halothane 62% vs sevoflurane 28% (P<0.005); halothane more ventricular dysrhythmias	Sevoflurane superior to halothane for dental anaesthesia as dysrhythmias problematic here.
Annila P 1998[12]	Prospective randomised double blind trial. 77 patients.	ASA I-II children having adenoidectomy.	IV atropine/glycopyrrolate/saline before IV induction then maintenance with halothane.	Incidence of cardiac dysrhythmias	Similar incidence of ventricular dysrhythmias all 3 groups.	Ventricular arrhythmias in 20%, 44.4%, 36% respectively.
Michalek-Sauberer A 1998-[13]	Prospective randomised trial. 42 patients.	Children aged 2-16y for surgery.	Halothane or sevoflurane for induction and maintenance.	Induction, emergence times, cardiac dysrhythmias,	No cardiac dysrhythmias either group.	Type of surgery not high risk for arrhythmias. Small study. Longer halothane emergence time (12.9 vs 16.3min but not significant – small study)
Agnor RC 1998[14]	Prospective randomised single blind trial. 51 patients.	Healthy children aged 5-12y for surgery.	Single breath induction of 8% sevoflurane in N2O, 8% sevoflurane in O2, or 5% halothane in N2O.	Induction times. Incidence of cardiac dysrhythmias	Lower incidence of dysrhythmias with both sevoflurane groups than halothane (<0.001)	Quicker induction with both groups of sevoflurane (38s and 34s vs 58s; P<0.01)
Blayney MR 1999[15]	Prospective randomised trial. 150 children.	Healthy children having dental extractions as outpatient.	Halothane or sevoflurane for induction and maintenance	Incidence of cardiac dysrhythmias	Dysrhythmias halothane 48% vs sevoflurane 8%. Dangerous types of dysrhythmias with halothane (12% were episodes VT; vs sevoflurane mostly single VE's.	Authors oted that in UK, 2 children a year died during paediatric dental GA and 5 in 1998. Suggested causal link between

						halothane induced dysrhythmias and sudden deaths during paediatric dental anaesthesia. Resulted in UK Committee on Safety of Medicines letter advising halothane should only be used in hospitals for paediatric dental anaesthesia (previously given in dental clinics)[16].
Viitanen H 1999[17]	Prospective randomised single blind trial. 70 patients.	Healthy children aged 1-3 for adenoidectomy.	Halothane or sevoflurane for induction and maintenance. Holter ECG monitor from induction to recovery.	Incidence of cardiac dysrhythmias	Lower incidence of dysrhythmias with sevoflurane than halothane (6% vs 23%, P=0.04)	In recovery, more children had dysrhythmias with halothane (P=0.04) and associated with hypoxia.
Allison C 2000[18]	Prospective randomised trial. 51 patients.	Healthy children 1-7y for strabismus repair.	Halothane or sevoflurane for induction and maintenance	Incidence of cardiorespiratory events	Higher incidence of oculocardiac reflex with halothane(79% vs 38%, P=0.009) and dysrhythmias (42% vs4%, P0.004)	Also more respiratory problems with halothane (32% vs 11%)
Desalu I 2004[19]	Prospective, descriptive study. 90 patients.	Healthy children age 6/12 -12y. In Niger.	Halothane for induction and maintenance.	Incidence of cardiac dysrhythmias and cardiovascular events.	Significant drop in blood pressure after induction (P<0.005).Dysrhythmias in 3.3%. Bradycardias in children older than 1y 9P<0.05)	Promethazine premedication resulted in less bradycardia.

Conclusion: halothane is associated with significantly more cardiac dysrhythmias than isoflurane or sevoflurane. These dysrhythmias may be life threatening. Halothane should therefore only be used if sevoflurane is not available. Halothane should only be used by medical practitioners trained and experienced in its use and the treatment of halothane induced cardiac dysrhythmias.

Paediatric dental anaesthesia is a type of surgery particularly associated with halothane induced dysrhythmias and deaths[20]. This has been attributed to stimulation of the sympathoadrenal system via the fifth cranial nerve in the presence of halothane, which sensitises the heart to adrenaline, and halothane induced slowing of the conduction systems in the heart, which allows re-entrant activity and dysrhythmias[21]. Children for dental surgery are often not premedicated as they are

usually day cases, and so often are agitated with high circulating catecholamine levels on induction. The administration of halothane and the surgical stimulation further increasing the circulating level of catecholamines, possibly in combination with respiratory obstruction, hypoxia and hypercarbia, can lead to fatal ventricular dysrhythmias.

In South Africa, paediatric dental anaesthesia is now considered a procedure suitable for Level 1 Hospitals. Here, the doctors administering anaesthesia are often junior doctors, mostly without a postgraduate qualification in anaesthesia, have limited resources and experienced assistance should complications such as halothane induced dysrhythmias arise. In this scenario it is particularly important that the safest inhalational agent should be used and therefore it is recommended that sevoflurane be available in hospitals where paediatric dental anaesthesia is performed.

3. Halothane Hepatitis (HH)

Pubmed search using the term "halothane hepatitis" and "clinical trials" and "human" only yielded 9 results of which only one could be identified from the abstract as quantifying cases of halothane hepatitis.

A. Halothane hepatitis article with clinical trial

Author	Study Description	Patient Inclusion criteria	Intervention	Primary Outcome	Results	Comment
Eghtesadi-Araghi P[22] 2008	Retrospective Case report series	Cases referred with HH 1994 - 2006	N/A	N/A	Median age 44 (18-80y), 81% women, 22% obese. Mortality 12%.	Previous halothane exposure 61%, of which 50% had reaction previously.

Pubmed search using the term "halothane hepatitis" and "human" and "English" yielded 387 articles. The abstracts of these articles were inspected for information regarding incidence and predisposing factors for halothane hepatitis and this yielded 14 articles. Table B relates to the articles including both adults and children and Table C the articles which specifically relate to children.

B. Halothane hepatitis articles relating to adults and children:

Author	Study Description	Patient Inclusion criteria	Intervention	Primary Outcome	Results	Comment
Trowell J [23] (Abstract only) 1975	Randomised controlled trial . 39 adult patients	Ca cervix for radium treatment under repeated general anesthesia.	Halothane GA or control.	Elevation of serum alanine aminotransferase (SGPT). If>100IU before next GA then removed from study.	SGPT rose in 4*/18 halothane before 3rd treatment vs 0/21 control group. Liver biopsy in 2/4* showed hepatitis.	Testing SGPT before repeated GA with halothane may have prevented severe hepatic damage.
Walton B[24] 1976	Prospective case series. 203 patients	All patients with postoperative jaundice 1970-1973 notified to the London Hospital, UK.	Records examined by hepatologists blind to type of GA given	Unexplained hepatitis after halothane exposure.	76 HH. Of these 55% had halothane <4/52 previously; 38% obese; 70% women; 68% 41-70y; mortality 17%.	Early evidence of HH and risk factors and mortality associate.
Neuberger JM [25]	Review				Incidence of HH 1/3500 – 1/35 000.	

(Abstract) 1990					Prevent by avoiding if family history of HH or previous unexplained postoperative fever or jaundice.	
Ray DC[26]	Review of studies.	Not specified – retrospective and prospective studies on HH. 187 references.			Describes epidemiology, risk factors, clinical features, pathology and aetiology of HH.	Maximum harm if repeated halothane in 28 days. No fixed safe time period.
Sutherland DE[27] (Abstract) 1992	Case report	Biochemist in animal laboratory	Administered halothane repeatedly to rats over 3y	HH.	HH resolved after removal from halothane exposure.	Occupational health hazard to repeatedly administering halothane
Voigt MD[28] 1997	Descriptive, retrospective analysis.	Hepatitis after inhaled GA, 1980-1994, Groote Schuur hospital	Halothane GA	HH	26 episodes in 22 patients. Mean age 49 (32-65). Female 68%. Obese 77%. Mortality 32%, and one liver transplantation.	Poor awareness: 3 patients had repeat halothane after previous HH (1 died).
Bjornsson E[29] 2005	Retrospective case series review. 151 reports	All fatal hepatic adverse drug reactions reported to Swedish Adverse Drug reactions Advisory Committee 1966-2002	N/A	Drug induced fatal hepatic failure	Halothane the most common drug associated with fatalities (16 cases; 11% of all fatalities)	Females (75%). Mean age 59(41-82). Duration of treatment 1 (1-3) days). No cases since 1980.
Bjornsson E[30]	Retrospective case series review. 4690 reports.	All fatal hepatic adverse drug reactions reported to National Centres participating in WHO International Drug Monitoring Programme	N/A	Death from drug induced hepatic failure.	Halothane ranked 5th. Caused 85 deaths. (Paracetamol 1st with 305 deaths)	89% of halothane cases before 1990.
Holdcroft A[31]	Retrospective case series review. 6603 patients, 11 199 reactions.	Anaesthetic agents with adverse drug reactions reported to UK Medicines and Healthcare products database up to 2004.	N/A	Anaestheic drug related adverse drug reaction.	Halothane caused most fatal events. 548 reports (822 reactions) with 211 (39% of reports) fatality rate. Cause of death not identifiable from this database.	Authors comments that halothane is no longer used in UK. Also Desflurane 8 and isoflurane 9 deaths. None from sevoflurane
Qureshi MA[32] (Abstract)	Single case report.	22y old male, laparotomy under halothane.	Halothane GA.	Developed liver failure two days postoperatively	Died after 6 days	

C. Halothane Hepatitis Articles specifically relating to children:

Author	Study Description	Patient Inclusion criteria	Intervention	Primary Outcome	Results	Comment
Warner LO[33]	Retrospective case series review. 200 311 cases.	All children receiving halothane GA at Children's	Halothane GA.	Life-threatening complications or deaths	15 patients had life-threatening complications: hepatitis (1), malignant	Hepatitis in 17y old boy. Dysrhythmias with 1mcg/kg adrenaline

		Hospital, Ohio, USA 1958-1983.			hyperthermia (10), cardiac arrhythmias (4). No deaths.	infiltration or less. MH incidence with halothane 1;20 000
Wark H[34] 1986	Descriptive prospective study. 186 patients, 1362 GA's.	Children having repeated minor, surgery, 1981-1984	Repeated halothane GA	Postoperative jaundice. Liver function tests if repeated GA after <28days	25 patients had halothane >10x one year. 69 had repeated GA<28 days, postoperative liver enzymes increased in 16 (23%) but no jaundice.	Author comment that is safe to give children repeated halothane GA; Only 20 cases of fatal halothane hepatic failure worldwide.
Plummer JL[35] (Abstract)	Descriptive, prospective study. 9 children.	Children having daily halothane GA for 2-7 weeks.	Repeated halothane GA.	Indicators of halothane metabolism: serum bromide concentrations and exhaled CTF.	A total of 10-31 GA's per child . Bromide levels non-toxic. Exhaled CTF only rose in child with viral hepatitis.	Repeated halothane GA's did not induce reductive metabolism of halothane (risk factor for HH).
Kenna JG[36]	Case series. 7 children	Children with HH referred to Kings College Hospital, London. 1978-1985	Halothane GA.	Fulimant hepatic failure after halothane GA.	7 children, 11months – 15y. Boy 3y died. Median GA's 3 (2-6). 6/7 had positive serological test for halothane liver damage.	Report establishes that fatal HH can occur in children. Same time period: 86 adults with HH and 56% mortality.

In 1986, the UK Committee on Safety of Medicines issued recommendations regarding the repeated use of halothane following reports of cases of halothane hepatitis to this Committee[37,38]. Here it was recommended that halothane not be used within 3 months of previous halothane use or if a patient developed unexplained jaundice or pyrexia after its use.

This was as a result of the analysis of 313 reports of halothane hepatitis from 1964-1985. The mortality rate in those who developed halothane hepatitis after single exposure was 29-35% and 51-56% in those exposed more than once to halothane. The incidence of halothane hepatitis given in this article was 1: 6 000 - 22,000 adults and 1 in 80,000 to 200,000 children.

The above articles show that halothane can cause hepatitis, particularly but not exclusively, after repeat exposure. Halothane hepatitis can be an occupational health hazard. Halothane hepatitis can occur in both adults and children, although more rarely in the latter. Halothane hepatitis can be fatal (the fatality rate in the above studies was 17-39%).

Due to medical records pertaining to previous anaesthetics often not being available when patients return for a second anaesthetic in South African Hospitals, and the medicolegal consequences of a patient developing life-threatening halothane hepatitis after a repeat halothane anaesthetic, it is therefore recommended by the reviewer that sevoflurane should replace halothane in South Africa in order to avoid cases of halothane hepatitis occurring.

4. Slow onset and emergence times

Speed of onset of anaesthesia and speed of awakening after the inhalational agent is discontinued, is related to how soluble an anaesthetic vapour is in blood i.e. the blood gas solubility coefficient. The faster agents have the lowest coefficient. Sevoflurane has a blood gas solubility coefficient of 0.68 which is much lower than that of halothane (2.54) or isoflurane (1.4). This results in faster induction and emergence time with sevoflurane.

In the study by Kataria[10], induction with sevoflurane was smoother (less coughing, laryngospasm, bronchospasm) and quicker than induction with halothane (2.1 vs 2.9 min, P=0.037). Sevoflurane was associated with a more rapid emergence time (10.3 vs 13.9 min, P=0.003). Similar results were also found regarding faster onset and emergence times with sevoflurane compared to halothane in the studies by Meretoja[9], Michalek-Sauberer[13] and Agnor[14].

The slow recovery from halothane anaesthesia can be prolonged and this can lead to patients being at risk for developing hypoxia postoperatively.
Froese recently discussed the 1978 study by Grocott and Miller on the effect of subanaesthetic levels of halothane in healthy adults.[39] Here it was found that due to the slow offset of halothane, low anaesthetic concentrations of halothane persisted for an hour in recovery room with the responses of these adults to hypoxaemia being blunted. Postoperatively this will increase the risk of patients developing hypoxia, particularly as usually by this time they are back in the ward and may have also received a respiratory depressant drug such as morphine.

The other alternative inhalational agent available is isoflurane. Whilst isoflurane is not suitable for inhalational induction as it is irritant to the airway at light levels of anaesthesia, resulting in laryngospasm and a “stormy”, prolonged induction[5,6], once anaesthesia has been induced with sevoflurane or halothane, then maintenance can be continued with isoflurane.

A multicentre, prospective randomised trial comparing maintenance and recovery characteristics in healthy adult patients after sevoflurane or isoflurane by Ranieri et al, found that patients could be extubated quicker after sevoflurane (9 min vs 13 mins; P=0.002)) and discharged quicker from the recovery room (19min vs 22min: P<0.05).[40]

Peduto et al did a similar study comparing sevoflurane to isoflurane but used elderly patients instead, some with severe but not incapacitating comorbid illnesses. Here it was also found that patients could be extubated quicker with sevoflurane (8 min vs 11min: P<0.001) and discharged from the recovery room quicker (21min vs 27.5min: P<0.01).[41]

For theatre lists requiring a rapid turnover of patients, it is therefore recommended that sevoflurane be used in preference to halothane for induction of anaesthesia. Isoflurane is a cheaper inhalational agent than both halothane and sevoflurane and

is therefore recommended for maintenance of anaesthesia unless rapid awakening is necessary, in which case sevoflurane should be used.

5. Postoperative nausea and vomiting

The study by Kataria[10] found a higher incidence of postoperative nausea and vomiting with halothane than sevoflurane (46% vs 31%, P=0.002). This has cost implications for additional treatment.

6. Lack of familiarity with halothane

Reviewer conducted a questionnaire survey, distributed to all SASA (South African Society of Anaesthesiologists) members and all Head of Departments of academic institutes in South African, for distribution to members of their academic departments. There were a total of 153 respondents, 2/3 of whom were specialists in anaesthesia.

Only 10% of respondents were still using halothane and 21% had not used it for more than 10 years. 72% did not feel comfortable at having to use halothane if sevoflurane were not available. 10% had never used halothane before.

This highlights that training/refresher courses in the use of halothane will have to be given if halothane were to now replace sevoflurane.

7. Many modern anaesthetic machines not compatible with halothane

The questionnaire conducted by the reviewer (see **6.**) found that of 346 anaesthetic machines in the respondents' work places, 70 could not be used with a halothane vapouriser.

8. Many institutions do not have halothane vapourisers.

The questionnaire conducted by the reviewer (see **6.**) found that for the 346 anaesthetic machines in the respondents work places, there were only 86 halothane vapourisers.

9. Halothane is becoming obsolete internationally

Personal communication by the reviewer with Safeline, the company currently manufacturing halothane for South Africa, found that halothane production by this company was being gradually reduced, with probable complete discontinuation in the next decade, due to international reduced demand for halothane.

This reduced use of halothane internationally is also noted in the literature.
For example:
Weinberg reported on the (sevoflurane 13) costs of various anaesthetic agents in state hospitals in Victoria, Australia: only isoflurane, sevoflurane and desflurane were used[42].

An editorial by Splinter[43] , for the international journal "Anesthesia and Analgesia" in 2002 was titled "Halothane: the end of an era?". Here Splinter describes how halothane was the "gold standard" inhaled anaesthetic for paediatric anaesthesia

but has now been replaced by sevoflurane as the "gold standard". Older anaesthetists were initially reluctant to change to halothane as they had learnt the art of using it but they have gradually changed to sevoflurane due to its better side effect profile. They had gone through the "more challenging learning curve" associated with halothane use and new anaesthetists can learn to use sevoflurane more easily than halothane. Studies on other paediatric anaesthetic drugs are mostly done now whilst using the "gold standard" ie sevoflurane, as maintenance.

Sevoflurane for maintenance of anaesthesia

Sevoflurane can be used for maintenance of anaesthesia (ie after induction of anaesthesia is complete). The other inhalational agent currently on the Essential Medicines List for maintenance of anaesthesia is **isoflurane**. For most clinical cases it is appropriate that isoflurane is used for maintenance as it is cheaper than sevoflurane (and halothane).[44] However, sevoflurane had greater cardiovascular stability than isoflurane and in situations in which a patient develops cardiovascular instability, then it may be appropriate to use sevoflurane until cardiovascular stability has been regained.

Another situation in which sevoflurane may be advantageous during maintenance of anaesthesia, is when laryngospasm develops. Isoflurane is irritant to the airways at light levels of anaesthesia (which is why it cannot be used as an inhalational agent, as previously described). If laryngospasm develops intraoperatively, during isoflurane use, the level of anaesthesia can be rapidly deepened using sevoflurane, before critical, life-threatening laryngospasm develops, before continuing with isoflurane maintenance.

Sevoflurane use for maintenance has been associated with agitation on emergence, particularly in children.[45] It is therefore not recommended to routinely use sevoflurane for maintenance of anaesthesia if isoflurane is available.

Evidence for cardiovascular stability of sevoflurane:

1. Ebert et al reviewed the cardiovascular responses to sevoflurane using data from published research and unpublished Phase I and III single and multicentre trials of sevoflurane sponsored by Abbott.
   In adults, sevoflurane had a more stable heart rate profile than isoflurane – in particular, sevoflurane was not associated with the increase in heart rate seen with isoflurane when inhaled concentration is increased. Sevoflurane caused less hypotension and coronary artery vasodilation and "steal" (coronary blood flow redistribution that leads to regional cardiac ischaemia) than isoflurane.[46]
2. In the study by Peduto et al comparing GA with sevoflurane and isoflurane in elderly patients, there was less hypotension with sevoflurane (10% vs 29% of patients: $P<0.02$) and fewer adverse events during induction and maintenance ($P<0.02$ and $P<0.001$ respectively).[41]

However, not all studies have shown sevoflurane to have superior cardiovascular stability intraoperatively compared to isoflurane. For example, Rooke et al studied the hemodynamic and renal effects of sevoflurane and isoflurane in patients with coronary artery disease and hypertension having non-cardiac surgery. Patients were randomly assigned to receive either sevoflurane or isoflurane (106 and 108 patients) for maintenance of anaesthesia. Both agents had similar haemodynamic profiles intraoperatively and renal outcomes.[47]

Furthermore, there is a paucity of studies which show a better clinical outcome after maintenance with sevoflurane compared to isoflurane and the evidence for benefit in patients with brain trauma is also conflicting.[48,49]

Pharmacoeconomic Considerations

A. Cost of halothane compared to sevoflurane

Halothane is currently cheaper than sevoflurane: one 250ml bottle of halothane costs R472 and one 250ml bottle of sevoflurane costs R925. However, one needs to investigate the amount of halothane and sevoflurane used per induction of anaesthesia to determine the true cost difference between these two agents.

Research into cost saving when inducing anaesthesia with sevoflurane (a fixed 8% technique versus an incremental technique) has shown that inhalational induction of anaesthesia uses 3-6ml of sevoflurane, with the fixed technique using almost twice as much sevoflurane as the incremental technique.[50] This research also enables one to estimate the cost of sevoflurane inhalational induction as **R11 – R22**, according to technique used. The amount of sevoflurane used per induction was independent of age, weight and gender, so this figure can be used as an estimate for most children.

Another study in which sevoflurane was used for induction and maintenance of anaesthesia for short procedures (total time 12 minutes) found the mean volume of sevoflurane used was 6.4ml (±2.1ml) ie cost about **R24**.[51]

As regards the amount of halothane used induction of anaesthesia, this is estimate to be up to about 12ml (personal communication with Safeline), due to the increased time that induction takes and solubility characteristics of halothane. This equates to a cost per induction with halothane of up to about **R23**.

There is therefore no or minimal cost savings when using halothane for induction compared with sevoflurane (and if the incremental induction of anaesthesia technique is used, sevoflurane may even be cheaper).

Furthermore, it should be noted that in recent years the price of sevoflurane has dropped considerably in recent years whilst the cost of halothane has increased. The price of sevoflurane is expected to fall more in future, due to increased use.

The higher cost of sevoflurane has to be offset against the following:

I. Medicolegal costs if a patient suffers a fatal or permanently disabling complication as a result of a halothane induced cardiovascular event or

halothane hepatitis.

II. Increased theatre time with halothane
III. Increased use of antidysrhythmic drugs with halothane
IV. Increased use of antiemetic drugs with halothane
V. Cost of halothane vapourisers
   Each vapouriser costs about R30 000. As mentioned in point **8**, hundreds of halothane vapourisers will have to be purchased if every anaesthetic machine in South Africa is to have halothane vapourisers instead of sevoflurane. If in the next decade the supply of halothane ceases, then this will have been a fruitless expenditure.
VI. Cost of servicing halothane vapouriser
   Due to the accumulation of thymol, the preservative required to stabilise halothane, halothane vapourisers require servicing every 6 months. This should be compared to sevoflurane vapourisers, which only have to be calibrated once a year and serviced every 5 years (10 years for the most modern sevoflurane vapourisers) as there is no preservative required for sevoflurane.
VII. Cost of anaesthetic machines
   As mentioned in point **7**, there are many modern anaesthetic machines in South African public hospitals, which are currently not compatible with halothane. These will have to be replaced for ones compatible with halothane if halothane were to replace sevoflurane.
   This number of anaesthetic machines may be in the hundreds (70 were reported as non-compatible by the respondents to the questionnaire). A modern anaesthetic machine costs in the region of R700 000 to over R1 000 000. A thorough investigation into this problem is therefore mandatory lest millions of rands worth of anaesthetic equipment becomes redundant.

B. Supply of halothane and sevoflurane to South Africa

There are currently two companies (Safeline and Abbott) manufacturing sevoflurane so there is no monopoly of supply or price.

Conversely, there is only one company (Safeline) which manufactures halothane for South Africa. This company has stated that they will reduce production of halothane in future as halothane is becoming obsolete world wide. If Safeline does not supply halothane, then South Africa will have to find another manufacturer to supply halothane. This manufacturer will have to apply for Medicines Control Council Registration for halothane and this process can take 2-3 years. There is therefore a risk that there may be a time period of a few years where South Africa can be without halothane but only have halothane vapourisers in hospitals. This would have a severely detrimental effect on anaesthesia, particularly paediatric anaesthesia. This situation is unlikely to arise if sevoflurane were to replace halothane and sevoflurane vapourisers purchased for hospitals.

C. Use of low flow anaesthesia

Modern anaesthetic machines can now use very low fresh gas flow rates. These have cut the cost of inhalational anaesthesia dramatically. Previous cost analyses of

inhalational anaesthesia have used fresh gas flow rates of up to 4l/min. In current practice it is usual to use fresh gas flow rates of 1l/min or less, which can result in very small volumes of inhalational agents being used.[52]

This article by Golembiewski also noted how vapourisers are an important consideration when choosing which inhalational agents to use in an institution. Some anaesthetic machines may only fit one vapouriser at a time. Safety problems can arise with changing vapourisers between or during cases, so one may have to select the vapourisers to start the theatre list according to predicted case mix in theatre – often mixed paediatric and adult cases so need vapourisers for agents suitable for all age groups. If only one vapouriser can be fitted to an anaesthetic machine, then sevoflurane is preferable to isoflurane as can be used for both induction and maintenance, and for both adults and children, without the risks of halothane.

D. Cost of theatre times

The more rapid emergence seen with sevoflurane than isoflurane results in faster recovery and shorter time spent in theatre, with cost saving implications.[53]

Conclusion

There is minimal cost difference between halothane and sevoflurane if the cost per induction of anaesthesia is calculated.

Halothane is associated with more life threatening complications than sevoflurane and sevoflurane should now replace halothane on the Essential Medicines List.

Sevoflurane use allows for rapid theatre turnover and can be used for maintenance in short cases where this rapid recovery is required.

There is otherwise no evidence of benefit for the use of sevoflurane for maintenance of anaesthesia and isoflurane should routinely be used for maintenance of anaesthesia.

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