National Essential Medicines List Cost analysis
Adult Hospital Level
Component: Anaesthesiology

Date: 10 September 2014
Medication: Sevoflurane vs halothane
Indication: Induction of anaesthesia in adults

Background: During the review of the 2012 Adult Hospital level Standard Treatment Guidelines, it was proposed that sevoflurane be considered for induction of inhalational anaesthesia in place of currently recommended halothane, based on safety and efficacy. A detailed medicine review showing the safety, efficacy and effectiveness of sevoflurane was developed. Information relating to adults in this medicine review is considered for this costing analysis. The medicine review concludes that halothane is associated with more life threatening complications (halothane hepatitis) than sevoflurane and that sevoflurane use allows for rapid theatre turnover (sevoflurane was shown to have faster onset and emergence times during induction, with sevoflurane compared to halothane). Of note, is the price differential between isoflurane and sevoflurane favours the use of isoflurane for maintenance of general anesthesia; available evidence does not show that sevoflurane is more beneficial than isoflurane.

Aim: Costing analysis was performed to compare costs of sevoflurane versus halothane for induction of anaesthesia in adults at secondary level of care, based on available evidence published in the literature.

Method: A search of the literature was performed to source evidence that compared the duration to induction, and MAC of sevoflurane and halothane when used for induction of general anaesthesia. The comparative costs were calculated using Dion's formula[1], commonly accepted in the anaesthesiology and pharmacology communities for cost analysis of inhalational anaesthesia gases. (Dion's formula - Cost = P x F x T x M x C/ 2 142 x d; where P: vapouriser (%), F: fresh gas flow (l/minute), T: duration (minutes), M: molecular weight (g), C: cost (rands/ml), D: density (g/ml)). Utilising statistically significant and clinically appropriate outcomes and the current contract circular prices, the cost per MAC hour, defined as the administration of the inhaled anaesthetic agent at 1 MAC for one hour[2] was calculated for sevoflurane and halothane in the context of the clinical evidence published in the literature. A sensitivity analysis was then performed, incorporating the upper and lower limits of the confidence intervals. Direct costs (medication costs) were only considered for the purpose of this analysis.

Results: A PUBMED search was done using the following seacrh strategy: "sevoflurane"[Supplementary Concept] OR "sevoflurane"[All Fields]) AND ("halothane"[MeSH Terms] OR "halothane"[All Fields]) AND induction [All Fields] AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields]) and of the 46 articles retrieved, one single RCT[3] was found to be relevant. The small RCT compared sevoflurane (n=17) or halothane (n=15) for inducing general technique. All study subjects were unpremedicated and breathed approximately 2.6 X MAC of either agent. "The mean time for induction of anaesthesia with halothane (153 ± 46 sec, SD) was slower than with sevoflurane (81 ± 22 sec, SD, $P < 0.05$), reflecting its higher blood:gas solubility".

Limitations:

i. The available evidence is a small RCT.

Assumptions:

i. Fresh gas flow rate was assumed to be the same for induction with halothane and sevoflurane.
ii. Direct cost of inhaled anaesthetic calculated using formula: Cost per MAC hour = (concentration x F x T x M x cost per mL) /(2412 x d).

[1] Dion P. The cost of anaesthetic vapours. Can J Anaesth. 1992 Jul;39(6):633.
[2] Meyer T. Clinical and economic considerations in the use of inhaled anesthesia from the perspective of health-system pharmacists and anesthesiologists. Introduction. Am J Health Syst Pharm. 2010 Apr 15;67(8 Suppl 4):S2-3.
[3] Yurino M, Kimura H. Vital capacity rapid inhalation induction technique: comparison of sevoflurane and halothane. Can J Anaesth. 1993 May;40(5 Pt 1):440-3.

iii. Cost per MAC hour reflects the cost per induction; as the volume of agent used = (concentration x F x T x M) /(2412 x d)[4].
iv. MAC% 40 for halothane = 0.75 sourced from Mapleson *et al*. (1996)[5].
v. MAC% 40 for sevoflurane = 1.80 sourced from Mapleson *et al.* (1996).
vi. Anaesthesia induction of inhalational agent in oxygen.
vii. Duration of inhaled anaesthesia delivery assumed to be mean time for induction of anaesthesia.

From a provider perspective, the comparative costs (comparing halothane to sevoflurane) were as follows:

Evidence-based cost analysis:

Agent	Concentration %	Flow rate (L/min)	Duration (min)	M (g/mol)	cost/mL	Density (g/mL)	Cost per MAC hour/ Cost per induction
Halothane	2.6x40%MAC= 2.6x0.75= 2.00	8	2.55	197.381	R 1.54	1.868	R 2.76
Sevoflurane	2.6x40%MAC= 2.6x1.8= 4.50	8	1.35	200.055	R 2.84	1.51	R 7.58

Sensitivity analysis (lower limit of the 95% confidence interval)

Agent	Concentration %	Flow rate (L/min)	Duration (min)	M (g/mol)	cost/mL	Density (g/mL)	Cost per MAC hour/ cost per induction
Halothane	2.6x40%MAC= 2.6x0.75= 2.00	8	1.78	197.381	R 1.54	1.868	R 1.93
Sevoflurane	2.6x40%MAC= 2.6x1.8= 4.50	8	0.98	200.055	R 2.84	1.51	R 5.52

Sensitivity analysis (upper limit of the 95% confidence interval)

Agent	Concentration %	Flow rate (L/min)	Duration (min)	M (g/mol)	cost/mL	Density (g/mL)	Cost per MAC hour/ cost per induction
Halothane	2.6x40%MAC= 2.6x0.75= 2.00	8	3.32	197.381	R 1.54	1.868	R 3.59
Sevoflurane	2.6x40%MAC= 2.6x1.8= 4.50	8	1.72	200.055	R 2.84	1.51	R 9.64

Clinical practice:

In clinical practice, fresh gas flow rate used varies between 0.5-2 L/minute (based on expert opinion). However, duration of administration of sevoflurane and halothane to induce anaesthesia could not be provided, and it is assumed that this would increase proportionally as the flow rate decreases. Thus, costing analysis for these scenarios was not considered.

Vapourisers:

A national picture of the different anaesthetic machines and the related vapourisers required to administer inhalational anaesthetic gases is currently not available. (A small survey of halothane use is described in the Sevoflurane medicine review).

The following table provides an overview of the some variants of vapourisers and the respective anaesthetic machine.

Anaesthetic machine	Vapouriser	Anaesthetic agent

[4] Singh PM, Trikha A, Sinha R, Borle A. Measurement of consumption of sevoflurane for short pediatric anesthetic procedures: Comparison between Dion's method and Dragger algorithm. J Anaesthesiol Clin Pharmacol. 2013 Oct;29(4):516-20. doi: 10.4103/0970-9185.119160. PubMed PMID: 24249990

[5] Mapleson WW. Effect of age on MAC in humans: a meta-analysis. Br J Anaesth. 1996 Feb;76(2):179-85.

Dräger Vapor 2000	• DW-2000 • **Selectatec** • Auto-exclusion	Halothane, Isoflurane, Sevoflurane
Dräger Vapor 3000	• Auto-exclusion	Isoflurane, Sevoflurane
Penlon Sigma Delta	• **Selectatec**	Halothane, Isoflurane, Sevoflurane
Spacelabs Blease Datum	• **Selectatec**	Halothane, Isoflurane, Sevoflurane
Datex-Ohmeda Tec 7	• **Selectatec**	Isoflurane, Sevoflurane
Datex-Ohmeda Aladdin 2	• Cassette vapourisers	Isoflurane, Sevoflurane

Anaesthetic machines with a selectec back bar enables use with all vapourisers.

Comparative direct costs of vapourisers (excluding maintenance and breakage costs) that could be sourced are listed below:

Manufacturer	Halothane vapouriser	Sevoflurane vapouriser
Dräger[6]	R 32 844.14	R 31 010.67
Penlon Sigma Delta[7]	R 19 608.00	R 19 608.00

Filling systems and filling adaptors:

A safety mechanism (mandated by ISO) is that all vapourisers must have a keyed/funnel filling system that is agent specific. Specific filling adaptors/connectors are attached to bottles of specific agents to match the filling port of the vapouriser. The bottle end of the connector has got slots that match the projections on specific agent bottle's collar Furthermore, filling systems have been colour-coded: internationally accepted colours are halothane-red, enflurane-orange, isoflurane-purple, sevoflurane-yellow and desflurane-blue.

Locally, two brands have integrated filling systems secured to the agent's bottle, which require "brand-specific" vapourisers. A piramal filler system is available to enable use of all brands of sevoflurane with a brand-specific sevoflurane vapouriser.

Conclusion:

Modelled comparative cost analysis of halothane *vs*. sevoflurane for induction of general anaesthesia showed that sevoflurane was more expensive, when direct costs of the agents were only considered. This was likewise shown in a South African economics evaluation[8] that showed that low flow sevoflurane was more expensive than low flow halothane; although this was analysed over a period of 3 hours for both induction and maintenance of anaesthesia.

It is important to note the limitations and assumptions of this model and the contribution of other components of this technology (e.g. anaesthetic machines; vapourisers; fillers, etc.) to the overall cost of using inhalational anaesthesia gases in clinical practice, as well as the safety profiles of the various agents, needs consideration during the decision-making process.

[6] Email communication from Dräger Medical South Africa (Pty) Ltd, 11th June 2015.
[7] Email communication from Philips Healthcare, 9th June 2015.
[8] Ryksen E, Diedericks BJS. Calculation of comparative utilisation and cost: a South African perspective on intravenous vs. inhalational anaesthesia for procedures of differing duration. South Afr J Anaesth Analg 2012;18(6):310-317.