Sevoflurane

Section: 1. Anaesthetics, preoperative medicines and medical gases > 1.1. General anaesthetics and oxygen > 1.1.1. General anaesthetics and oxygen > Inhalational medicines

EMLc | ATC codes: N01AB08

Indication	Anaesthetics and therapeutic gases ICD11 code: XM1880792884
INN	Sevoflurane
Medicine type	Gas
List type	Core
Formulations	**Respiratory > Inhalation > liquid:**
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Sevoflurane
DrugBank	Sevoflurane

Expert Committee recommendation

The Expert Committee noted that the use of anaesthetics has steadily increased globally over the past few years, with the expansion of health care services. The Committee recognized that volatile anaesthetics are greenhouse gases, with detrimental environmental impact due to their contribution to global warming if leaked into the atmosphere. The Committee noted that among the volatile anaesthetic gases, sevoflurane has a lower global warming potential than the alternatives, primarily desflurane, which is not currently included on the Model Lists, but also halothane and isoflurane, which are included. The Committee noted that the clinical efficacy and safety of sevoflurane appears to be similar to isoflurane, with consistent findings across type of surgery and setting. Sevoflurane is indicated for induction and maintenance of general anaesthesia in adult and paediatric patients for inpatient and outpatient surgery. The Committee also noted that vaporizers are essential components of anaesthesia equipment with inhaled anaesthetics. As with other inhalational anaesthetics, degradation and production of degradation products can occur when sevoflurane is exposed to desiccated absorbents. Since the level of anaesthesia may be altered rapidly, only vaporizers producing predictable concentrations of sevoflurane should be used. In consideration of the volatile anaesthetics already included on the Model Lists, the Committee noted that halothane is no longer used in many countries because of its harm profile. The Committee also noted that the price difference between halothane, isoflurane and sevoflurane had decreased since sevoflurane was previously considered for inclusion in the Model Lists in 2011. Therefore, the Committee recommended the inclusion of sevoflurane on the core list of the EML and EMLc as an inhalational anaesthetic based on evidence of similar efficacy and safety to isoflurane, and a lower global warming potential than the currently listed alternatives. The Committee considered that more efficient use of sevoflurane in preference to halothane and isoflurane can contribute to reducing greenhouse gas emissions. In addition, given the limited role of halothane

among anaesthetic gases, the Committee recommended that halothane be flagged for deletion from the Model Lists without further discussion in 2025, unless an application is received in support of its retention.

Background

The Model Lists currently include halothane, isoflurane and nitrous oxide as inhalational gases for general anaesthesia. A review of the evidence on inhalational anaesthetics was considered by the Expert Committee in 2011. At that time, the Model List included only halothane (with a square box) and nitrous oxide. The Committee noted that halothane was widely used in both induction and maintenance in adults and children but had been gradually replaced in high-income countries by isoflurane, enflurane, desflurane, and sevoflurane for safety reasons. Furthermore, it was noted that ensuring the availability of halothane was increasingly problematic in many settings. The Committee considered that none of these medicines was best in all situations, with choice determined by the availability of the medicines and specific vaporizers. While isoflurane causes less hepatic failure than halothane and has advantages for maintenance, it is unsuitable for induction. Enflurane also has a lower rate of hepatic failure and less cardiovascular toxicity than halothane but increases the risk of seizure and has to be avoided in patients with epilepsy. Isoflurane and enflurane have more rapid onset and recovery times than halothane. Sevoflurane and desflurane have the most rapid onset and offset of action and few adverse effects, such as airway irritation (desflurane), agitation in more than 20% of children during recovery, and convulsions (sevoflurane). Both sevoflurane and desflurane were noted to be more expensive than halothane, isoflurane or enflurane. The Committee recommended the inclusion of isoflurane but not enflurane (due to the risks of convulsions) or sevoflurane (due to cost). The Committee recommended that halothane remain listed, but the square box be removed. The Committee concluded that where available, halothane provides an affordable option for induction and maintenance of anaesthesia. However, where availability is a problem, isoflurane would provide an acceptable option for maintenance. The Committee noted that nitrous oxide can be used as a single agent where general anaesthesia is not required, or in combination with inhalational anaesthetics. Use in combination reduces the dose, toxicity and costs of inhalational drugs. The Committee therefore recommended nitrous oxide remain listed (1).

Public health relevance

According to estimates from 2016, about 6% of the world’s population requires surgery each year and about 92% of the surgeries will require anaesthesia (2). The overarching goal of anaesthesia is to block sensation to a specific area or the whole body. In general anaesthesia, the patient is kept in a safe and controlled state of unconsciousness by a mixture of medicines and sensation is blocked to the entire body. In 2008, it was estimated that about 234 million major surgical procedures are performed worldwide every year (3). Inhalational anaesthetics, including sevoflurane, are not only used in major surgeries, but may also be used in outpatient surgeries and dental procedures. The most commonly used inhalational anaesthetics are halothane, sevoflurane, desflurane, isoflurane and nitrous oxide (4). Of these, sevoflurane is the most used because of its low blood–gas solubility allowing for rapid induction and quick recovery time, less irritation to the airway passages, lower pungency and acceptable cardiovascular side-effects (5–7).

Benefits

The application presented summaries of the findings of multiple meta-analyses and clinical trials comparing sevoflurane and other EML-listed inhalational anaesthetics for various outcomes. A summary from the United States Food and Drug Administration (FDA)-approved product information for the AbbVie brand of sevoflurane was also presented (8). Meta-analyses A meta-analysis of 56 studies in adults and children found that sevoflurane reduced mean extubation time after surgery by 13% (95% confidence interval (CI) 1.4% to 23%) compared with isoflurane. Sevoflurane was also associated with reduced incidence of prolonged extubation (51%, 95% CI 49% to 54%) and reduced mean time to following commands (27%, 95% CI 18% to 36%) compared with isoflurane (9). A meta-analysis of nine studies (1562 participants) found that sevoflurane was associated with statistically significant shorter recovery times (in minutes) than isoflurane for time of emergence (mean difference (MD) –2.9, 95% CI –3.1 to –2.7), extubation (MD –1.6, 95% CI –1.9 to –1.3), response to commands (MD –3.0, 95% CI –3.3 to –

2.7), orientation (MD –4.5, 95% CI –4.8 to –4.2) and first post-operative analgesic (MD –8.9, 95% CI –10.8 to –7.0). There was no significant difference between the anaesthetics for time to discharge from recovery room (MD 0.7 minutes, 95% CI –2.7 to 4.1 minutes) (10). A meta-analysis of six studies (634 participants) compared the recovery profile after ambulatory anaesthesia for isoflurane and sevoflurane (11). Statistically significant differences were reported between isoflurane and sevoflurane, favouring sevoflurane, for time to opening eyes (2.4 minutes; 95% CI 1.8 to 2.9 minutes), time to obeying commands (2.4 minutes, 95% CI 1.8 to 2.9 minutes), time to transfer from phase I to phase II recovery (8.2 minutes, 95% CI 5.7 to 10.6 minutes), time to home readiness (5.1 minutes, 95% CI 2.8 to 7.4 minutes) and time to home discharge (25 minutes, 95% CI 0.4 to 50.0 minutes). In addition, sevoflurane patients showed significantly less postoperative drowsiness. There were no significant differences between treatments for postoperative nausea, vomiting or dizziness. A network meta-analysis of 38 randomized controlled trials (3996 participants) evaluated survival in patients undergoing cardiac surgery receiving inhalational or intravenous (IV) anaesthesia (12). Sevoflurane and desflurane were each associated with significantly reduced mortality compared with total IV anaesthesia. The posterior mean of odds ratios (OR) and 95% credible intervals (CrI) were OR 0.31 (95% CrI 0.14 to 0.64) for sevoflurane and OR 0.43 (95% CrI 0.21 to 0.82) for desflurane. A meta-analysis of 16 randomized controlled trials (961 participants) compared sevoflurane with isoflurane on postoperative outcomes of cardiac surgery (13). There were no significant differences between anaesthetics for length of time in the intensive care unit, length of hospital stay, time to extubation or levels of S100β (a marker of cerebral ischaemia) and troponin after surgery. Levels of creatinine kinase (CK)-MB 24 hours after surgery were significantly higher with isoflurane than with sevoflurane. The authors concluded that the choice of anaesthetic does not have a significant impact on postoperative outcomes. Another systematic review and meta-analysis of 68 randomized controlled trials (7104 participants) evaluated the effects of inhalational anaesthetics on mortality and postoperative pulmonary and other complications following cardiac and non-cardiac surgery (14). Overall, inhalational anaesthetics were associated with significantly reduced mortality, and fewer pulmonary and other complications compared with total IV anaesthesia. In non-cardiac surgery, inhalational anaesthetics were not associated with reduced mortality or complications. Compared with isoflurane in cardiac surgery, sevoflurane showed reduced mortality and fewer pulmonary and other complications but the differences were not statistically significant. In non-cardiac surgery, sevoflurane showed reduced mortality and fewer other complications than isoflurane, while isoflurane was associated with fewer pulmonary complications than sevoflurane. All differences were not statistically significant. A meta-analysis of six randomized controlled trials (873 participants) evaluated the effect on kidney function of sevoflurane and isoflurane 24 and 72 hours after anaesthesia (15). There were no statistically significant differences between the groups at either time point for serum/plasma creatinine, blood urea nitrogen, urinary protein or glucose excretion. Another meta-analysis of 41 randomized controlled trials also reported on the effect of sevoflurane versus other anaesthetics (inhaled and total IV anaesthesia) on renal function (16). No difference was found between the groups for serum creatinine, creatinine clearance or blood urea nitrogen at 24 hours. A meta-analysis of 23 randomized controlled trials (2363 participants) evaluated the incidence of emergence agitation in children younger than 12 years anaesthetized with sevoflurane versus halothane (17). Emergence agitation was significantly more common with sevoflurane in pooled meta-analyses of all studies (OR 2.21, 95% CI 1.77 to 2.77) and only high-quality studies (OR 1.82, 95% CI 1.37 to 2.41). Other studies A retrospective study and a prospective trial of adult patients undergoing non-cardiac surgery compared length of hospital stay for inhalational anaesthetics (18). In the retrospective analysis, the adjusted geometric mean for length of hospital stay was significantly longer for isoflurane (2.85 days) than sevoflurane (2.55 days) and desflurane (2.64 days). There was no difference between isoflurane and sevoflurane on the secondary outcome of mean 72-hour verbal response scale pain scores. In the prospective trial, no significant differences were found between sevoflurane and isoflurane for length of hospital stay. A randomized study compared the induction characteristics of maximum initial inspired concentrations of 8% sevoflurane and 5% halothane in 51 children aged 3 months to 3 years (19). There was no significant difference between treatments in the mean time to loss of consciousness, although the time was shorter with sevoflurane than halothane (72 seconds versus 76 seconds). Similarly, mean time to acceptance of the face mask and mean time taken to reach complete induction were shorter with sevoflurane but neither difference was statistically significant. Ten (of 25) and 17 (of 26) patients in the sevoflurane and halothane groups, respectively, had severe

struggling. Another study compared 2% sevoflurane with 0.75% halothane, supplementing 66% nitrous oxide in oxygen for induction, maintenance and recovery in 63 children aged 5–12 years undergoing outpatient dental extractions (20). The mean time to loss of eyelash reflex was significantly shorter with sevoflurane than halothane (89 seconds versus 127 seconds). Mean time to eye opening after anaesthesia was significantly longer with sevoflurane than halothane (167 seconds versus 102 seconds). Times to walking and standing and discharge were not significantly different between the treatment groups. Complications did not differ significantly between treatment groups during recovery, but nausea was significantly lower in sevoflurane patients than halothane patients after discharge from the hospital. A third study compared sevoflurane and halothane during induction, surgery and recovery in 100 patients aged 2–12 years undergoing outpatient dental anaesthesia (21). Mean time to loss of eyelash reflex was significantly shorter with sevoflurane than halothane (1.5 minutes versus 1.9 minutes). Mean time to insertion of mouth prop was significantly longer with sevoflurane than halothane (3.9 minutes versus 3.5 minutes). Times to eye opening and discharge were shorter for sevoflurane than halothane but the differences were not statistically significant. The incidence of arrhythmias was significantly greater for halothane than sevoflurane (62% versus 28%). A randomized trial compared recovery times with isoflurane and sevoflurane in 80 children undergoing spinal surgery (22). Sevoflurane patients had significantly shorter mean extubation times compared to isoflurane patients (6.4 minutes versus 10.7 minutes). Compared with isoflurane, sevoflurane was associated with significantly shorter mean emergence time (7.8 minutes versus 12.8 minutes) and time to full modified Aldrete score (13.9 minutes versus 20.3 minutes). Meeting the discharge criteria and postoperative events were similar for both treatment groups. Another study compared recovery times with isoflurane and sevoflurane in 84 children aged 2–24 months following cleft lip surgery (23). Sevoflurane patients had significantly shorter mean extubation times than isoflurane patients (320 seconds versus 583 seconds). The sevoflurane group also had significantly shorter mean times for spontaneous respiration, hip flexion and eye opening. A third study assessed recovery times with sevoflurane, isoflurane and desflurane in 60 children aged 7–18 years undergoing craniotomy for supratentorial tumour excision (24). Compared with isoflurane, sevoflurane patients had significantly shorter mean extubation times (14.0 minutes versus 21.3 minutes), mean emergence times (11.7 minutes versus 15.5 minutes) and mean times to reach Aldrete score ≥9 (29.3 minutes versus 35.6 minutes). The desflurane group also had significantly shorter times on all three measures versus the isoflurane group. No significant differences were seen between the sevoflurane and desflurane groups. A prospective randomized trial compared sevoflurane and isoflurane for maintenance of and recovery from anaesthesia in 104 elderly patients (25). Sevoflurane patients had significantly shorter median extubation time than isoflurane patients (8 minutes versus 11 minutes). The sevoflurane group also had significantly shorter time to eye opening (8.5 minutes versus 12.5 minutes) and time to discharge from the post-anaesthesia care unit (21 minutes versus 27.5 minutes) compared with the isoflurane group.

Harms

The application stated that most adverse events with sevoflurane were mild or moderate in severity and transient in duration. Nausea and vomiting were observed in the postoperative period, which are common sequelae of surgery and general anaesthesia and may be due to inhalational anaesthetic, other agents administered intra-operatively or postoperatively and the patient’s response to the surgical procedure. As with all potent inhaled anaesthetics, sevoflurane may cause dose–dependent cardiorespiratory depression. The most commonly reported adverse reactions with sevoflurane described were: • adults – hypotension, nausea and vomiting; • elderly people – bradycardia, hypotension and nausea; and • children – agitation, cough, vomiting and nausea. A summary of the most frequent adverse drug reactions in sevoflurane clinical trials is shown in Table 15. Table 5 (refer to TRS 1049). Important risks for sevoflurane include: • cardiovascular changes, including cardiac arrhythmias/cardiac events in children, • hepatic disorders, • malignant hyperthermia, • perioperative hyperkalaemia, • convulsions, • history of Pompe disease, • mitochondrial disorders, and • hypothermia. Systematic standardized surveillance for reports associated with these risks are conducted by AbbVie. Reports of these risks are reviewed as cases are received, and reviews of aggregate reports are performed on a quarterly basis. The application reported that no new safety signals had been detected through these surveillance activities coincident with sevoflurane therapy during the current reporting interval. Common adverse effects of halothane include hypotension, bradycardia,

arrhythmias (particularly in neonates and children) and mild liver dysfunction. Halothane has also been associated with hepatotoxicity that in some cases can lead to liver failure, so-called halothane hepatitis, which has a high mortality rate. Halothane-related hepatotoxicity has been the main reason for the declining use of this medicine in many settings (26).

Cost / cost effectiveness

Anaesthetics generally contribute to less than 5% of a hospital pharmacy budget and account for about 3–4% of the cost of a surgical procedure (27). The cost of anaesthesia is driven by the choice of volatile agent and depends on several other factors, including patient populations, duration of anaesthesia, length of surgical unit stay, and cost of the anaesthesia delivery system. Specific information on the cost of sevoflurane marketed by AbbVie was not provided in the application. Rather, the application described studies in which factors including reduced mean extubation time (9) and reduced length of hospital stay (18) associated with sevoflurane use were proposed as potentially resulting in reduced overall costs. The cost–effectiveness of general anaesthetic agents in adult and child day surgery patients was evaluated in a 2003 study in the United Kingdom (28). Total costs were calculated for individual patient resource use up to 7 days after discharge. Incremental cost–effectiveness ratios were expressed as cost per episode of postoperative nausea and vomiting avoided. In both adults and children, induction and maintenance anaesthesia with sevoflurane had higher costs and a higher incidence of postoperative nausea and vomiting and was dominated by the alternative regimens (total intravenous anaesthesia (propofol) or intravenous induction with propofol or inhalational maintenance with halothane, isoflurane or sevoflurane). In most settings, the direct costs of sevoflurane are higher than for halothane and isoflurane. A full evaluation of the comparative cost–effectiveness needs to take into account many other associated costs (e.g. delivery systems, carrier gases and disposables) (29).

WHO guidelines

WHO guidelines for surgical anaesthesia are not currently available.

Availability

Sevoflurane, in innovator and generic brands, has wide global marketing approval.

Other considerations

Global warming potential of inhaled anaesthetics The global warming potential of desflurane, isoflurane and sevoflurane have been evaluated to determine their impact on climate change (30). Various techniques were used to estimate the potential for each gas. The 20-year global warming potential values (a higher number indicates a greater impact) for sevoflurane, isoflurane and desflurane were 440, 1800 and 6810, respectively (global warming potential for carbon dioxide being 1; a ton of sevoflurane in the atmosphere thus corresponds to an emission of 440 tons of CO2). The gases atmospheric lifetimes were estimated to be 1.1, 3.2 and 14.0 years for sevoflurane, isoflurane, desflurane, respectively.

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