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Sevoflurane in Paediatric Anaesthesia

A Review

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Data Selection
Sources: Medical literature published in any language since 1966 on sevoflurane, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.
Search strategy: AdisBase search terms were 'sevoflurane', 'paediatrics' and 'anaesthesia.' Medline and EMBASE search terms were the same. Searches were last updated 22 Mar 1999.
Selection: Studies in children undergoing anaesthesia with sevoflurane. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic, pharmacokinetic and pharmacoeconomic data are also included.
Index terms: sevoflurane, paediatrics, anaesthesia, pharmacokinetics, pharmacodynamics, clinical use.

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Summary

Abstract

Sevoflurane is an ether inhalation anaesthetic agent with low pungency, a non-irritant odour and a low blood : gas partition coefficient. It can be rapidly and conveniently administered without discomfort, and its low solubility facilitates precise control over the depth of anaesthesia and a rapid and smooth induction of, and emergence from, general anaesthesia.

As an induction and maintenance agent for ambulatory and nonambulatory surgery in children, sevoflurane provides more rapid induction of, and emergence from, anaesthesia than halothane, and has similar or better patient acceptability. Time to discharge from the recovery area is usually at least as fast with sevoflurane as with halothane.

While rapid emergence from sevoflurane lessens the time spent under anaesthesia, postoperative pain may be more intense and occur earlier than during more gradual emergence.

Sevoflurane has been used successfully as an induction agent for tracheal intubation and laryngeal mask airway (LMA) insertion: time to LMA insertion is faster with sevoflurane than halothane, but the 2 drugs provide similar conditions for tracheal intubation.

The pattern and incidence of induction and emergence events such as cough, laryngospasm and agitation/excitement is similar with sevoflurane and halothane; however, sevoflurane may cause less postoperative nausea and vomiting. At present, differences have not been consistently shown between the 2 drugs in their propensity to cause postoperative excitement or agitation. Compared with halothane, sevoflurane has low potential for arrhythmogenicity.

Clinical experience does not substantiate concerns over the potential nephrotoxicity of the sevoflurane byproducts pentafluoroisopropenyl fluoromethyl ether ('Compound A') and plasma F^- ions; no renal impairment has been documented in children receiving sevoflurane in clinical trials. The potential for sevoflurane hepatotoxicity also appears negligible.
There are few trials comparing sevoflurane with agents other than halothane in paediatric anaesthesia. As well, pharmacoeconomic analyses are scarce and incompletely published; further studies are needed to determine whether shortened times to emergence will translate into cost savings.
Conclusion: Sevoflurane is a preferred anaesthetic agent for induction and maintenance of paediatric anaesthesia because of its rapid induction and recovery characteristics, lack of pungency and agreeable odour, and acceptable cardiovascular profile. Although the issue of postoperative excitement requires clarification, sevoflurane anaesthesia can be considered a rational choice for ambulatory and nonambulatory surgery in children.

Physical and Pharmacodynamic Properties

Sevoflurane is a nonpungent ether inhalation anaesthetic agent. The anaesthetic potency of sevoflurane is age-dependent, sevoflurane being less potent in children than in adults. Concomitant use with nitrous oxide (N_2O), clonidine, or opioids increases the potency of sevoflurane.

The effects of sevoflurane on various body systems generally parallel those produced by other inhalation anaesthetics (most systems are depressed in a dose-related manner). The cerebrovasodilatory effect of sevoflurane was similar to that of halothane in 18 children. Sevoflurane also has cardiovascular depressant effects that are similar in type to those of desflurane and isoflurane in patients and healthy volunteers, although comparisons with halothane in children give variable results. Administration with N_2O 60%, spontaneous ventilation or prolonged exposure to sevoflurane attenuate cardiovascular depression and myocardial contractility.

Statistically significant increases in heart rate occur in infants and children aged ≤12 years during or soon after induction of anaesthesia with sevoflurane (see also Tolerability summary). Blood pressure is decreased in this population but to a lesser extent than with desflurane, a similar extent to that with isoflurane and generally to a similar or significantly lower extent versus halothane.

Sevoflurane, in common with other inhalation anaesthetic agents, causes dose-dependent ventilatory depression which can lead to a decrease in blood pH and to apnoea. Sevoflurane caused greater respiratory depression or changes than halothane at 1 minimum alveolar concentration (MAC) in 30 infants aged 6 to 24 months. Comparison of sevoflurane and isoflurane (both at 1 MAC) in 40 children showed the 2 agents to produce a similar extent and pattern of respiratory depression.

Sevoflurane has the advantage over several other inhalation anaesthetic agents, including desflurane, isoflurane and enflurane, of causing negligible airway irritation.

Sevoflurane is degraded by CO_2 absorbents (used in the anaesthesia circuit) to pentafluoroisopropenyl fluoromethyl ether (PIFE; 'Compound A'), which is nephrotoxic in rats but has not been shown to cause clinically significant renal injury in patients undergoing anaesthesia. Many studies conducted in adults receiving sevoflurane anaesthesia have detected laboratory markers of renal injury but, overall, sevoflurane does not appear to be associated with a higher risk of

renal toxicity than isoflurane, enflurane or propofol, even when sevoflurane is administered at low flow rates in comparisons with isoflurane.

Pharmacokinetic Properties

Because of its low blood : gas solubility, sevoflurane is rapidly taken up and eliminated. The alveolar 'wash-in' rate in children is about 50% higher with sevoflurane than with halothane when either is given with N_2O.

Like other fluorinated ethers, sevoflurane undergoes dose-independent hepatic biotransformation by cytochrome P450 (CYP) 2E1, principally to inorganic fluoride ions (F^-) and hexafluoroisopropanol (HFIP). Up to 50% of plasma F^- is cleared via uptake into bone. Sevoflurane undergoes negligible renal defluorination compared with methoxyflurane.

Sevoflurane is eliminated more rapidly than halothane in children; the alveolar 'washout' rate is halved.

Clinical Efficacy

Sevoflurane reduces time to induction and emergence compared with halothane in children undergoing ambulatory and nonambulatory surgery, although the clinical importance of the difference in time to induction has been questioned. Time to induction is reduced with increasing sevoflurane concentration, use of high concentration versus incremental concentrations and the addition of N_2O.

The rapid emergence from sevoflurane anaesthesia is desirable but appears to result in earlier and more intense discomfort or pain (as measured by objective pain/discomfort scores and use of postoperative analgesia). Time to discharge from the recovery area is generally at least as fast, and patient acceptability of the anaesthetic is at least as good, with sevoflurane as with halothane.

Data are insufficient to allow any firm conclusions regarding the relative anaesthetic efficacy of sevoflurane compared with desflurane or propofol.

Several clinical studies demonstrate that children can successfully undergo tracheal intubation without a muscle relaxant or LMA insertion while receiving sevoflurane induction anaesthesia.

Although sevoflurane has been the subject of a number of theoretical cost analyses, detailed data are scarce and well designed formal cost effectiveness comparisons with other agents are not available.

Tolerability

The incidence of adverse events occurring most often during induction and emergence – coughing, laryngospasm, breath-holding and agitation/excitement – is generally similar for sevoflurane and halothane. Available evidence does not consistently show differences between the 2 drugs in their propensity to cause postoperative excitement. EEG patterns for the 2 drugs have been shown to be dissimilar, but seizure-like movement seen during sevoflurane anaesthesia has not been causally related to the drug.

Sevoflurane increases heart rate to a greater extent than halothane during induction but causes fewer instances of arrhythmias and bradycardia during anaesthesia. Sevoflurane may cause postoperative nausea and vomiting (PONV) less often than halothane; individual trials show a similar incidence of PONV for sevoflurane compared with desflurane, isoflurane and propofol.

Despite elevated plasma F^- levels, sevoflurane and other inhalation anaesthetic agents are not associated with nephrotoxicity. Numerous trials in children demonstrate that plasma F^- levels remain below the theoretical 'toxic threshold' of 50 μmol/L (for methoxyflurane) during sevoflurane anaesthesia lasting up to 9 MAC • h, with no renal impairment evident. There have been no reports of

PIFE-associated nephrotoxicity in children or adults anaesthetised with sevoflurane.

The potential for hepatic injury with sevoflurane is expected to be negligible; sevoflurane does not generate antigenic trifluoroacetyl proteins and its organic metabolite HFIP has a low binding affinity for hepatic tissue and is rapidly glucoronidated and excreted. Increases in levels of serum glutathione *S*-transferase α seen in one series of children anaesthetised with sevoflurane or halothane were not evident in another group given sevoflurane.

Like other inhalation anaesthetic agents, sevoflurane has the potential to cause malignant hyperthermia; only 2 such cases have been reported in children to date.

Drug Interactions

Sevoflurane prolongs the duration of neuromuscular blockade induced by nondepolarising muscle relaxants such as vecuronium to a greater extent than halothane or isoflurane. Dosages of neuromuscular blockers should be reduced when sevoflurane anaesthesia is used.

Agents such as isoniazid and alcohol that induce cytochrome P450 2E1 may increase sevoflurane metabolism. Whether sevoflurane may displace highly bound drugs such as phenytoin is unknown, but this interaction has occurred with other volatile fluorinated anaesthetics. Sevoflurane is synergistic with lidocaine (lignocaine) and procainamide in prolonging ventricular activation time.

Dosage and Administration

Sevoflurane is administered by inhalation with a vaporiser specifically calibrated for the agent. Delivery should be individualised according to the patient's response. Sevoflurane concentrations needed to induce anaesthesia are greater in children than in adults.

Inspired sevoflurane concentrations of 7 or 8% have been used successfully to induce anaesthesia in many studies in children. Sevoflurane is most often administered with N_2O plus O_2. Sevoflurane concentrations of 0.5 to 3% are sufficient to maintain anaesthesia during surgery. There are no flow rate restrictions in most countries where sevoflurane is approved.

Sevoflurane is contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia and should be used with caution in patients with renal insufficiency. Levels of the organic metabolite PIFE are higher when barium hydroxide lime rather than soda lime is used as a CO_2 absorbent.

1. Introduction

1.1 Physical Properties

Sevoflurane is a colourless, liquid fluoromethyl polyfluoroisopropyl ether inhalation general anaesthetic that is nonpungent and has a mild ethereal odour.[1] Table I compares the general physical properties of sevoflurane with those of other inhalation anaesthetics.

Unlike that for several other inhalation agents, the solubility of sevoflurane did not vary significantly with age.[2] The solubility of sevoflurane, halothane, desflurane and enflurane in blood increased with decreasing temperature (by about 4.5% for each degree decrease from 37°C for the first 4 agents and by about 6% for enflurane).[3]

The solubility of sevoflurane in the plastic and rubber components of an anaesthesia breathing circuit is less than that of halothane and isoflurane but greater than that of desflurane, according to partition coefficients.[4] The relatively low vapour pressure of sevoflurane (table I) allows delivery of the drug to be facilitated using conventional product-specific vaporiser technology.[1]

Sevoflurane is degraded by soda lime and barium hydroxide lime, which are used to sequester carbon dioxide (CO_2) in the anaesthesia breathing circuit. Barium hydroxide lime degrades the drug

Table I. Some physical properties of sevoflurane and other inhalation anaesthetics[1]

Parameter	**Sevoflurane (S)**	Desflurane (D)	Isoflurane (I)	Halothane (H)	Relative magnitude of effect
Odour	Pleasant	Unpleasant	Unpleasant	Pleasant	
Specific gravity at 20°C (g/ml)	1.52	1.47	1.50	1.87	H>S≈I≈D
Vapour pressure at 20°C (mm Hg)	157	669	238	243	D>H≈I>S
Boiling point at 760mm Hg (°C)	58.6	23.5	48.5	49-51	S>H≈I>D
Partition coefficient (solubility)[a]					
oil : gas	47.2-53.4	18.7	91	224	H>I>S>D
blood : gas	0.68	0.42	1.38	2.57	H>I>S>D
tissue : blood					H>S>I>D
brain	1.70	1.29	1.57	1.94	
heart	1.78	1.29	1.61	1.84	
liver	1.85	1.31	1.75	2.07	
kidney	1.15	0.94	1.05	1.16	
muscle	3.13	2.02	2.92	3.38	
fat	47.50	27.20	44.90	51.10	

a Ratio of the concentration of the drug at equilibrium in the 2 phases or tissues; **>** indicates greater than; ≈ indicates similar to.

4- to 5-fold more quickly than soda lime.[5] The main degradation product of sevoflurane is pentafluoroisopropenyl fluoromethyl ether (PIFE; 'Compound A') which is nephrotoxic in rats (as a result of β-lyase-mediated metabolism).[1,6,7] However, PIFE has not caused clinically significant nephrotoxicity in patients receiving anaesthesia [minor transient changes in renal parameters have been observed (see sections 2.5 and 5.5.2)]. This has been attributed to low PIFE concentrations and the relatively low activity of β-lyase in humans compared with rats.[7] Trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether (PMFE; 'Compound B') are also produced when sevoflurane is exposed to CO_2 absorbents.

Exposure to and generation of PIFE is strongly correlated with total sevoflurane exposure and only weakly correlated with sevoflurane concentration.[8] In contrast, the maximum inspired PIFE concentration correlates well with sevoflurane concentration.[8] In addition to the type of CO_2 sequestrant used, the rate at which sevoflurane is degraded by CO_2 absorbents is also generally dependent on the quantity of the anaesthetic, the amount of CO_2 expired and passing through the absorbent, the fresh gas flow rate and the temperature and water content of the CO_2 absorbent (barium hydroxide lime may produce more PIFE than soda lime).[1,6,9] Children, who produce a relatively small amount of CO_2 in expired gas, may have a lower risk of exposure to PIFE than adults.

Although administration of inhalation anaesthetics at low fresh gas flow rates is less costly than administration at higher rates (3 to 6 L/min) [section 4.7], a sevoflurane flow rate <2 L/min has been associated with increased production of PIFE.[10-12] However, findings of recent trials generally, although not consistently,[13,14] show no correlation between PIFE and changes in laboratory renal parameters in patients receiving sevoflurane.[11,15,16] Based on results in cynomolgus monkeys (a more appropriate model for PIFE nephrotoxicity than rats), it has been suggested that more than 25 minimum alveolar concentration (MAC) · h of sevoflurane (an exposure level rarely seen in clinical practice) could be given to patients without evidence of altered renal function.[17]

Addition of water to soda lime significantly reduced the generation of PIFE, without altering CO_2 elimination, in low-flow sevoflurane anaesthesia.[10] Interestingly, dehydration also reduced PIFE production from sevoflurane by soda lime, but increased production by barium hydroxide lime; the change from production in a 'normal' hydrated state was greater with the latter absorbent.[18] This was despite increased degradation of

sevoflurane after dehydration of both absorbents.[18]

Clinically significant, and potentially toxic, concentrations of carbon monoxide can also be produced by the degradation of inhalation anaesthetic agents by soda lime and barium hydroxide lime. However, sevoflurane produces negligible amounts of carbon monoxide compared with desflurane, with the amounts of carbon monoxide produced being less with sevoflurane than with most other inhalation anaesthetic agents (desflurane > enflurane > isoflurane >> halothane ≡ sevoflurane).[19] In swine, sevoflurane anaesthesia did not result in detectable quantities of carbon monoxide, in contrast with desflurane, enflurane and isoflurane.[20]

Sevoflurane can also be administered using molecular sieves instead of soda lime to avoid generation of breakdown products.[21]

1.2 Ideal Properties of an Inhalation Anaesthetic Agent

Inhalation anaesthetics ideally have the following main properties:

- rapid and tolerable induction of, and recovery from, anaesthesia
- rapid adjustment of the depth of anaesthesia
- adequate skeletal muscle relaxation
- a wide therapeutic index
- no toxic effects or adverse effects at doses that are normally used.[1]

Sevoflurane was first developed as an inhalation general anaesthetic agent many years ago. A previous review has indicated that, in addition to being an effective agent in adults, the drug is also useful in children.[1] This review focuses on the use of sevoflurane in the paediatric population. In general, sevoflurane meets many of the requirements for an ideal anaesthetic.

2. Pharmacodynamic Properties

The precise mechanisms by which anaesthetic agents exert their effects are not well understood. It appears that protein receptors, rather than lipid membranes, are the key targets of anaesthetic action. In addition, modulation of other intracellular activities or pharmacological receptors, such as the γ-aminobutyric acid (GABA) A receptor, may also contribute.[1]

In common with other inhalation anaesthetic agents, sevoflurane affects a number of body systems including the CNS and cardiovascular and respiratory systems as well as neuromuscular activity. These effects are generally dose-dependent and are generally, but not always, similar to those of other such agents. Table II summarises the important pharmacodynamic effects of sevoflurane, and sections 2.2 to 2.5, where possible, focus on information related to the use of the drug in children.

2.1 Potency of Sevoflurane versus Other Inhalation Anaesthetic Agents

The anaesthetic potency of sevoflurane is age-dependent (increasing with increasing age).[1,33] The drug is therefore less potent in children than in adults. When given in oxygen, the MAC (mean percentage atmospheres) that, at steady state, produces immobility in 50% of individuals exposed to a noxious stimulus was as follows:

- fullterm neonates (1 month): 3.3
- children aged 1 to <6 months: 3.0
- children aged 6 months to <3 years: 2.8
- children aged 3 to 12 years: 2.5
- adults aged 25, 40, 60 and 80 years: 2.6, 2.1, 1.7 and 1.4, respectively[5] (MAC values reported for adults aged up to 30 years were 0.73 for halothane,[34] 1.28 for isoflurane[35] and 7.25 for desflurane.[36])

Concomitant use with nitrous oxide (N_2O),[37] clonidine[38] or opioids decreases the MAC (increases the potency) of sevoflurane.[1,39] In children, administration of sevoflurane with N_2O 60% or clonidine 4 μg/kg decreased the MAC by about 25 and 40%, respectively, compared with the value in oxygen (O_2) alone.[33,37-39] The effects of clonidine and N_2O on the MAC of sevoflurane were partially additive (a 56% reduction when both agents were given with sevoflurane).[39]

Table II. Summary of the pharmacodynamic properties of sevoflurane (data obtained from reviews[1,6] and supplemented with more recent information)

CNS effects	
Intracranial pressure	↔ in patients[22,23]
Cerebrovascular resistance	↑ or ↓ in patients[22,23]
Cerebral blood flow	↑ in patients undergoing surgery ↓ or ↔ responsiveness to $paCO_2$ ↓ or ↔ responsiveness to mean arterial BP (autoregulation)
Cerebral artery flow velocity	↓ or ↔ in patients[22,24,25]
Cerebral metabolic rate of oxygen consumption	↓ or ↔ in patients[23]
EEG activity	↓ (dose dependent) in humans
Electrocorticographic spike frequency	↑ in patients with seizure disorders[26]
Psychomotor function	↓ in healthy volunteers (subanaesthetic doses)[27]
Amnesia, sedation	↑ in healthy volunteers (subanaesthetic doses)[27]
Cardiovascular effects	
Heart rate	↔ or ↑ in patients
Cardiac output	↓ in healthy volunteers
Systemic vascular resistance	↓ in healthy volunteers ↓ in patients undergoing CPB
Blood pressure	↓ (dose dependent) in humans
Mean pulmonary artery pressure	↓ in volunteers
Cardiovascular function	↓ in humans
Myocardial contractility	↓ in humans
Coronary artery blood flow	↔ in animals
Coronary vascular resistance	↓ in animals
Coronary vasodilation	↑ in animals
Regional blood flow	↓ in healthy volunteers
Peripheral vascular resistance	↓ in healthy volunteers
Temperature regulation	↓ in humans and animals
Sympathetic nervous activity	↔ in humans
Baroreflex function	↓ in humans
Respiratory function	
Ventilatory function	↓ (dose dependent) in humans
Respiration rate	↑ in humans
Minute respiratory volume	↓ in humans
Other effects	
Muscular relaxation	↑ in humans
Glucose tolerance	↓ in patients[28]
Endocrine parameters[a]	↔ (generally) in patients[29]
Serum creatinine and BUN levels	↔ or ↓ after surgery in patients (irrespective of flow rate)[8,11,12,16,30,31]
Other effects (contd)	
Other markers of renal injury[b]	↔ or ↑ in healthy volunteers (3% at 2 L/min for 8 hours)[13,15,32] ↔ or ↑ in patients[8,11]
Markers of hepatic injury[c]	↔ in healthy volunteers[13,15] ↔ or ↑ in patients[8,31]

a Plasma cortisol, aldosterone, corticotropin (adrenocorticotrophic hormone), β-endorphin–like immunoreactivity, growth hormone, glucagon and glucose levels were unaffected by sevoflurane-induced anaesthesia. Plasma prolactin levels increased by about 200% and plasma insulin levels decreased by 67%.

b Urinary albumin and total protein excretion (glomerular function) and/or urinary glucose and α-glutathione-S-transferase levels (proximal tubular function) and/or π-glutathione-S-transferase levels (distal tubular function).

c ALT and/or AST and/or total or direct bilirubin and/or alkaline phosphatase levels.

BP = blood pressure; **BUN** = blood urea nitrogen; **CPB** = cardiopulmonary bypass surgery; **$paCO_2$** = mean arterial carbon dioxide tension; ↓ indicates a decrease; ↑ indicates an increase; ↔ indicates no change.

2.2 CNS Effects

The neurohaemodynamic effects of sevoflurane generally parallel those produced by other inhalation anaesthetics.[1] Indeed, the cerebrovasodilatory effect of sevoflurane was similar to that of halothane in 18 children.[40]

Sevoflurane, in common with other halogenated anaesthetic agents, is a cerebral vasodilator that increases cerebral blood flow with a parallel decrease in the cerebral metabolic rate of oxygen consumption. However, data from adults have not clarified whether the drug maintains cerebral blood flow responsiveness to changes in mean arterial CO_2 tension or mean arterial blood pressure.[1,6]

The effects of sevoflurane on the EEG in children are discussed in section 5.2.2.

2.3 Cardiovascular Effects

Cardiovascular adverse effects are among the most common causes of postoperative complications in infants and children given inhalation anaesthetics. In general, sevoflurane has cardiovascular depressant effects that are similar in type to those of desflurane and isoflurane in patients and

healthy volunteers (reviewed by Patel and Goa[1]). Variable results have been obtained in comparisons of the effects of sevoflurane and halothane on cardiovascular function in children.

Although sevoflurane causes little fluctuation in heart rate in adults and does not alter myocardial sensitivity to epinephrine (adrenaline),[1] statistically significant ($p < 0.05$) increases in heart rate have been reported in numerous studies in infants and children aged ≤12 years during or soon after induction of anaesthesia with sevoflurane (increase of about 3 to 40 beats/min or 20% versus awake values).[33,41-48]

In 2 studies[41,43] these increases were significantly ($p < 0.05$) greater than those seen with halothane, but in another[44] the difference was not significant. Results of a study conducted in 30 infants (mean age about 6 months) indicate that sevoflurane (1 to 1.5 MAC), unlike halothane, had no significant effect on heart rate versus awake measurements; halothane-induced decreases in this parameter were significant versus sevoflurane values.[49] Heart rate was stable with both sevoflurane and halothane (1 and 1.5 MAC for both agents) in a study in 20 children.[50] Although a reduction in myocardial contractility was seen with both drugs, the decrease was significantly greater with halothane than with sevoflurane and values for the latter agent remained within the normal range.

Sevoflurane generally decreased blood pressure in infants and children.[33,42-45,49] The decreases were smaller than with desflurane,[51] similar to those with isoflurane[45] and generally similar to[49] or significantly lower[44] than with halothane. Changes in blood pressure and the incidence of hypotension (≥30% decrease in systolic blood pressure) were inversely related to age (the study included neonates aged ≤30 days and children aged 0.5 to 12 years).[33]

Administration of suxamethonium chloride 1.5 mg/kg to 22 children receiving sevoflurane caused a significant increase in mean heart rate and no change in blood pressure.[44] In 19 children receiving halothane, administration of the muscle relaxant did not significantly alter mean values of these parameters, but 4 children developed bradycardia requiring treatment. Mean heart rate and blood pressure were significantly higher in sevoflurane versus halothane recipients after administration of suxamethonium.[44] Administration with N_2O 60%, spontaneous ventilation and prolonged exposure to sevoflurane attenuate its cardiodepressant effects.[1]

In 38 children (aged 1 to 6 years), equipotent doses of the 2 agents (with 100% oxygen) caused a significant reduction in stroke volume index but only slight nonsignificant decreases in cardiac index.[43] Cardiac index significantly decreased from awake values in 15 halothane- but not 15 sevoflurane-treated infants (mean age about 6 months) receiving equipotent doses of the drugs with N_2O 50% ($p < 0.05$ for halothane *vs* sevoflurane also).[49] Halothane had a significantly greater depressant effect on most indices of contractility than sevoflurane in this[49] and another trial in 20 children.[50] Halothane but not sevoflurane significantly reduced heart rate and ejection fraction in 22 infants with congenital heart disease.[52]

Measurements of myoglobin and creatine phosphokinase levels in 22 children aged 2 to 11 years indicate that sevoflurane caused less release of these markers of cardiac injury than halothane.[53]

Preliminary results of an electrophysiological study indicate that neither sevoflurane nor halothane had significant effects on cardiac conduction in 16 children with supraventricular tachydysrhythmias.[54] However, halothane is associated with more frequent arrhythmias than sevoflurane (section 5.3).

2.4 Respiratory Effects

Compared with adults, children are at increased risk of hypoxaemia during anaesthesia. In addition, hypoxia occurs more rapidly in younger than in older children.[55] Sevoflurane, in common with other inhalation anaesthetic agents, causes dose-dependent ventilatory depression. The decrease in ventilation rate and tidal volume and an increase in mean arterial CO_2 tension can lead to a decrease in blood pH and to apnoea. Studies in animal models

indicate that these effects may be the result of a combination of depressed diaphragmatic function and contractility and central depression of medullary respiratory neurons.[1]

Studies conducted in adults and children have produced differing results regarding the relative propensities of sevoflurane and halothane to cause respiratory depression. Both sevoflurane and halothane (at about 1 MAC) with N_2O 66% caused mild respiratory depression in 30 infants aged 6 to 24 months; there was no significant difference in end-tidal CO_2 between the 2 anaesthetic agents.[56] However, minute ventilation and respiratory frequency were lower, expiratory time was longer, inspiratory flows peaked later and expiratory flows peaked earlier with sevoflurane than with halothane in these children. In contrast, significantly greater respiratory depression occurred with sevoflurane than with halothane at 1.4 MAC but not at 1 MAC in 14 adults.[57] A comparison of sevoflurane and isoflurane (up to 1.3 MAC) in 40 children showed the 2 agents to produce a similar extent and pattern of respiratory depression.[45]

Lung and respiratory system resistance routinely increase after tracheal intubation and, on rare occasions, can cause clinical bronchospasm. Sevoflurane, halothane or isoflurane reduced respiratory resistance in 66 patients undergoing tracheal intubation, but the effects of sevoflurane were significantly greater than those of the other anaesthetics.[58] Sevoflurane has shown bronchodilatory effects and inhibited tracheal smooth muscle contraction in a number of studies in animals.[1,59-61]

Sevoflurane has the advantage over several other inhalation anaesthetic agents, including desflurane, isoflurane and enflurane of causing negligible airway irritation[1] (see section 5.1).

2.5 Renal Effects

As indicated in section 1.1, the degradation product of sevoflurane, PIFE, has been associated with nephrotoxicity in rats. Data concerning the renal effects of sevoflurane in children are discussed in section 5.5.2. Many studies conducted in adults receiving sevoflurane anaesthesia have detected markers of renal injury (table II), but clinically significant nephrotoxicity has not been seen.

Sevoflurane did not appear to be associated with a higher risk of renal toxicity than isoflurane, enflurane or propofol,[8,12,16,30,31,62] even when sevoflurane was administered at low flow rates in comparisons with isoflurane.[8,12,16,31] In contrast, Higuchi et al.[11] reported increased *N*-acetyl-β-glucosaminidase levels with low- and high-flow rate sevoflurane such that levels were significantly different from those reported with isoflurane, although other markers of renal function did not differ between any of the anaesthetic regimens. All changes in renal function were subclinical. Repeat anaesthesia with sevoflurane within 30 to 90 days of the first administration did not appear to alter the risk of renal (or hepatic) damage, and all markers returned to normal after the end of the study.

In a crossover comparison with desflurane, conducted in 10 healthy volunteers, sevoflurane 3% at a flow rate of 2 L/min for 8 hours significantly increased levels of markers of renal injury.[13] Such changes were not observed with desflurane 9% at the same flow rate. Sevoflurane-induced changes ranged from no significant injury to transient nephrotic range proteinurea. In contrast, 8 hours' administration of sevoflurane 1.5 MAC (at 2 L/min) to 13 healthy volunteers produced no clinically significant changes in biochemical renal markers.[15]

The effects of sevoflurane on renal function have also been assessed in patients with renal impairment at study entry. In general, the drug did not cause significant alterations in markers of renal injury in patients with mild to moderate kidney dysfunction (creatinine clearance 10 to 15 mg/L or ≥15 mg/L)[63] or chronic renal failure (haemodialysis for >2 years).[64] When compared with isoflurane, sevoflurane produced similar changes in markers of renal function in patients with moderate kidney dysfunction.[65]

3. Pharmacokinetic Properties

As there are few data on the pharmacokinetics of sevoflurane in children, this section relies mainly on information obtained in adults and re-

viewed previously in *Drugs*[1] and on the manufacturer's prescribing information.[5]

3.1 Uptake and Distribution

Because of its low blood : gas solubility (section 1.1), sevoflurane is rapidly taken up and eliminated (see section 3.3). In children, data from an abstract showed that, within the first minute, the alveolar 'wash-in' rate [the rate at which fractional end-tidal alveolar concentration (F_A) approaches the fractional inspired concentration (F_I)] for sevoflurane 7%/N_2O was about 50% higher than for halothane 4.3%/N_2O and was also about 15% higher than for sevoflurane 7%/O_2 (data presented graphically).[66]

In adults, F_A/F_I is faster for sevoflurane than for isoflurane or halothane but slower than for N_2O or desflurane.[1]

Sevoflurane is distributed to the lung, vessel-rich organs and the adjacent fat, muscle, and peripheral fat, as characterised in a 5-compartment model. The pattern and extent of tissue distribution estimated for sevoflurane is similar to that for isoflurane.[67]

3.2 Metabolism

Like other fluorinated ethers, sevoflurane undergoes dose-independent hepatic biotransformation, primarily by cytochrome P450 (CYP) 2E1,[1] but also by nonenzymatic processes,[68] to organic and inorganic fluoride metabolites.[1] Up to 5% of the absorbed sevoflurane dose is metabolised, producing inorganic fluoride ions (F^-) and hexafluoroisopropanol (HFIP) as the principal by-products. HFIP accounts for about 80% of the organic fluorinated metabolites of sevoflurane. This compound is rapidly glucuronidated and excreted in the urine.[1]

Up to 50% of fluoride clearance is nonrenal and occurs via uptake into bone. The elimination half-life ($t_{1/2}$) of F^- is 15 to 23 hours in the general population.[5]

Sevoflurane undergoes negligible renal defluorination compared with methoxyflurane, as demonstrated *in vitro*.[69] The lack of significant intrarenal metabolism may explain the lack of nephrotoxicity with sevoflurane use, despite elevations in plasma F^- levels (section 5.5.1). There appear to be no other metabolic pathways for sevoflurane;[5] however, plasma F^- levels increased significantly ($p < 0.05$) in a study of 10 children when sevoflurane was substituted for isoflurane during the anhepatic phase of orthotopic liver transplantation.[70]

3.3 Elimination

Sevoflurane is eliminated more rapidly than halothane in children. The alveolar 'washout' rate (F_A/F_{AO}, where F_{AO} is the F_A at the moment the anaesthetic is discontinued) was 0.23 for sevoflurane (n = 14) and 0.47 for halothane (n = 15) in children aged 1 to 7 years, and the $t_{1/2}$ for expired alveolar concentration (time to decline to half the steady-state value) was 80 and 280 seconds, respectively.[71]

4. Clinical Efficacy

Sevoflurane has been extensively studied for induction and maintenance of anaesthesia in children aged ≤18 years [usually American Society of Anesthesiologists (ASA) class I and II] undergoing ambulatory (day-case or outpatient) surgery (section 4.1) and, to a lesser extent, in nonambulatory surgery lasting ≤5 hours (section 4.2). A few trials specifically investigated induction parameters only, including rapid inhalation induction (section 4.3), and the use of sevoflurane for tracheal intubation and laryngeal mask airway (LMA) insertion (section 4.4).

Most trials were randomised, nonblind or evaluator-blind comparisons with other agents, most often halothane but less frequently desflurane or the intravenous agent propofol. All studies in children undergoing ambulatory dental extraction were double-blind. Various sevoflurane concentrations were used for induction (≤8%) and maintenance (≥4%) of anaesthesia; some trials measured exposure to sevoflurane or comparators according to MAC • h.

The usual objective efficacy parameters monitored were time to induction (loss of eyelash reflex) and time to early/intermediate recovery (eye opening, orientation, obeying verbal commands, time to discharge from recovery area). Emergence was either not defined or was defined as time to eye opening or first purposeful movement. Tests of postanaesthesia recovery of psychomotor or cognitive function were specified infrequently. In most cases a modified Aldrete score ≥8 signified the patient's ability to be discharged from the recovery area.

Postoperative pain was evaluated in some trials according to an objective pain score or time to first postoperative analgesia (section 4.5). Some trials assessed subjective factors such as patient cooperation with, or preference for, the anaesthetic procedure and patient rating of the drug's odour (section 4.6). A few cost analyses have been published as abstracts (section 4.7).

4.1 Ambulatory Anaesthesia

Table III summarises the largest trials (containing 80 to 525 patients) which compared sevoflurane with other inhalation anaesthetic agents in ear, nose and throat (ENT) and general surgery and the 2 studies comparing sevoflurane with the intrave-

Table III. Induction and recovery parameters of sevoflurane (S) compared with other anaesthetic agents in children undergoing ambulatory surgical procedures in randomised trials

Reference (type of procedure)	No. of pts	Anaesthetic[a]	Time to induction and recovery (min)					
			loss of eyelash reflex	extubation	emergence	obeying verbal commands	orientation	discharge from recovery area[b]
Comparisons with inhalation anaesthetic agents [halothane (H) or desflurane (D)]								
Binstock et al.[72]c (not stated)	268	S	1.7***		11.9***	17.6***		67
	257	H	2.2		19.4	26		71
Furuya et al.[73] (ENT)	50	S	2.1*	11.9**	10.1**			
	50	H	2.4	15.4	13			
Lerman et al.[74] (general)	250	S	1.3***			12.3***	22***	19.3***
	124	H	1.6			19.9	29.9	24.8
Meretoja et al.[75] (bronchoscopy/gastroscopy)[d]	60	S	0.8*		10.5-12.5*		13.5-14*	32-34*
	60	H	1.3-1.8		18.5-29.4		21.5-33.8	47-64.5
Welborn et al.[76] (ENT)	20	S		11			17	(139[f])
	20	H		10			21	(123[f])
	20	S[e]		11			19	(136[f])
	20	D[e]		5†			11†	(142[f])
Comparisons with intravenous propofol (P)								
Guard et al.[77] (urology)	25	S		7.8	18.1	23.9	26.8	29.5 (134)[f]
	25	P[g]		6.7	14.5	19.2	24.8	30.2 (131)[f]
Picard et al.[78]c (ENT)	50 in total	S		14		21		45
		P[h]		14.7		21		50

a Nitrous oxide and oxygen were included as part of the induction sequence and maintenance of anaesthesia.

b Time to achieve modified Aldrete scores of ≥8.

c Abstract.

d Values in this study are ranges of means for 3 age groups (3 to 11 months, 1 to 5 years and 6 to 15 years).

e Induction of anaesthesia with halothane.

f Time to meet home discharge criteria.

g 2 to 3 mg/kg then 7.5 to 10 mg/kg/h.

h 3 mg/kg then 6 to 15 mg/kg/h.

ENT = ear, nose and throat; **pts** = patients; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, † $p < 0.0001$ *vs* comparator(s).

Table IV. Induction and recovery parameters for sevoflurane (S) compared with halothane (H) in children undergoing ambulatory dental extraction in randomised double-blind trials

Reference	No. of patients	Anaesthetic[a]	Time to induction and recovery (min)				
			loss of eyelash reflex	loss of jaw tone	eye opening	sitting in a chair or standing	discharge
Ariffin et al.[79]	40	S	1.5*	2.1*	2.8*		23.5
	40	H	2.1	2.4	1.7		23.7
Fairgrieve et al.[46][b]	101 in total	S (≈4 MAC) H (≈4 MAC) H (≈6.66 MAC)	S≡H		H_4>S≡$H_{6.66}$	H_4>S≡$H_{6.66}$	H_4>S≡$H_{6.66}$
Paris et al.[80]	50	S	1.5**	3.9*[c]	2.3		23
	50	H	1.9	3.5[c]	2.9		23.2

a Anaesthetics were given in nitrous oxide plus oxygen.

b Abstract.

c Time to insertion of mouth prop.

MAC = minimum alveolar concentration; * $p < 0.05$, ** $p = 0.0003$ *vs* H; > indicates significantly faster with H, $p < 0.05$; ≡ indicates similar to H.

nous agent propofol (n = 50 for each). Dental extraction studies (n = 80 to 101) are outlined in table IV.

4.1.1 Sevoflurane versus Halothane

Sevoflurane consistently reduces time to induction and emergence compared with halothane (table III). However, the difference in time to induction is small (usually 0.3 to 1 minute) and its clinical importance has been questioned.[74] Discrepancies in results from various trials make it difficult to draw conclusions regarding time to discharge from the recovery area. This parameter did not differ to any significant extent between the 2 drugs in 2 studies, including the largest,[72] but differences were statistically significant in 2 other studies, notably the large well-designed trial by Lerman et al.[74]

In children undergoing dental surgery (table IV), time to induction was similar[46] or faster[79,80] with sevoflurane compared with halothane, but time to awaken was similar[80] or slower.[79] Time to discharge was generally similar.

Most of the numerous small trials conducted in ≤50 paediatric patients undergoing general[81-86] or ENT surgery[85,87,88] demonstrated significantly shorter[82,84,87,88] times to induction and faster[81,83-86,88] times to recovery with sevoflurane compared with halothane. In a few studies the times to induction[81,86] or emergence[82,87] were similar between treatment groups and 1 study found a longer time to recovery with sevoflurane.[89]

4.1.2 Sevoflurane versus Desflurane

Data are insufficient to draw any meaningful conclusions regarding the relative efficacy of sevoflurane and desflurane. Time to extubation and orientation were significantly faster with desflurane than with halothane or sevoflurane (induction with sevoflurane or halothane) in children aged 1 to 7 years.[76] Despite this, time to discharge from the recovery area did not differ among the 3 agents (table III).

Emergence as measured by limb movement, eye opening and extubation[90] was also more rapid ($p < 0.01$) with desflurane than with sevoflurane or halothane in a small trial in 40 infants with a post-conception age <60 weeks who were undergoing herniotomy.[90]

4.1.3 Sevoflurane versus Propofol

Data from 2 small studies (1 published only as an abstract) indicate similar times to recovery from anaesthesia for sevoflurane compared with intravenous propofol in children undergoing tonsillectomy[78] or urological surgery[77] (table III) [quantitative data on induction were not reported].

4.2 Nonambulatory Anaesthesia

Time to induction, extubation and emergence from anaesthesia are shorter with sevoflurane than with halothane (table V). While not all trials demonstrated statistically significant differences between the 2 drugs for all of these parameters, most did, including the largest trial.[48] Time to intubation was longer with sevoflurane plus O_2 than with sevoflurane or halothane plus N_2O/O_2;[47] otherwise, intubation times did not differ between groups.

Although time to discharge from the recovery area was significantly shorter with sevoflurane than with halothane in most trials, the largest study[48] showed no significant difference between the 2 drugs (table V).

4.3 Rapid Inhalation Induction

Induction times for various sevoflurane regimens ranged from 0.62 to 1.4 minutes in trials examining this parameter only (table VI). Time to sevoflurane induction is decreased significantly with increasing sevoflurane concentration,[95] the use of high concentration versus incremental induction[94] and the addition of N_2O.[93]

4.3.1 Sevoflurane versus Halothane

Induction time was significantly shorter with sevoflurane than with halothane in 2 of 3 small studies of rapid inhalation using differing methodologies (table VI). Sevoflurane in O_2 or N_2O produced significantly faster induction than halothane in N_2O when used as single breath vital capacity rapid inhalation induction (VCRII)[96] Immediate 8% sevoflurane induction produced significantly faster anaesthesia than incremental sevoflurane or halothane induction when given with N_2O.[97] However, in another study, onset of anaesthesia with immediate sevoflurane induction was similar to that with immediate halothane (both agents given in N_2O/O_2 by a standard inhalation technique).[98] The latter result contrasts with findings in most other clinical trials examining induction and recovery parameters (sections 4.1 and 4.2).

4.4 Tracheal Intubation and Laryngeal Mask Airway Insertion

Several clinical studies demonstrate that children can undergo tracheal intubation using sevoflurane induction and no muscle relaxant.[99-104] Time to intubation with sevoflurane was either similar to[105] or shorter[102] or longer[103] than with halothane. Among 106 patients undergoing ENT

Table V. Induction and recovery parameters of sevoflurane (S) compared with halothane (H) anaesthesia in children undergoing nonambulatory surgical procedures in randomised trials

Reference	No. of pts	Anaesthetic agent[a] (MAC • h)	Time to induction and recovery (min)						
			loss of eyelash reflex	intubation	extubation	emergence	obeying verbal commands	orientation	discharge from recovery area[b]
Funk et al.[91][c]	40 in total	S+N_2O/O_2 (1.6)	2.2**		9.1**	7.8**			33*
		H+N_2O/O_2 (1.77)	3		13.7	12.9			42
Kataria et al.[48]	214	S+N_2O/O_2 (2.2)	2.1*	10.5	11.3*	10.3**	14*	31	87.2
	214	H+N_2O/O_2 (2.2)	2.9	10.5	14.1	13.9	18.3	39.5	85.1
Sarner et al.[47]	40	S+O_2 (2.8)	1.9	6.2†	7.7				46.2
	40	S+N_2O/O_2 (2.6)	1.6	5.1	8.3				50
	40	H+N_2O/O_2 (2.5)	1.7	5.2	11.4†				60.2†
Taivainen et al.[92]	25	S+N_2O/O_2 (2)	1*	4.5	3.5	15.4***	19.5***	25.2***	S>H 0-30min
	25	H+N_2O/O_2 (2.3)	1.7	5.1	3.8	33	38.4	42.8	

a Used for induction and maintenance.

b Time to achieve modified Aldrete score of ≥8.

c Abstract.

MAC • h = area under the end-tidal concentration-time curve; **pts** = patients; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* H; † $p < 0.05$ *vs* other regimens; **>** indicates S faster than H, $p < 0.05$.

surgery in the largest trial,[105] vocal cord visibility was insufficient in significantly more sevoflurane than halothane recipients but body movement occurred in a similar percentage in each group.[105] Intubation times and conditions were similar in children receiving propofol/succinylcholine or sevoflurane.[104]

LMA insertion is becoming more frequent in paediatric ambulatory surgery. A muscle relaxant is not needed but anaesthesia must be adequate for smooth insertion. Sevoflurane has been used successfully for LMA insertion in children,[100,106-109] at a concentration less than that required for tracheal intubation,[100] and generally provides similar conditions for insertion to halothane.[106,109] However, time to insertion was faster with sevoflurane than halothane[107-109] and coughing and laryngospasm necessitated tracheal intubation in some patients treated with halothane.[107]

4.5 Postoperative Pain

Patients who emerge rapidly from anaesthesia may experience a higher degree of postoperative discomfort or pain than those who experience more gradual emergence. In several studies, objective pain/discomfort scores during the first 30 to 40 minutes in the recovery room were significantly[74,88] or markedly (statistical analysis not reported)[81,83] higher in sevoflurane than in halothane recipients.

Time to first postoperative analgesia was significantly faster (43.5 *vs* 77.1 minutes with halothane, $p = 0.002$)[72] or did not differ significantly[74,110] with sevoflurane versus halothane in patients undergoing ambulatory surgery. Similarly, time to first postoperative analgesia in patients not given intraoperative analgesia was significantly shorter with sevoflurane (with O_2 or N_2O/O_2) than with halothane in 1 trial in ambulatory surgical patients (18 and 14.2 *vs* 36.8 minutes, $p < 0.05$)[47] and tended to be shorter in another (35.3 *vs* 50.5 minutes). In the latter comparison the difference, although not statistically significant, was felt to be clinically important.[48]

Table VI. Rapid induction of anaesthesia with sevoflurane (S) in children in randomised studies unless otherwise stated

Reference	No. of patients	Anaesthetic	Mean induction time (min)
Comparisons of S regimens			
Dubois et al.[93]a	23	S 7% + O_2	1
	22	S Inc[b] + O_2	1.4
	20	S 7% + N_2O/O_2	0.77***
Epstein et al.[94]	20	S 8% + N_2O/O_2	0.7**
	20	S Inc[c] + N_2O/O_2	1.1
Haga et al.[95]	90	S 4% + N_2O/O_2	0.93
	90	S 6.4% + N_2O/O_2	0.78*
Comparisons with halothane (H)			
Agnor et al.[96]	12	S 8% + N_2O[d]	0.63†
	16	S 8%+ O_2d	0.57†
	14	H 5% + N_2O[d]	0.97
Baum et al.[97]	17	S 8% + N_2O	0.62‡
	19	S Inc[e] + N_2O	1.16
	10	H Inc[e] + N_2O	1.35
Sigston et al.[98]	25	S 8% + N_2O/O_2	1.2
	26	H 5% + N_2O/O_2	1.27

a Abstract. Study was not randomised; patients were allocated to groups consecutively.

b Incremental concentrations of S 2, 4, 6 and 7% every 5 breaths.

c Concentrations increased from S 1% by 1% every 2 to 3 breaths.

d Anaesthetics were given by single-breath vital capacity rapid inhalation.

e Concentrations increased from 0% by 1% (S) or 0.5% (H) every 3 to 4 breaths.

Inc = incremental; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* other S regimens; † $p < 0.01$ *vs* H; ‡ $p < 0.001$ *vs* other regimens.

4.6 Acceptability of Sevoflurane Anaesthesia

The acceptability of sevoflurane as an anaesthetic agent is similar to or better than that of halothane. In a number of studies, significantly more sevoflurane than halothane recipients, or their parents, rated induction as pleasant and would have the same anaesthetic again.[75,92,98] Sevoflurane was preferred by the parents of 11 of 15 children who had received halothane for previous anaesthesia, whereas the present halothane induction was preferred by the parents of only 3 of 14 children who had also previously received halothane ($p <$

0.05).[98] The reason for this parental preference was not given but may have related to the lower struggling score with sevoflurane ($p < 0.02$)[98] (see also section 5.2.1).

In contrast, there were no differences between sevoflurane or halothane in the percentage of patients or parents who would request the same anaesthetic again, who remembered the technique or who remembered an odour, in a large, well reported trial.[74] Similarly, children's ratings of the smell of the anaesthetic and the preference expressed for the same agent for future VCRII did not differ significantly between groups given sevoflurane or halothane.[96]

Mask acceptance was rated as 'good' in 100% of 20 patients given high concentration sevoflurane with N_2O/O_2, compared with 87% of the high concentration sevoflurane plus O_2 group and 95.5% of the incremental sevoflurane plus O_2 group, in the only induction trial to assess this parameter.[93] The finding in 1 study[94] that slower induction times were associated with improved cooperation in children was not confirmed in another.[97] Patient cooperation at induction was similar for sevoflurane and halothane in children undergoing dental extraction.[46,80]

4.7 Pharmacoeconomic Aspects

Cost is an important factor when considering whether to supplant an existing anaesthetic agent with a newer one. Direct costs relevant to anaesthetic agents are acquisition costs and those related to the delivery of the agent (i.e. type of anaesthetic circuit used, wastage of the agent, flow rates). Other components of the overall expenditure include use of medication such as neuromuscular blockers and analgesics. These costs should be balanced against the potential to shorten the patient's stay (rapid emergence from anaesthesia would be expected to reduce time spent in the recovery unit and hasten discharge).[1,111]

There is a lack of prospective, well designed, fully published pharmacoeconomic analyses comparing sevoflurane with other agents in paediatric anaesthesia; several theoretical cost analyses are available only as abstracts. Using retrospective clinical data and measuring costs of maximum delivered drug concentration, sevoflurane induction was found to be more costly than propofol alone but considerably less expensive than propofol plus lidocaine (lignocaine)-prilocaine.[112] The costs of anaesthetic agent used during a 25-minute surgery were much lower for halothane than for sevoflurane ($US0.25 *vs* $US5.45), but the shorter emergence time of 5.8 minutes with sevoflurane was postulated to be potentially cost-saving by allowing an additional procedure to be performed during an 8-hour shift.[113] However, sevoflurane induction and maintenance anaesthesia did not reduce the time to hospital discharge compared with halothane anaesthesia[89] or halothane induction and isoflurane maintenance.[114]

Costs of anaesthetics are related to the amounts used and thus to fresh gas flow rates during the procedure. Lower flow rates during maintenance reduce hourly and total costs of inhalation anaesthetics, as well as improving the maintenance of the anaesthetic's humidity and reducing atmospheric pollution (primarily from N_2O).[115,116] Accumulating evidence, albeit preliminary, suggests that low-flow sevoflurane anaesthesia can provide a similar recovery profile[117] for half the cost of high-flow techniques.[117,118] Using an acquisition cost of $US0.72/ml, the cost per case for induction with sevoflurane 2.7 L/min (mean) and low-flow maintenance with sevoflurane 0.9 L/min (mean) was $US6.45 for a 30-minute procedure.[119] Direct comparisons with other inhalation anaesthetic agents in well designed pharmacoeconomic analyses are required to put these findings in perspective.

5. Tolerability

5.1 General Profile

Sevoflurane is generally well tolerated. Adverse events seen most often during induction are coughing, laryngospasm, breath-holding and agitation/excitement. The incidence of induction events is generally similar with sevoflurane and halothane, as shown by collated data from controlled

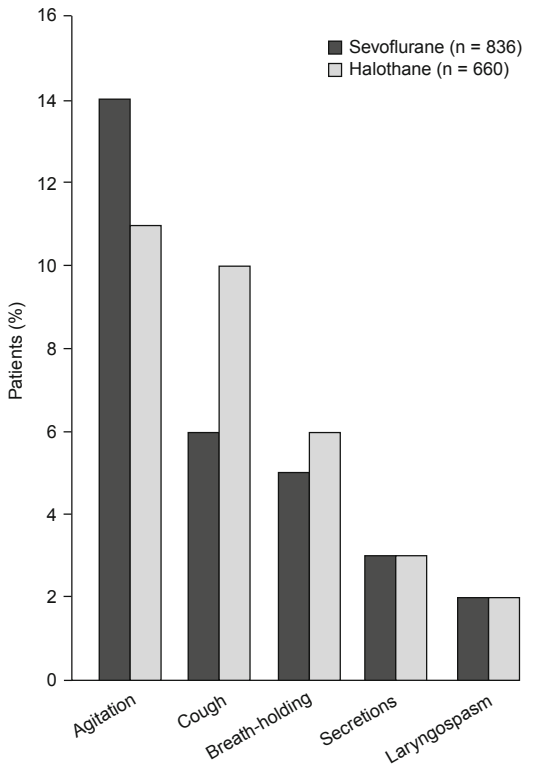

Fig. 1. Incidence of adverse events occurring during induction of anaesthesia with sevoflurane or halothane. Data are collated from controlled clinical trials.[5]

clinical trials in children (fig. 1).[5] Significant differences between the 2 drugs, generally favouring sevoflurane, in the incidence of such induction events as coughing, laryngospasm or movement reported in small clinical trials[93,96,98,107] have not been substantiated in larger studies.[48,74,80]

Induction excitement was, however, more frequent with sevoflurane when administered with O_2 than with either sevoflurane or halothane given with N_2O and O_2 (35 *vs* 5% for both latter groups, $p < 0.05$).[47]

The types of events occurring during emergence from sevoflurane anaesthesia are similar to those seen during induction. Figure 2 illustrates the incidence of various emergence events with sevoflurane and halothane in 2 large multicentre trials in children undergoing ambulatory[74] or nonambulatory[48] surgery.

The following text provides a more detailed discussion of several important aspects of the tolerability profile of sevoflurane and other inhalation anaesthetics. These include postoperative agitation/excitement, effects on cardiac parameters, and potential for postoperative nausea and vomiting (PONV), hepato- and nephrotoxicity and malignant hyperthermia.

5.2 Neuroexcitatory Events

5.2.1 Postoperative Excitement

There has been much interest in the relative incidence of postoperative agitation or excitement during emergence from sevoflurane compared with halothane anaesthesia. Present evidence does not consistently show differences between sevoflurane and halothane in the propensity to produce postoperative agitation or excitement, with some studies reporting higher, and others similar, rates of this event.

Postoperative excitement was significantly more common with sevoflurane than with halothane in a large trial (fig. 2)[74] and several smaller ones (n = 40 to 112 patients) in children undergoing ambulatory surgery.[87,120-122] The severity, rather than the incidence, of this event was greater with sevoflurane than halothane in 100 children undergoing dental extraction ($p = 0.044$).[80] More sevoflurane than halothane recipients required drug treatment for postoperative agitation (23 *vs* 3%, $p < 0.05$) among another 80 children.[121]

In contrast, there was no difference between sevoflurane and halothane in the incidence of postoperative agitation or excitement in several trials.[48,76,110] These included the largest study, in 428 patients (fig. 2),[48] and a double-blind trial in 200 children.[110]

The reasons for these disparate results among studies are unclear and may relate to differences in study methodology, patient demographics (e.g. age) or use of premedication or analgesia during surgery. Delirium during recovery was significantly more common with sevoflurane (40%) than with halothane (10%, $p < 0.009$) in 60 boys aged 3 to 5 years.[122] In contrast, in the same study, there

was no such difference between sevoflurane and halothane in older children (6 to 10 years). However, no significant difference in postoperative excitement was seen between sevoflurane and halothane in 200 children with a mean age of ≈2 years.[110] Paracetamol (acetaminophen) intake before sevoflurane induction reduced the incidence of postoperative excitement compared with paracetamol given during surgery in 1 small trial (33 *vs* 100%, $p < 0.01$).[87]

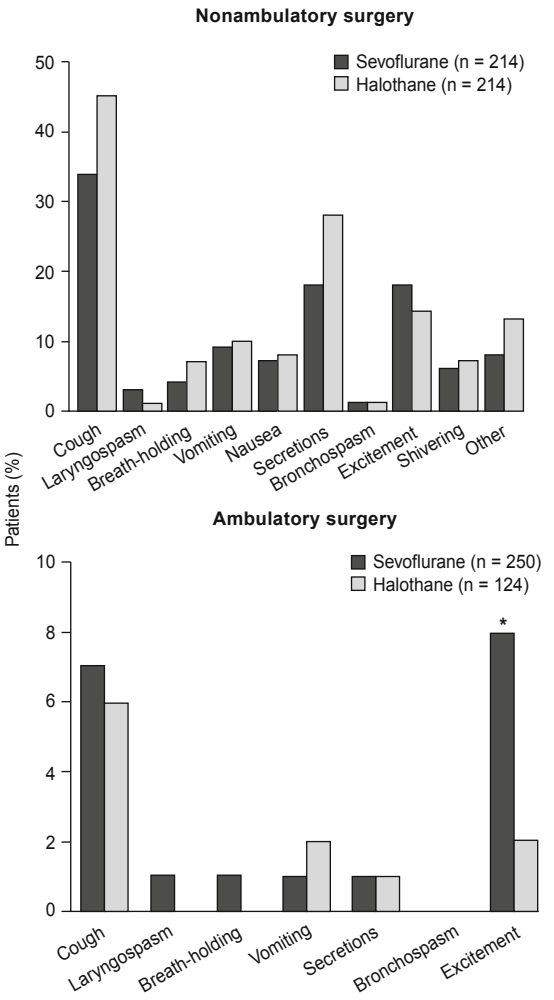

Fig. 2. Incidence of adverse events occurring during emergence from anaesthesia with sevoflurane or halothane. Data are from 2 multicentre randomised trials in children undergoing non-ambulatory[48] or ambulatory[74] surgery. * $p < 0.017$ *vs* halothane.

As well, significantly fewer patients became agitated when ketorolac rather than placebo was administered as intraoperative analgesia, regardless of whether sevoflurane or halothane was used (fig. 3); indeed, the degree of agitation paralleled the need for postoperative medication, which did not differ between sevoflurane- and halothane-treated children.[110] This suggests that agitation may be related to postoperative pain or discomfort rather than being a property of a specific agent. Lastly, midazolam premedication was given in the trials showing no difference between the 2 drugs,[48,76,110] but in only some of the trials favouring halothane.[87,121]

Data are insufficient to assess the incidence of this event in patients given comparator anaesthetic agents other than halothane. In single, small studies, postoperative agitation was significantly more frequent with sevoflurane than with propofol in unpremedicated children (46 *vs* 9%, $p = 0.008$)[78] but was less common than with desflurane in children premedicated with midazolam (10 *vs* 50%, $p < 0.008$).[76]

5.2.2 Seizure-Like Movements and Effects on EEG

There have been several case reports of seizure-like movements during sevoflurane induction in children.[123-126] The association, if any, between sevoflurane induction and the observed movement has not been determined, and in 1 child the convulsions were attributed to mepivacaine toxicity.[126]

EEG abnormalities in the absence of convulsive movements have occurred during sevoflurane induction in a few children,[124,127,128] including some with epilepsy.[129] EEG patterns have been shown to be dissimilar during sevoflurane and halothane induction at 1 MAC: delta power and median power frequency were higher with halothane than with sevoflurane ($p < 0.05$) in a study of 26 children. No seizure-like activity occurred in any of these patients.[130]

Sevoflurane is not contraindicated in children with a history of seizure disorders.

5.3 Cardiac Events

Sevoflurane increases heart rate[46-48,131] to a greater extent than halothane during induction, but causes fewer instances of arrhythmias[46,74,75,132] and bradycardia[48,74,133] during anaesthesia. These differences were statistically significant in the trials cited.

Adverse cardiac events (15 *vs* 36%, $p < 0.007$) and abnormal ECGs ($p < 0.04$) were fewer overall with sevoflurane than with halothane in the study by Lerman et al.[74] in 375 children. Results of another large trial in 428 children[48] typify the increased frequency of elevated heart rate (8 *vs* 1%, $p = 0.001$) and the lower rate of bradycardia (11 *vs* 2%, $p < 0.001$) with sevoflurane versus halothane, but the incidence of dysrhythmias did not vary between groups in this trial.

The incidence of the oculocardiac reflex (OCR) during anaesthesia for correction of strabismus was significantly higher (76 *vs* 35%, $p < 0.01$), and the heart rate during OCR lower ($p < 0.01$), with halothane than with sevoflurane in 37 children.[132]

5.4 Postoperative Nausea and Vomiting

PONV was reported in up to 45% of children receiving sevoflurane in clinical trials.[46,74-76,87,134,135] The incidence of PONV did not differ between groups given sevoflurane or desflurane,[76] isoflurane,[135] enflurane[135] or propofol.[134]

Sevoflurane may cause less PONV than halothane. The incidence of PONV with sevoflurane was similar to[46,74,76,110] or significantly lower than[48,75,87] with halothane in clinical trials.

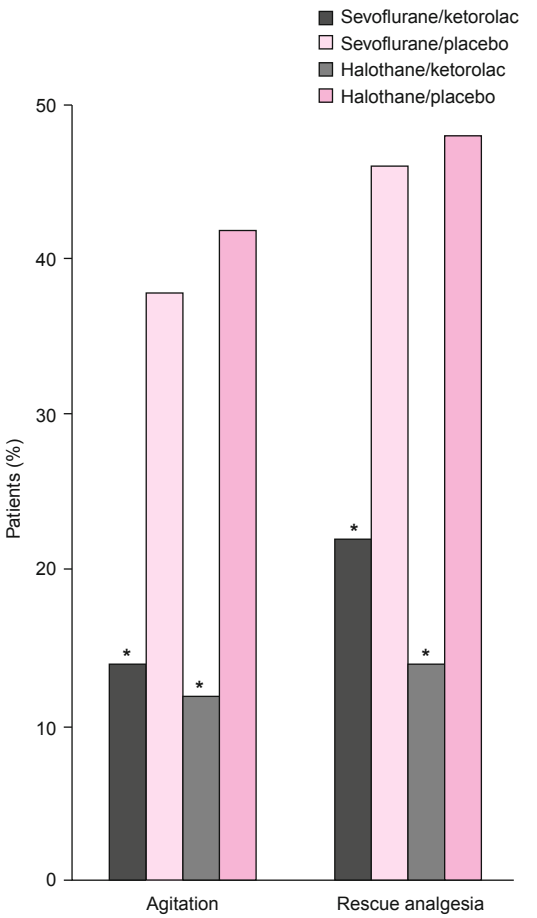

Fig. 3. Incidence of postoperative agitation and need for rescue medication [oral paracetamol (acetaminophen)] in patients treated with sevoflurane or halothane. Children undergoing bilateral myringotomy were anaesthetised with either sevoflurane or halothane and received intravenous ketorolac 1 mg/kg or placebo intraoperatively (n = 50 in each group).[110] * $p < 0.05$ *vs* corresponding placebo groups.

5.5 Nephrotoxicity

5.5.1 Inorganic Fluoride Ions

Despite elevated plasma F^- levels, sevoflurane and other inhalation anaesthetic agents are not associated with nephrotoxicity. Numerous, mostly comparative, trials in children demonstrate that plasma F^- levels remain below the theoretical 'toxic threshold' of 50 μmol/L (for methoxyflurane) during sevoflurane anaesthesia lasting up to 9 MAC • h.[47,74,91,92,136-140] Levels peak within an hour of ending anaesthesia and in most instances return to baseline within 24 hours.[47,92,136-138] Plasma F^- levels are significantly higher with sevoflurane than with halothane[47,48,74,92,138] or enflurane.[140]

Renal impairment did not develop in any child treated with sevoflurane in these clinical trials. These results are consistent with the lack of potentially injurious intrarenal fluoride production with sevoflurane (section 3.2).

5.5.2 Haloalkenes

The haloalkene PIFE ('Compound A') is generated when sevoflurane comes into contact with CO_2 absorbents during anaesthesia (section 1.1). PIFE is nephrotoxic in rats at threshold concentrations estimated to be 50 to 200 ppm, depending on length of exposure to the anaesthetic.[1] These concentrations exceed those normally reached during sevoflurane anaesthesia in clinical practice, which are on average 19 (maximum 32) ppm using soda lime.[5]

Use of soda lime and a 2 L/min fresh gas flow rate in 19 children produced maximum inspired PIFE concentrations of 15 ppm, with no sign of renal toxicity.[139] To date, there have been no reports of PIFE-associated nephrotoxicity in children anaesthetised with sevoflurane.

5.6 Hepatotoxicity

Sevoflurane does not generate antigenic trifluoroacetyl proteins implicated in the hepatotoxicity of halogenated ethers, and its organic metabolite HFIP, unlike that of halothane, has a low binding affinity for hepatic cells.[1] The potential for hepatic injury with sevoflurane is therefore expected to be negligible.

Specific evidence in children is scant. In 50 children who received sevoflurane or halothane, levels of serum glutathione *S*-transferase α (GST; a sensitive marker of liver damage) increased significantly for up to 2 hours without evidence of hepatic dysfunction and with no difference seen between the 2 groups.[92] This suggests a possible effect on hepatic cells with both drugs. However, no such increase in GST occurred in 8 children with liver disease who were anaesthetised with sevoflurane.[141] Serum aspartate amino transferase levels were significantly higher ($p < 0.05$) in children anaesthetised with isoflurane ($n = 40$) than with sevoflurane ($n = 40$).[142]

5.7 Malignant Hyperthermia

Inhalation anaesthetics such as sevoflurane have the potential, albeit low, to trigger malignant hyperthermia. Malignant hyperthermia associated with sevoflurane in children is very rare: 2 case reports have been identified in the literature.[143,144] The children who developed this syndrome during sevoflurane anaesthesia were successfully treated with intravenous dantrolene sodium.

6. Drug Interactions

6.1 Neuromuscular Blocking Agents

Sevoflurane, like other volatile anaesthetics,[145,146] prolongs the duration of neuromuscular blockade induced by nondepolarising muscle relaxants such as cisatracurium,[147] vecuronium[145,146,148] and mivacurium.[149-151] The extent of potentiation depends on dose and duration of exposure. Neuromuscular blockade was potentiated by about 50% and was greater with sevoflurane than with halothane[146,148,149] or isoflurane[145] in a number of studies. Dosages of neuromuscular blocking agents should be reduced when sevoflurane anaesthesia is used, but children require higher dosages of these drugs than adults.[150]

6.2 Other Drugs

Opioids, N_2O and clonidine reduce the MAC of sevoflurane (section 2.1). The metabolism of sevoflurane may be increased by agents which induce CYP2E1, such as isoniazid and alcohol, but is unaffected by barbiturates.[5]

It is unknown whether sevoflurane may displace drugs such as phenytoin that are highly protein bound and have a small volume of distribution; this interaction has been documented with other volatile fluorinated anaesthetics.[5] Sevoflurane does not affect the magnitude of lidocaine serum protein binding[152] but is synergistic with lidocaine and procainamide in prolonging ventricular activation time.[153] It does not interact pharmacodynamically with nicardipine[154,155] or diltiazem.[155]

7. Dosage and Administration

Sevoflurane is indicated for induction and maintenance of general anaesthesia in paediatric patients undergoing inpatient or outpatient surgery.[5] It is administered by inhalation with a vaporiser

specifically calibrated for the agent. Delivery should be individualised according to the patient's response.

Concentrations needed to induce anaesthesia increase with decreasing age (section 2.1). Induction of anaesthesia, with or without pre-anaesthetic medication, was achieved using inspired concentrations of 7 or 8% in most major clinical studies in children. Sevoflurane concentrations of 0.5 to 3%, with or without N_2O, are adequate to maintain anaesthesia during surgery.[5] There are no flow rate restrictions in most countries where sevoflurane is approved.

Sevoflurane is contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia. The drug should be used with caution in patients with renal insufficiency, as clinical experience is too limited to establish its tolerability in this group at present.[5] Clinicians should be aware that levels of the organic metabolite PIFE are higher when barium hydroxide lime rather than soda lime is used as a CO_2 absorbent.

8. Place of Sevoflurane in Paediatric Anaesthesia

Inhalation induction of anaesthesia is the preferred method in children, in whom intravenous needle insertion is poorly endured or physically difficult. While the availability of coloured or flavoured inhalation masks has to some extent improved patient acceptability of this method, the development of inhaled anaesthetic agents with low pungency, rapid onset and improved tolerability signalled a turning point in paediatric anaesthesia.[156]

For several decades halothane, with its negligible pungency and minimal effects on airway reactivity, has been the cornerstone of paediatric induction anaesthesia despite its propensity to cause bradycardia, hypotension and arrhythmias. As well, its high blood : gas solubility ratio is a drawback, as this lessens the flexibility in facilitating control of depth of anaesthesia during maintenance.[1]

Isoflurane, enflurane and desflurane have properties that reduce their desirability as anaesthetic agents in children; for example, all three are associated with more frequent airway irritation than halothane. Although desflurane allows more rapid induction than the older agent isoflurane, its high pungency precludes its use as an induction anaesthetic in children.[156-158]

Sevoflurane has the following desirable properties:

- low pungency and a nonirritant odour, which permit easy administration without discomfort or airway irritation
- low blood : gas partition coefficient which facilitates precise control over the depth of anaesthesia and a rapid and smooth induction of, and emergence from, general anaesthesia
- lack of arrhythmogenicity
- cardiovascular and peripheral haemodynamic stability.[1]

As an induction and maintenance agent for ambulatory and nonambulatory surgery in children, sevoflurane provides more rapid induction of, and emergence from, anaesthesia than halothane (although the clinical significance of differences in induction have been questioned). Time to discharge from the recovery area is at least as fast with sevoflurane as with halothane, as is acceptability to patients.

Although rapid emergence lessens the time spent under anaesthesia and may hasten recovery, postoperative pain may occur sooner and be more intense than during more gradual emergence. This appears to be the case with sevoflurane: in most analyses times to postoperative analgesia were shorter and/or objective pain scores higher with sevoflurane than halothane, suggesting the need for optimal pre- or intraoperative analgesia.

An area where sevoflurane might be expected to find increasing use is that of tracheal intubation and LMA insertion. Time to LMA insertion is faster with sevoflurane than halothane but the 2 drugs provide similar conditions for tracheal intubation.

Preliminary data showing sevoflurane to be efficacious and well tolerated in children undergoing cardiac catheterisation deserve follow-up with further study, as this type of patient is particularly difficult to manage. Data comparing sevoflurane with agents other than halothane (e.g. desflurane, propofol) as maintenance anaesthesia are also too few to reliably draw any conclusions about relative efficacy.

Sevoflurane has a similar pattern and incidence of induction events such as cough, laryngospasm and agitation/excitement to halothane and may cause less PONV. The cardiodynamic profiles of the 2 drugs differ: halothane is associated with a higher incidence of bradycardia and arrhythmias, whereas sevoflurane increases heart rate and systolic blood pressure more than halothane, but is otherwise well tolerated in this regard.

Postoperative excitement can be distressing to patients and particularly to parents if present during the event. Whether sevoflurane causes more postoperative excitement/agitation than halothane is a current topic of interest; available data are conflicting (section 5.2.1). Reasons for the discrepancies between studies are unknown but may pivot on such points as use of intraoperative analgesia, premedication or differences in study methodology.

A cause-effect relationship, if any, has not been established between sevoflurane administration and seizure-like movements and/or EEG abnormalities observed in some children during anaesthesia.

Sevoflurane is susceptible to degradation by CO_2 absorbents to the haloalkene PIFE at high temperatures and undergoes biotransformation to yield plasma F^- ions. Concerns over the potential nephrotoxicity of these byproducts as demonstrated in animals have not been substantiated in humans. No renal impairment has been documented in children receiving sevoflurane in clinical trials.

The potential for sevoflurane hepatotoxicity is also low given its limited hepatic biotransformation, lack of transformation to antigenic proteins and the low reactivity and rapid glucuronidation of HFIP, the major metabolite. Experience with sevoflurane in patients with renal or hepatic impairment is, however, limited. Caution is advised when considering the use of sevoflurane in patients with renal impairment in particular.

Like other inhalation anaesthetic agents, sevoflurane has the potential to precipitate malignant hyperthermia, and clinicians should be alert to the possible development of this rare event.

As for any other drugs, costs of anaesthetic agents are increasingly becoming an important part of clinical decision-making. At present, the lack of fully published, well designed pharmacoeconomic trials precludes any informed conclusions about the relative costs and benefits of sevoflurane and other inhalation agents. Future pharmacoeconomic studies should investigate whether the rapid emergence from sevoflurane anaesthesia will translate into concrete economic benefits.

In summary, sevoflurane is a preferred anaesthetic agent for induction and maintenance of paediatric anaesthesia because of its rapid induction and recovery characteristics, lack of pungency and agreeable odour, and acceptable cardiovascular profile. Although the issue of postoperative excitement remains to be resolved with certainty, and acquisition costs may be an issue for some healthcare providers, sevoflurane anaesthesia can be considered a rational choice for ambulatory and non-ambulatory surgery in children.

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