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Induction, Recovery, and Safety Characteristics of Sevoflurane in Children Undergoing Ambulatory Surgery

A Comparison with Halothane

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Background: **Sevoflurane is an inhalational anesthetic with characteristics suited for use in children. To determine whether the induction, recovery, and safety characteristics of sevoflurane differ from those of halothane, the following open-labeled, multicenter, randomized, controlled, phase III study in children undergoing ambulatory surgery was designed.**

Methods: **Three hundred seventy-five children, ASA physical status 1 or 2, were randomly assigned in a 2:1 ratio to receive either sevoflurane or halothane, both in 60% N_2O and 40% O_2. Anesthesia was induced using a mask with an Ayre's t piece or Bain circuit in four of the centers and a mask with a circle circuit in the fifth center. Maximum inspired concentrations during induction of anesthesia were 7% sevoflurane and 4.3% halothane. Anesthesia was maintained by spontaneous ventilation, without tracheal intubation. End-tidal concentrations of both inhalational anesthetics were adjusted to 1.0 MAC for at least 10 min before the end of surgery. Induction and recovery characteristics and all side effects were recorded. The plasma concentration of inorganic fluoride was measured at induction of and 1 h after anesthesia.**

Results: **During induction of anesthesia, the time to loss of the eyelash reflex with sevoflurane was 0.3 min faster than with halothane ($P < 0.001$). The incidence of airway reflex responses was similar, albeit infrequent with both anesthetics. The total MAC · h exposure to sevoflurane was 11% less than the exposure to halothane ($P < 0.013$), although the end-tidal MAC multiple during the final 10 min of anesthesia was similar for both groups. Early recovery as evidenced by the time to response to commands after sevoflurane was 33% more rapid than it was after halothane ($P < 0.001$), although the time to discharge from hospital was similar for both anesthetics. The mean (±SD) plasma concentration of inorganic fluoride 1 h after discontinuation of sevoflurane was 10.3 ± 3.5 μM. The overall incidence of adverse events attributable to sevoflurane was similar to that of halothane, although the incidence of agitation attributable to sevoflurane was almost threefold greater than that attributable to halothane ($P < 0.004$).**

Conclusions: **Sevoflurane compared favorably with halothane. Early recovery after sevoflurane was predictably more rapid than after halothane, although this was not reflected in a more rapid discharge from the hospital. The incidence of adverse events was similar for both anesthetics. Clinically, the induction, recovery, and safety characteristics of sevoflurane and halothane are similar. Sevoflurane is a suitable alternative to halothane for use in children undergoing minor ambulatory surgery. (Key words: Age, pediatrics. Anesthetics, volatile: halothane; sevoflurane.)**

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SEVOFLURANE, a polyfluorinated methyl, isopropyl ether anesthetic, is unique among the ether series of inhalational anesthetics in that it does not trigger airway reflex responses during inhalational inductions in infants and children.[1–6] This attribute, together with its low blood and tissue solubilities[7,8] and cardiorespiratory stability[9] would suggest that it may be a suitable alternative to halothane for ambulatory surgery in infants and children. To determine whether the induction, recovery, and safety characteristics of sevoflurane differ from those of halothane in children undergoing ambulatory surgery, we designed the following open-labeled, multicenter, randomized, controlled, phase III study.

Methods

With approval from the federal regulatory agencies in the United States and Canada and the ethics committees of all five participating institutions, written informed consent was obtained from the parents of 375 ASA physical status 1 and 2 children, aged 1–12 yr, who were scheduled for elective ambulatory surgery (including genitourinary, superficial lower abdominal, and plastic or superficial orthopedic surgery) lasting 0.5–2 h. Seventy-five children were enrolled in each center. Within each center, the children were randomly assigned to receive either sevoflurane or halothane in a 2:1 ratio using a computer-generated randomization schedule after consent was obtained.

All children were fasting and unpremedicated. After application of standard monitors, including an electrocardiogram, pulse oximeter, and noninvasive blood pressure, anesthesia was induced with 60% N_2O and 40% O_2 followed by stepwise increases in the inspired concentrations of either sevoflurane (1.5–2.0% increments) or halothane (0.5–1.0% increments) every three to four breaths. The maximum inspired concentration of sevoflurane was 7% and that of halothane was 4.3%. Sevoflurane was delivered using an Ohmeda SevoTec-3 vaporizer (Maruishi, Osaka, Japan). Anesthesia was delivered *via* a nonscented mask through a Mapleson D or F circuit (Bain or Ayre's t piece) in four centers and a circle system with a carbon dioxide absorber filled with soda lime in the fifth center. Fresh gas flows during induction of anesthesia were 7–10 $l \cdot min^{-1}$ for all children.

Inspired and exhaled gases were sampled through a 2-inch catheter positioned either at the entrance to one of the nares or in the oropharynx.[10] The anesthetic concentrations and carbon dioxide partial pressure in the sample gas were analyzed using a Datex Capnomac airway gas monitor (Helsinki, Finland). The gas monitor was calibrated using a commercial standard gas before each study.

Immediately after induction of anesthesia, intravenous access was established. Whole blood (2 ml) was collected in plastic syringes containing heparin and transferred to plastic tubes. The contents were centrifuged within 30 min of collection, and the plasma supernatant was pipetted into plastic tubes that were sealed and stored at −20°C until analysis for the inorganic fluoride concentration.

Lactated Ringer's solution was administered during anesthesia at a maintenance rate appropriate for the child's age and fasting interval. Anticholinergic medication was administered only for the treatment of bradycardia (defined as a heart rate < 100 beats/min).

A single-dose caudal block was administered after induction of anesthesia to those children in whom it was clinically indicated. Bupivacaine (without epinephrine) in a concentration and volume appropriate for the level of desired blockade (maximum dose of 2.5 $mg \cdot kg^{-1}$) was used. Wound infiltration with local anesthetics was permitted as an alternative.

During the maintenance period, the children breathed spontaneously through a face mask and an anesthetic circuit. Fresh gas flows were adjusted to 3–6 $l \cdot min^{-1}$ for children aged 1–7 yr and 6–10 $l \cdot min^{-1}$ for those aged 8–12 yr. The inspired anesthetic concentration was adjusted to produce an end-tidal concentration of 1.3 × MAC of the inhalational anesthetic[4,11] in 60% N_2O and oxygen. A heat and moisture exchanger was interposed between the elbow of the circuit and the fresh gas sleeve in the Ayre's t piece or at the distal end of the Bain circuit at the discretion of the staff.

The algorithm for the control of the depth of anesthesia follows: In the presence of light anesthesia (heart rate or systolic blood pressure >30% of baseline, movement, swallowing, or tearing), the inspired concentration of the anesthetic was increased appropriately. If these increases resulted in clinically unacceptable cardiovascular or respiratory depression, the inspired concentration was decreased to an acceptable value, and only then was fentanyl administered. Fentanyl was not given within 30 min of the conclusion of surgery. If vital signs were within the 20% of baseline limits, the inspired anesthetic concentration was adjusted to produce an end-tidal concentration of 1.0 ×

MAC of the inhalational anesthetic (excluding nitrous oxide) during the maintenance period.

For a minimum of 10 min before the conclusion of surgery, the inspired anesthetic concentration was adjusted to an end-tidal concentration of 1.0 × MAC of the inhalational anesthetic (excluding nitrous oxide).[4,11] At the time of placement of the last suture, all anesthetic agents were discontinued, and 100% O_2 was administered for 1–2 min. In the recovery room, vital signs (including heart rate, blood pressure, transcutaneous hemoglobin oxygen saturation, respiratory rate, and temperature) were assessed as described below. All recovery and discharge data were collected by a registered nurse who was blinded to the treatment assignment. Sixty minutes after discontinuation of anesthesia, a second whole blood sample (2 ml) was obtained from the indwelling intravenous cannula, and the plasma was stored as described above. Discharge criteria from the recovery room included restoration of stable vital signs, a modified Aldrete recovery score ≥8, absence of pain or bleeding (objective pain/discomfort ≤6), orientation to name and place if appropriate for age, and tolerance of oral clear fluids.

During the recovery period, pain was managed with rectal acetaminophen (10–25 $mg \cdot kg^{-1}$), intramuscular codeine (1–1.5 $mg \cdot kg^{-1}$), or intravenous morphine sulfate (0.05–0.10 $mg \cdot kg^{-1}$) as needed. Fentanyl (1–2 $\mu g \cdot kg^{-1}$) was administered intravenously if required postoperatively.

Demographic data, including age, weight, and type of surgery, were recorded for all subjects. Vital signs, including heart rate, systolic and diastolic blood pressures, and respiratory rate were recorded at the time of consent and 1 min before induction of anesthesia (baseline). Vital signs, inspired and expired concentrations, end-tidal carbon dioxide tension, hemoglobin oxygen saturation, and temperature were recorded every minute until incision, at 1-min intervals for the first 5 min after incision, and every 5 min until the conclusion of surgery.

Induction and emergence characteristics, including coughing, laryngospasm, breathholding, nausea, vomiting, secretions, bronchospasm, excitement, and any other unanticipated events, were recorded.

The induction interval (time from application of the face mask until loss of the eyelash reflex), duration of anesthesia (defined as the interval from application of the mask until discontinuation of the anesthetics), and duration of surgery (defined as the interval from skin incision until the final skin suture was inserted) were recorded. The times from the discontinuation of anesthesia until the child responded appropriately to commands or demonstrated purposeful movement and until the first postsurgical analgesic was administered were recorded by a nurse who was blinded to the treatment administered.

All postoperative vital signs and discharge criteria were recorded by a nurse who was blinded to the treatment administered. Vital signs, a modified Aldrete recovery score (appendix A), and the objective pain discomfort scale (appendix B) were recorded on arrival in the recovery room and then every 10 min for 60 min. Before discharge from hospital, each child was questioned about any recall of events during the intraoperative period.

Each patient and/or parent was telephoned 24 h after discharge from hospital by a research nurse or assistant who was unaware of the anesthetic administered. The parents were questioned regarding the presence of fever, nausea and vomiting, coughing, dizziness, and drowsiness after discharge from hospital. Depending on the child's age, either the child or a parent was asked the following: (1) whether they would request the same anesthetic again, (2) whether they recalled how they were put to sleep, (3) whether they remembered going to sleep, and (4) whether the anesthetic had an odor (If the answer was yes, they were asked whether the odor was mild, strong, or very strong.).

The MAC · h for each child were calculated based on the area under the end-tidal anesthetic concentration *versus* time curve (using the trapezoidal rule) and were normalized using age-adjusted MAC values.[4,11]

All analyses were performed with the SAS (Statistical Analysis System) procedures GLM and FREQ. Descriptive statistics were used to summarize age, weight, and gender. Continuous data were compared using a two-way analysis of variance model with effects for the investigator, anesthetic, and interaction between investigator and anesthetic. Nominal data were compared using Cochrane-Mantel-Haenszel test or Fisher's exact test. Data are mean ± SD except where indicated. Statistical significance was accepted for $P < 0.05$.

Results

Data from 374 of the patients were analyzed; one child who received halothane was eliminated from the analysis because of severe airway obstruction and hypoxia caused by a mucous plug. Demographic data, including the duration of anesthesia and surgery, were

similar for the two treatment groups (table 1). Demographic data did not differ significantly among the five centers. The distributions of race and gender were similar in the two treatment groups.

The time to loss of the eyelash reflex during sevoflurane anesthesia was minimally but significantly faster than during halothane anesthesia (table 2). The time to loss of the eyelash reflex did not vary among the five centers, nor did it depend on the type of circuit used. During the interval between application of the mask and skin incision, the maximum end-tidal sevoflurane concentration (normalized for MAC), 1.7 ± 0.58, was significantly less than the maximum halothane concentration (normalized for MAC), 2.7 ± 0.57 ($P < 0.001$). The average end-tidal concentration of sevoflurane (normalized to its MAC) during this interval, 1.10 ± 0.24, was also significantly less than the average halothane concentration (normalized for MAC), 1.4 ± 0.24 ($P < 0.001$).

The total mean (±SD) MAC · h exposure to sevoflurane was significantly less than the exposure to halothane ($P < 0.013$) (table 1). The duration of surgery was less than 10 min in 4%, or 10 of 250, children who received sevoflurane and 6%, or 8 of 125, children who received halothane (P = NS). Although the duration of anesthesia was less than stipulated in the protocol, these data were included in the analysis on the basis of "intent to treat."

The times to emergence and early recovery after sevoflurane anesthesia were significantly more rapid than after halothane anesthesia (table 2). Recovery milestones, including a modified Aldrete score ≥8 (fig. 1) and time to orientation after sevoflurane, were reached more rapidly than after halothane ($P < 0.001$; table 2). Orientation could be evaluated only in a subset of children, because some were too young to cooperate (table 2). Suitability for discharge after intake of clear fluids could be evaluated only in a subset of children, because some of the children refused to ingest fluids (table 2). Objective pain/discomfort scores at 1, 10, 20, and 30 min after arrival in the recovery room after sevoflurane anesthesia were significantly greater than those after halothane ($P < 0.001$) but were similar for the two groups at all times thereafter.

A regional block was provided with bupivacaine in 92% of patients in the sevoflurane group and 90% in the halothane group. Lidocaine was used for regional blockade in nine (3.6%) in the sevoflurane group and four (3.2%) in the halothane group. Fentanyl (1.6 μg/kg) was administered during anesthesia to four children (1.6%) in the sevoflurane group and three children (2.4%) in the halothane group more than 30 min before the end of surgery. In the recovery room, supplementary analgesia in the form of acetaminophen alone was administered to 20% of the children in the sevoflurane

Table 1. Demographic Data and Times of Anesthesia and Surgery

	Sevoflurane	Halothane
No. of patients	250	125†
Age (yr)	4.0 ± 2.9	3.8 ± 2.8
Weight (kg)	20.3 ± 12.7	19.3 ± 9.1
Gender		
No. (%) of male	206 (82)	99 (79)
No. (%) of female	44 (18)	26 (21)
Duration of anesthesia (min)	50.6 ± 23.7	48.3 ± 24.5
Duration of surgery (min)	30.1 ± 20.6	28.3 ± 21.2
Total MAC · h exposure	1.09 ± 0.54*	1.23 ± 0.55

Data are mean ± SD except where indicated.

* $P < 0.013$ *versus* halothane.

† One child who developed airway difficulties during induction was removed from the statistical analysis, leaving 124 children in this group.

Table 2. Induction and Recovery Indexes

	Sevoflurane	Halothane	*P* Values
Induction			
Time to loss of the eyelash reflex	1.3 ± 0.79	1.6 ± 1.1	<0.001
Recovery*			
Responds to commands or purposeful movement	12.3 ± 10.8	19.9 ± 10.9	<0.001
Time to first postsurgical analgesia	32.1 ± 74.8	50.0 ± 57.7	0.16
Discharge criteria*			
Modified Aldrete score ≥8	19.3 ± 14.0	24.8 ± 13.3	<0.001
Orientation†	22.0 ± 11.3	29.9 ± 13.2	<0.001
OPS ≤6	18.4 ± 12.6	17.1 ± 13.4	0.38
Tolerating clear fluids	63.8 ± 44.0	71.9 ± 44.8	0.14
Suitable for discharge*			
Without fluids	31.8 ± 12.6	33.8 ± 13.4	0.18
With fluids‡	66.4 ± 42.6	73.1 ± 43.9	0.22

All times are in minutes.

* Reported times are referenced to the discontinuation of anesthesia.

† Orientation is the time from the end of anesthesia to when the patient was oriented to name and place. For sevoflurane, 158 subjects were evaluated and for halothane, 78 subjects.

‡ For sevoflurane, 189 subjects were evaluated and for halothane, 95 subjects.

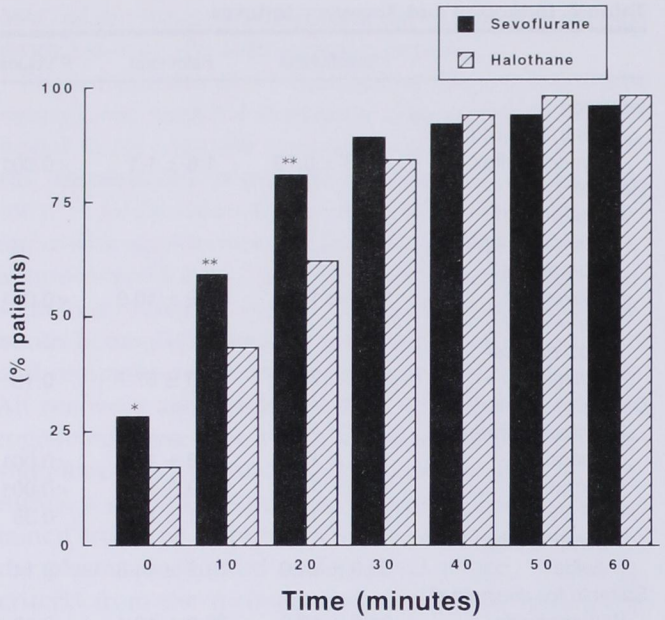

Fig. 1. Proportion of children who achieved a modified Aldrete recovery score ≥8 (appendix A) during the first 60 min of recovery after sevoflurane or halothane. The proportion of children in the sevoflurane group who achieved a score ≥8 at 0, 10, and 20 min after arrival in recovery was significantly greater than that in the halothane group. *$P < 0.03$ between treatments. **$P < 0.003$ between treatments.

group and 31% in the halothane group. Intravenous morphine (with or without supplemental acetaminophen per rectum) was administered to 30% of those in the sevoflurane group and 18.4% of those in the halothane group ($P < 0.018$). Codeine and fentanyl were administered to fewer than 1.6% of the children in each of the two treatment groups.

Side effects, including airway reflex responses, vomiting, and excitement, were similar during both induction of and emergence from anesthesia with sevoflurane and halothane (table 3).

All study-related side effects listed in table 4 were considered mild or moderate in intensity by the investigators. Cardiovascular events, including bradycardia, occurred significantly less frequently with sevoflurane than with halothane anesthesia (table 4). Seven had abnormal electrocardiogram results during the study that were considered by the investigators to be either possibly or probably related to the anesthetic: <1%, or 2 of 250, in the sevoflurane group and 4%, or 5 of 125, in the halothane group ($P < 0.04$). The electrocardiographic abnormalities in the sevoflurane group consisted of premature ventricular contractions intermittently for 1 h, 40 min during maintenance anesthesia without evidence of hemodynamic instability in one child and 30 s of a nodal rhythm in a second child. In both instances, the arrhythmias resolved spontaneously. The abnormalities in the halothane group consisted of three children with premature ventricular contractions, one with bigeminy for 45 s and one with a nodal rhythm that lasted 2 min. None of the arrhythmias were associated with hypotension. Similarly, gastrointestinal side effects, including vomiting, occurred less frequently

Table 3. Complications during Induction and Emergence

	Sevoflurane	Halothane
Induction		
Coughing	7 (3%)	9 (7%)
Laryngospasm	0	0
Breathholding	6 (2%)	4 (3%)
Bronchospasm	0	0
Secretions	3 (1%)	3 (2%)
Excitement	17 (7%)	4 (3%)
Vomiting	0	0
Emergence		
Coughing	18 (7%)	7 (6%)
Laryngospasm	1 (<1%)	0
Breathholding	1 (<1%)	0
Bronchospasm	0	0
Secretions	1 (<1%)	1 (1%)
Excitement	19 (8%)*	2 (2%)
Vomiting	1 (<1%)	2 (2%)

More than one complication may have been experienced by a patient during the same study interval.

* $P < 0.017$ *versus* halothane.

Table 4. Incidence of Study Drug-related Adverse Experiences

	Sevoflurane	Halothane	*P*
Respiratory	47 (19%)	20 (16%)	0.57
Cardiovascular	37 (15%)	33 (26%)	0.007
Bradycardia*	0	3 (2%)	0.036
Digestive*	62 (25%)	46 (37%)	0.021
Vomiting	54 (22%)	44 (35%)	0.006
Nervous system*	75 (30%)	26 (21%)	0.064
Agitation	45 (18%)	9 (7%)	0.004
Overall	160 (64%)	90 (72%)	0.131

Data are the number of patients (% of the total patients in each group). The adverse events here summarize the incidence over a 24-h period. Cardiovascular events included arrhythmias, hypotension, and hypertension.

* Bradycardia was defined as a heart rate <100 beats/min. Digestive events included dyspepsia, flatulence, nausea, and vomiting. Nervous system included dizziness, somnolence, agitation, myoclonus, and insomnia.

with sevoflurane than with halothane (table 4). Agitation, defined as involuntary movement of one or more extremities during induction of or recovery from sevoflurane anesthesia, occurred 2.5 times more frequently than that during or after halothane anesthesia ($P < 0.004$). Six additional experiences (in five patients) were considered serious, although only two were considered study drug-related. One 3-yr-old boy in the sevoflurane group experienced apnea for 3 min after induction of anesthesia. The apnea occurred after a caudal block was administered but before skin incision. The lungs were ventilated manually for 3 min, after which time spontaneous ventilation resumed and the child completed the study. A 1-yr-old boy in the halothane group experienced severe obstruction of the airway that was thought to be due to thick secretions that became inspissated in a bronchus during induction of anesthesia. This event was associated with severe hypoxia, which required pharyngeal suctioning, tracheal intubation, and assisted manual ventilation. The data from this child were omitted from the analysis.

The plasma inorganic fluoride concentration measured 1 h after discontinuation of sevoflurane anesthesia was 10.3 ± 3.5 μM (maximum 23.2 μM) compared with 2.1 ± 1.7 μM (maximum 12.9 μM) measured 1 h after discontinuation of halothane.

When questioned before discharge from the recovery room, none of the children in either group experienced intraoperative recall.

In the 24-h followup questionnaire, the percentage of children or parents who would request the same anesthetic again was 96.3% in the sevoflurane-treated group and 95.6% of the halothane-treated group (P = NS). The percentage of children who remembered the induction technique was 64% in the sevoflurane group and 63.2% in the halothane group. A similar proportion of the children remembered an odor associated with the anesthetic: 61% in the sevoflurane group and 75% in the halothane group.

Discussion

The results of this multicenter study indicate that the clinical characteristics of sevoflurane are similar to those of halothane in children undergoing ambulatory surgery. Early recovery after sevoflurane is more rapid than that after halothane, although late recovery and discharge time from the hospital were similar for the two anesthetics. Both anesthetics appeared safe, with a low incidence of side effects.

In the design of this study, we included three strategies in an attempt to deliver equipotent end-tidal concentrations of sevoflurane and halothane during induction of anesthesia. First, because the maximum deliverable inspired concentration of sevoflurane was 7%, we limited the maximum inspired concentration of halothane to 4.3%. This maximum inspired concentration for halothane was based in part on the relative MAC values of the two anesthetics,[4,11] pharmacokinetic data for sevoflurane and halothane in adults,[12] and an assumption that MAC multiples of these anesthetics were equipotent. When these data are taken into consideration, a 7% inspired concentration of sevoflurane and a 4.3% inspired concentration of halothane should yield equipotent end-tidal anesthetic concentrations during induction of anesthesia. Second, the stepwise increase in the inspired concentration of sevoflurane was 2–3 times that of halothane, corresponding to a 250% difference in their MAC values.[4,9] These stepwise increases in concentrations should have increased the depth of anesthesia similarly for the two anesthetics. Third, the range of fresh gas flows used facilitated rapid changes in the inspired concentrations of both anesthetics with the Mapleson D, F, and circle circuits.

Notwithstanding the above, recent preliminary data suggest that the difference between the rate of increase in end-tidal to inspired concentrations of sevoflurane and halothane in children may be less than that reported in adults.[12,13] In assuming the pharmacokinetics of these two anesthetics in children are similar to those in adults, it is possible that we biased our study design in favor of a more rapid equilibration of end-tidal to inspired concentrations of halothane than of sevoflurane.

Despite these strategies, induction of anesthesia as measured by the time to loss of the eyelash reflex was statistically but not clinically more rapid with sevoflurane than with halothane. Four possible explanations could account for this surprising observation. First, the rate of increase in the partial pressure of sevoflurane within that portion of the central nervous system that controls the eyelash reflex was more rapid than that of halothane. Second, the assumption that a MAC multiple of one inhalational anesthetic is equipotent to the same MAC multiple of another anesthetic may be erroneous. Third, anticipation that an inhalational induction with sevoflurane would be free of airway reflex responses may have prompted the investigators to increase the inspired concentration of sevoflurane more rapidly than halothane. Fourth, it is possible that the halothane va-

porizers did not deliver the dialed concentration at the large fresh gas flows used, whereas the newer vaporizers for sevoflurane did. As a consequence, the delivered concentration of halothane may have been less than the dialed concentration, and induction with this agent may have been delayed.

The rate of emergence from inhalational anesthesia depends on the solubility of the anesthetic, the duration of exposure and concentration of anesthetic during the maintenance period, and the metabolism of the anesthetic. We found that emergence and early recovery were 25–50% more rapid with sevoflurane than they were with halothane. This is consistent with their relative blood solubilities and published recovery data.[6–8,14] Rapid emergence should parallel a rapid elimination of the anesthetic, provided the anesthetic exposure and rate of metabolism are comparable between the two anesthetics. We controlled the anesthetic exposure by restricting the anesthetic concentration during the maintenance period to $\approx 1.0 \times$ MAC when possible but, at the least, during the final 10 min of surgery in all children. However, the total exposure to sevoflurane in this study was 13% less than the exposure to halothane. This difference favors a more rapid recovery after sevoflurane but does not completely explain the magnitude of the differences in emergence and early recovery between sevoflurane and halothane.

We found that emergence and early recovery after sevoflurane anesthesia were significantly more rapid than after halothane, although the recovery scores 30 min or more after arrival in the recovery room and the times to discharge from the recovery room were similar. These data are consistent with published studies of sevoflurane and desflurane.[5,15,16] Our failure to recognize a difference between sevoflurane and halothane in the times to discharge is unexpected because we designed this study with strategies to minimize the variability in the anesthetic management during emergence among the five centers, including a strictly regimented anesthetic protocol during the final 10 min of the surgery, a nurse who was unaware of the treatment assignment to monitor recovery, identical criteria for discharge with both treatments, and discharge times both with and without tolerance for clear fluids. If sevoflurane facilitates a clinically significant more rapid discharge from the recovery room than halothane, our sample size should have been large enough and the study design adequate to detect such a difference.

The incidence of agitation and excitement during emergence from sevoflurane was almost threefold greater than the incidence after halothane anesthesia. The reason for the greater incidence of agitation after sevoflurane is not clear at this time. At least two hypotheses have been proposed. The first is that agitation is a central nervous system effect of this ether anesthetic. To date, there is little evidence to support increased cell membrane excitability during sevoflurane anesthesia, although electroencephalographic evidence of seizurelike activity has been reported in children.[17] The second is that agitation and excitement during emergence are manifestations of acute pain and anxiety when the anesthetic is rapidly eliminated. In this study, recovery from sevoflurane anesthesia was rapid, and the analgesia requirements in the recovery room after sevoflurane were greater than those anesthetized with halothane. Although these two observations are consistent with the second hypothesis, they do not establish a cause and effect relationship. To prove the second hypothesis, we would have to compare the incidence of agitation in two groups of children anesthetized with sevoflurane, one with and one without intraoperative analgesia. Further studies are warranted to clarify this issue and to determine whether this is an avoidable side effect of sevoflurane.

Sevoflurane is degraded *in vivo* by cytochrome P450 2E1 releasing inorganic fluoride.[18] Plasma inorganic fluoride concentrations in excess of 50 μM are believed to predispose to nephrotoxicity after methoxyflurane, although this opinion has been questioned.[19] The plasma concentration of inorganic fluoride reaches a maximum value approximately 1 h after discontinuation of sevoflurane, ≈ 28 μM 1 h after 2.5 MAC · h sevoflurane in children.[20] In this study, the mean plasma concentration of inorganic fluoride recorded 1 h after 1.05 MAC · h sevoflurane was only 10.3 ± 3.5 μM (maximum value recorded was 23.2 μM). These data indicate that inorganic fluoride is unlikely to pose a concern insofar as the use of sevoflurane in children undergoing ambulatory surgery is concerned.

Sevoflurane is adsorbed and degraded in the presence of soda lime (or Baralyme) to five compounds, the most common of which is compound A.[21] Compound A in large concentrations in rats has been associated with histologic changes in the kidney.[22] We chose not to measure the inspired concentration of compound A in this study for several reasons. First, degradation of sevoflurane in the presence of soda lime is a hydrolytic process that is time-dependent. Based on the anticipated brief duration of the anesthetic, it is unlikely that measurable concentrations of compound A would

have been produced in the anesthetic circuit in this study. Second, the fresh gas flows used in our study were large (at least 3 $l \cdot min^{-1}$ during maintenance). This would have diluted the concentration of compound A in the inspiratory limb of the circle circuit. Third, the rate of production of compound A decreases in parallel with body surface area in children.[23]

In summary, the results of this study indicate that the induction, recovery, and safety characteristics of sevoflurane in children undergoing ambulatory surgery are comparable to those of halothane.

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Appendix 1. Modified Aldrete Score

Respiration
- 0 = Apnea
- 1 = Dyspnea, shallow or limited respiration
- 2 = Able to deep breathe and cough freely

Activity (as appropriate for age, surgery)
- 0 = Unable to move any extremities
- 1 = Able to move 2 extremities voluntarily or on command
- 2 = Able to move 4 extremities voluntarily or on command

Level of consciousness
- 0 = Nonresponsive
- 1 = Responding to stimuli
- 2 = Awake

Circulation
- 0 = Systolic blood pressure >20% above preanesthetic values
- 1 = Systolic blood pressure within 11–20% of preanesthetic values
- 2 = Systolic blood pressure within 10% of preanesthetic values

Temperature (axillary or equivalent site)
- 0 = Axillary temperature <35°C or >37.5°C
- 1 = Axillary temperature 35–35.5°C
- 2 = Axillary temperature 35.6–37.5°C

Appendix 2. Objective Pain Discomfort Score

Blood pressure
- 2 = >20% preoperative
- 1 = 11–20% above preoperative
- 0 = ≤10% preoperative

Crying
- 2 = Crying, not responding to TLC (tender, loving care)
- 1 = Crying, but responds to TLC
- 0 = Not crying

Moving
- 2 = Thrashing
- 1 = Restless
- 0 = None

Agitation
- 2 = Hysterical
- 1 = Mild
- 0 = Patient asleep or calm

Verbal evaluation/language
- 2 = Moderate pain (localizes verbally or by pointing)
- 1 = Mild pain (cannot localize)
- 0 = Asleep or states no pain