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The Pharmacology of Sevoflurane in Infants and Children

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Background: **Sevoflurane is a new volatile anesthetic with physical properties that should make it suitable for anesthesia in children. In this study, the minimum alveolar concentration (MAC) of sevoflurane in oxygen alone and in 60% nitrous oxide, the hemodynamic, induction and emergence responses to sevoflurane and the metabolism to inorganic fluoride were studied in 90 ASA physical status 1 or 2 neonates, infants, and children.**

Methods: **MAC of sevoflurane in oxygen was determined in six groups of subjects stratified according to age: full-term neonates, infants 1–6 and > 6–12 months and children > 1–3, > 3–5 and > 5–12 yr. MAC in 60% nitrous oxide was determined in a separate group of children 1–3 yr of age. After an inhalational induction, the trachea was intubated (except for neonates in whom an awake intubation was performed). MAC for each age group was determined using the Up-and-Down technique of Dixon.**

Results: **MAC of sevoflurane in neonates, 3.3 ± 0.2% and in infants 1–6 months of age, 3.2 ± 0.1%, were similar; MAC in older infants 6–12 months and children 1–12 yr was constant at ≈ 2.5%; MAC of sevoflurane in 60% nitrous oxide in children 1–3 yr of age was 2.0 ± 0.2%. Systolic arterial pressure decreased significantly at 1 MAC before skin incision compared with awake values in all subjects except children 1–3 yr with 60% nitrous oxide and children 5–12 yr in oxygen, and then returned toward awake values after skin incision. Heart rate was unchanged at ≈ 1 MAC sevoflurane before incision compared with awake values in all subjects except children > 3–5 and > 5–12 yr in whom heart rate increased before incision. Induction of anesthesia, particularly with respect to airway irritability, and emergence from sevoflurane anesthesia were not remarkable. The plasma concentration of inorganic fluoride reached maximum values (8.8–16.7 μM) 30 min after discontinuation of anesthesia.**

Conclusions: **We conclude that sevoflurane appears to be a suitable anesthetic agent for use in neonates, infants and children undergoing ≤ 1 h of anesthesia. (Key words: Anesthesia: pediatric. Anesthesia, cardiovascular effects: blood pressure; heart rate. Anesthetics, volatile: sevoflurane. Complications: airway. Metabolism: fluoride. Potency: minimum alveolar concentration.)**

SEVOFLURANE, a volatile ether inhalational anesthetic, possesses several properties including low blood and tissue solubility, nonpungency, nonflammability, and limited cardiorespiratory depression that may be desirable for use in infants and children.[1–3]

Previous studies of halothane, isoflurane and desflurane have shown that MAC increases as age decreases in adulthood and childhood, reaching a maximum value in infancy and decreasing thereafter in the neonatal age range.[4–7] In the case of sevoflurane, however, only the MAC in adults, 1.7–2.05%,[8,9] and in children 3–5 yr, 2.5%,[10] have been determined. Although the MAC of sevoflurane in children is greater than that in adults, the relationship between the MAC of sevoflurane and age over the entire age range between neonates and children 12 yr of age or younger remains undetermined. In order to compare the physiologic effects of sevoflurane with those of other inhalational anesthetics at equipotent MAC values, the MAC of sevoflurane must be determined in neonates, infants and children.

Sevoflurane is a methyl isopropyl ether anesthetic with a trifluorinated methyl group on the α carbon atom. As a result of its chemical structure, sevoflurane is susceptible to degradation by hepatic microsomal enzymes P450IIE1 with the release of inorganic fluoride into the circulation.[11,§] Because increased plasma

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§ Kharasch ED, Thummel K: Human liver volatile anesthetic defluorination: Role of cytochrome P450IIE1 (abstract). ANESTHESIOLOGY 75:A350, 1991.

concentrations of inorganic fluoride are associated with an impaired renal-concentrating capability, we also measured the plasma concentration of inorganic fluoride in all infants and children exposed to sevoflurane.

Materials and Methods

After institutional approval and informed consent from the parents, 90 healthy full-term neonates, infants and children were studied. All infants and children were fasted, nonpremedicated, ASA physical status 1 or 2 and scheduled for either urgent surgery in the case of neonates (general surgery) or elective surgery (urologic (excluding kidney surgery), general, plastic and orthopedic) in the cases of older infants and children.

The MAC of sevoflurane in oxygen was determined in six groups of subjects who were stratified according to age: full-term neonates (≤ 30 days), infants 1–6 and > 6–12 months of age and children > 1–3, > 3–5 and > 5–12 yr of age. The MAC of sevoflurane in 60% nitrous oxide was determined in a separate group of children 1–3 yr of age.

Exclusion criteria included:

1. anticipated anesthetic time to exceed 1 h
2. anticipated blood loss to exceed 10% of the subject's blood volume
3. asthma, pneumonia, or bronchospastic lung disease, or difficult intubation
4. congenital heart disease, central nervous system disease (retardation, seizures, cerebral palsy, or hydrocephalus)
5. gastrointestinal disease (gastroesophageal reflex), renal dysfunction or disease, muscle disease (malignant hyperthermia), metabolic disease (glycogen storage disease or diabetes), obesity (> 20% above ideal body weight), or hepatitis
6. use of medication (*i.e.*, anticonvulsants, opioids, barbiturates, or sedatives), antibiotics (tetracycline, gentamicin, cephaloridine, polymyxin, or any other antibiotic that may be nephrotoxic), drugs that induce hepatic enzymes (phenobarbital, phenytoin, or isoniazid), or any other drugs known to affect MAC.

Upon arrival in the operating room, all subjects were monitored with an electrocardiogram, precordial stethoscope, automated blood pressure cuff, hemoglobin oxygen saturation (Sp_{O_2}) probe, and axillary temperature probe. For neonates and infants, body temperature was maintained by preheating the operating room, and by using a heating blanket, an overhead radiant heater and plastic sheets to cover exposed skin. A Humid-vent (Gibeck, Sweden) was interposed between the fresh gas sleeve and the elbow connector in the Ayre's T-piece anesthetic circuit for all subjects.

For neonates, the trachea was intubated with the infant awake. After the airway was secured, anesthesia was induced by inhalation of sevoflurane in oxygen and air (inspired oxygen fraction ≈ 30–40%), increasing the inspired concentration of sevoflurane in stepwise increments of 1.5% every three breaths until the desired level of anesthesia was achieved. For all subjects > 1 month of age, anesthesia was induced by inhalation of sevoflurane in oxygen, increasing the inspired concentration of sevoflurane in stepwise increments of 1.5% every three breaths up to a maximum of 7%. For the separate group of children 1–3 yr in whom the MAC of sevoflurane in nitrous oxide was measured, anesthesia was induced by inhalation of sevoflurane in 60% nitrous oxide and oxygen. When the depth of anesthesia was judged to be appropriate, the trachea was intubated with a tracheal tube appropriate for the subject's age.

For all subjects, anesthesia was delivered *via* an Ayre's T-piece with the Jackson Rees modification. Ventilation was assisted manually as soon as the eyelash reflex was lost. Intravenous access was secured and lactated Ringer's solution was infused at a rate of 4–8 $ml \cdot kg^{-1} \cdot h^{-1}$. Cuffed tubes were used for children ≥ 8 yr of age. The lungs were then mechanically ventilated with an Air Shields Ventimeter ventilator at a respiratory rate and fresh gas flow (minimum of 2 $l \cdot min^{-1}$) to maintain normocapnia (end-tidal carbon dioxide tension 35–45 mmHg). Positive end-expiratory pressure was avoided. All subjects were supine and horizontal throughout the study.

All sevoflurane and carbon dioxide gas concentrations were sampled continuously through a 16- or 19-G catheter inserted through the elbow of the breathing circuit to the distal end of the tracheal tube.[12] Gas concentrations were analyzed by a Capnomac Ultima gas analyzer (nominal sample flow rate of 200 $ml \cdot min^{-1}$) (Datex, Helsinki, Finland) that was calibrated immediately before each study using a cylinder that contained a mixture of gases of known concentrations.

The end-tidal concentration of sevoflurane administered to the first subject in each of the neonate and two older-infant age groups was 2.40%; the concen-

tration administered to the first subject in each of the age groups ≥ 1 yr of age was 1.90–2.40%.[9] The carrier gas for all anesthetics up to the time of the skin incision included an air–oxygen mixture for neonates and oxygen for infants and children. The end-tidal concentrations of sevoflurane administered to all subsequent subjects in their respective age group were determined by the response of the preceding subject: if the preceding subject had moved, the sevoflurane concentration was increased by 0.2% for the next subject, whereas if the preceding subject had not moved, the concentration was decreased by 0.2%. After the desired end-tidal concentration of sevoflurane was maintained for at least 10 min, the skin was incised with a scalpel blade and the move–no-move response recorded. A move response was defined by withdrawal of a hand or foot within 60 s of skin incision.

After skin incision, anesthesia was maintained with sevoflurane, 60% nitrous oxide and the balance as oxygen for all infants and children except for neonates in whom bowel obstruction was suspected. In those neonates, nitrous oxide was avoided and air was added to the fresh gas mixture to maintain a Sp_{O_2} between 90 and 95%. The end-tidal concentration of sevoflurane during maintenance was that concentration used for the MAC study if the subject had not moved or 20% greater than that if the subject had moved. During the operative period, temperature was maintained between 36.5 and 37.5° C. If neuromuscular blockade was required, 0.05–0.1 $mg \cdot kg^{-1}$ vecuronium was administered intravenously.

Before the end of surgery, a regional nerve block (caudal or epidural) using a maximum of 2.5 $mg \cdot kg^{-1}$ bupivacaine was administered whenever appropriate. When vecuronium had been administered, its neuromuscular effects were antagonized with neostigmine 40 $\mu g \cdot kg^{-1}$ and atropine 20 $\mu g \cdot kg^{-1}$ intravenously at the conclusion of surgery. Sevoflurane and nitrous oxide were discontinued simultaneously at the conclusion of anesthesia. Ventilation of the lungs continued either mechanically or manually until extubation. The trachea was extubated when the gag reflex had returned, the subjects were breathing spontaneously and making purposeful movements. Acetaminophen (administered in a dose of 10–20 $mg \cdot kg^{-1}$ per rectum) or morphine (administered in a dose of 0.05 $mg \cdot kg^{-1}$ intravenously) was given as required in the recovery room for pain.

MAC was determined using the Up-and-Down technique as described by Dixon.[13] Each subject contributed one datum point toward the measurement of MAC for the age group. Although the response of each subject was recorded, the determination of MAC for each age group began only *after* the first pair of opposite responses to skin incision of the subjects within the respective age group. Twelve subjects were used to determine the MAC in each age group, except for infants 1–6 months of age, for which 8 subjects were accepted. MAC was the mean of the concentrations of the patients in the specific age group. The standard error of MAC was the standard deviation of the mean concentrations of the three subgroups within each age group. A subgroup was defined as 4 sequential subjects.

Baseline measurements of systolic, diastolic, and mean arterial blood pressures, heart rate, Sp_{O_2}, and temperature were recorded at three times: awake, at the steady-state end-tidal concentration of sevoflurane before skin incision, and at the same steady state concentration approximately 1 min after skin incision (at the peak hemodynamic response to incision). In addition, heart rate, systolic blood pressure, Sp_{O_2}, end-tidal carbon dioxide, respiratory rate, and temperature were recorded every 2 min before incision, at 1-min intervals for 5 min after incision, and then every 5 min until the end of surgery.

The incidence of moderate and severe airway reflex responses including breathholding (> 15 s), coughing (more than two episodes), laryngospasm (> 5 s of phonation or inability to ventilate), bronchospasm (bilateral wheezing), and secretions (requiring suctioning), in addition to the incidence of excitement (nonpurposeful movement requiring restraint), hypotension (> 30% decrease in systolic blood pressure at ≈ 1 MAC preincision compared with awake values), and $Sp_{O_2} \leq$ 90% were recorded during both induction of anesthesia and emergence from anesthesia. The times from induction of anesthesia to loss of the eyelash reflex and to tracheal intubation and from discontinuation of anesthesia until eye opening, extubation and full recovery (defined as fully alert, oriented [where applicable], without excess pain or discomfort, and with stable vital signs) after discontinuation of sevoflurane were recorded.

During emergence, the end-tidal concentration of sevoflurane (F_A) was recorded on a Psion LZ64 computer every 10 s until extubation.[14] The washout of sevoflurane for each age group was the mean of the

ratios of the F_A to the end-tidal concentration of sevoflurane at the time of discontinuation of anesthesia (F_{AO}) for each subject within an age group calculated every 10 s from discontinuation of anesthesia until tracheal extubation. The F_A/F_{AO} ratios for the seven age groups were compared at 2 and 5 min after discontinuation of anesthesia.

Three milliliters of blood were obtained from an indwelling intravenous catheter at the time of induction of anesthesia, discontinuation of anesthesia and at 30, 60, 90, 120 and 240 min thereafter for measurement of the plasma concentration of inorganic fluoride. Each blood sample was heparinized and centrifuged within 1 h of collection. The supernatant plasma was separated and then frozen in a sealed plastic tube at −20° C until analysis. The concentration of inorganic fluoride in the plasma was determined using a fluoride specific ion analyzer, reverse-phase high-performance liquid chromatography, and a flame-ionization detector. The specifications of the assay were as follows: minimum detectable concentration of inorganic fluoride of 1 μM, coefficient of variation of intrabatch measurements of 7.9% and coefficient of variation of interbatch measurements of 8.6%.

The exposure to sevoflurane (MAC · hours) was the area under the MAC–time profile for each subject. The number of MAC · hours was calculated as the sum of the products of the end-tidal concentration of sevoflurane and the time exposed to that concentration for the period between intubation and extubation. The MAC · hour for each age group was the average of the MAC · hour measurement for all subjects within that age group.

Results are reported as means ± standard deviation. Parametric data were analyzed using one-way analysis of variance and the Newman-Keuls multiple-comparison test for between group differences in the lowest Sp_{O_2}, times to loss of eyelash reflex and intubation, duration of anesthesia, times to extubation, eye opening and full recovery (*i.e.*, satisfies discharge criteria from recovery room), and the MAC · h exposure to sevoflurane. Repeated-measures analysis of variance and the Newman-Keuls test were used for within-group differences of systolic arterial pressure and heart rate awake, at ≈ 1 MAC before skin incision and at ≈ 1 MAC after skin incision. Nominal data, including the incidences of all airway reflex responses during both induction and emergence and the incidences of Sp_{O_2} < 90%, hypotension, and arrhythmia, were analyzed using chi-square analysis and Fisher's exact test. $P < 0.05$ was accepted for statistical significance.

Results

Ninety infants and children were enrolled in this study. The demographic data and induction characteristics from the 68 subjects who were included in the determination of MAC in oxygen and from the 12 children 1–3 yr of age who were included in the determination of MAC in the presence of 60% nitrous oxide and 40% oxygen are presented in table 1. The 10 subjects who were enrolled before the first pair of opposite responses to skin incision in their respective age groups were not included in the data analysis. However, the induction, emergence, and hemodynamic responses of these 10 subjects to sevoflurane did not differ from the data presented below.

The individual responses to skin incision in each age group are shown at their respective end-tidal concentrations of sevoflurane (fig. 1). The mean (± standard deviation) MAC of sevoflurane in oxygen was greatest in neonates and infants 1–6 months of age (figs. 1 and 2). The MAC in infants and children between 6 months and 12 yr of age was approximately 25% less than that in neonates. The MAC of sevoflurane in 60% nitrous oxide in children 1–3 yr of age, 2.0 ± 0.18%, was 24% less than that in oxygen in children of the same age range (figs. 1 and 2).

Induction of anesthesia with sevoflurane was smooth and uncomplicated in all infants (n = 20) and children (n = 48). In those subjects anesthetized with sevoflurane in an oxygen–air mixture, coughing occurred in one infant 6–12 months of age and excitement occurred in 2 children 1–3 yr of age, in 5 children 3–5 yr of age and in 2 children 5–12 yr of age. In those children anesthetized with sevoflurane in 60% nitrous oxide, excitement occurred in one child, and Sp_{O_2} decreased to less than 90% in another. Apnea did not occur in any subjects.

The times from application of the face mask to loss of the eyelash reflex and intubation increased with increasing age (table 1).

Compared with awake values, systolic arterial pressure decreased significantly at ≈ 1 MAC sevoflurane in oxygen before skin incision in all infants and children up to 5 yr of age (fig. 3). The decrease in systolic pressure was greatest in the youngest subjects and decreased with increasing age (table 1). Hypotension, defined as

Table 1. Demographic Data and Induction Characteristics

Group	No. of Patients per Group	Age	Weight (kg)	Face Mask to Loss of Eyelash Reflex (s)	Face Mask to Intubation (min)	% Decrease in SAP*	Incidence of Hypotension* (%)	Lowest Sp_{O_2}† (%)
Neonates								
≤30 days	12	16 ± 10.8 days	3.5 ± 0.6	—	—	34 ± 16.2	8/12 (66)§·††	—
Infants								
1–6 mo	8	2.4 ± 1.1 mo	6.0 ± 1.5	51 ± 17.2‡·¶	2.3 ± 0.4¶	26 ± 20.1	4/8 (50)‡‡	97.8 ± 0.9¶
6–12 mo	12	7.7 ± 1.2 mo	8.8 ± 1.1	56.5 ± 12.7‡·¶	2.5 ± 0.4¶	15 ± 12.5	3/11 (27)	97.2 ± 1.8¶
Children								
1–3 yr	12	1.7 ± 0.5 yr	11.7 ± 2.0	58.2 ± 12.2‡·¶	3.0 ± 0.6¶·**	8 ± 11.5	1/12 (8)	97.8 ± 1.4¶
1–3 yr (with 60% N_2O)	12	1.8 ± 0.6 yr	12.0 ± 1.5	57.2 ± 7.0‡·¶	2.9 ± 0.6¶·**	11 ± 12.8	1/12 (8)	96.8 ± 2.7¶
3–5 yr	12	3.9 ± 0.7 yr	16.0 ± 2.4	79.7 ± 11.8	3.8 ± 0.6	10 ± 6.7	0	97.2 ± 2.0
5–12 yr	12	7.7 ± 1.5 yr	26.1 ± 4.1	72.8 ± 12.7	5.5 ± 1.3	0 ± 9	0	96.9 ± 1.8
Total				63.0 ± 15.5	3.4 ± 1.3	14 ± 16	(22)	97.2 ± 1.9

Values are mean ± SD except where indicated. MAC was determined in 97% oxygen except where indicated.

* At ~1 MAC before skin incision *versus* awake values.

† During induction of anesthesia.

‡ $P < 0.001$ *versus* 3–5 yr.

¶ $P < 0.025$ *versus* 5–12 yr.

** $P < 0.025$ *versus* 3–5 yr.

†† $P < 0.01$ *versus* 1–3 yr with and without 60% N_2O.

‡‡ $P < 0.014$ *versus* 3–5 and 5–12 yr.

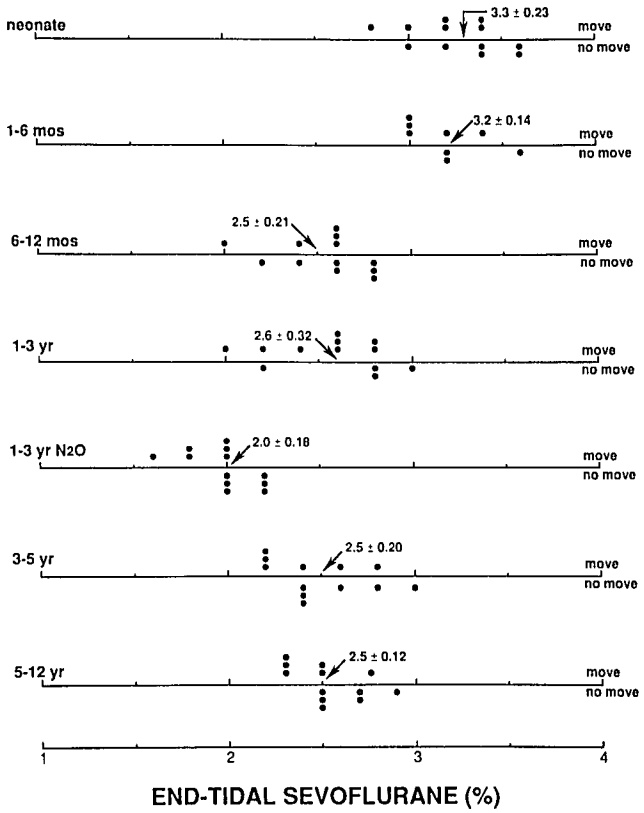

Fig. 1. The individual subjects' response (filled circle) to skin incision at their respective end-tidal concentrations of sevoflurane. The responses shown for the subjects in each age group include all of the responses beginning with the first pair of opposite responses to skin incision. MAC (mean ± standard error) of sevoflurane for each age group is indicated (*arrow*).

≥ 30% decrease in systolic arterial pressure compared with awake values, also occurred more frequently in neonates and infants (27–66% of subjects) than it did in children 1–12 yr of age (0–8% of subjects) (table 1). Two of the neonates who developed hypotension were treated with 6 and 11 ml/kg, respectively, of Ringer's lactate. The remainder of the subjects did not require fluid resuscitation during the anesthetic. Systolic pressure returned toward awake values after skin incision but remained less than awake values in neonates and infants 6–12 months of age. Systolic pressure was maintained at ≈ 1 MAC sevoflurane in children 5–12 yr and in those 1–3 yr who received 60% nitrous oxide.

Compared with awake values, heart rate remained unchanged at ≈ 1 MAC before skin incision in all infants and children up to 3 yr of age (fig. 4). In children 3 yr and older, heart rate increased significantly above awake values at ≈ 1 MAC sevoflurane before skin incision. Nodal rhythm occurred in two subjects during the study: in one child in the 1–3-yr age group (sevoflurane in oxygen) before skin incision that lasted 4

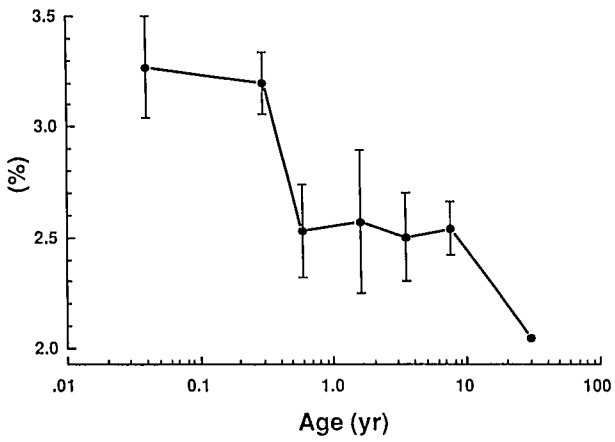

Fig. 2. The mean (± standard deviation) end-tidal concentration of sevoflurane in oxygen for each of the six age groups from neonates to older children up to 12 yr of age. The data for MAC at 30 yr of age were obtained from reference 9.

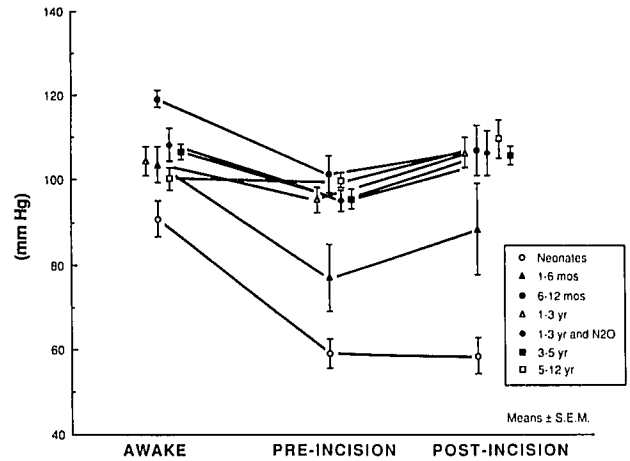

Fig. 3. Systolic arterial pressure (mean ± standard error of the mean) for each of the six age groups while awake and at ≈ 1 MAC sevoflurane before and after skin incision. Systolic pressure decreased significantly at ≈ 1 MAC compared with awake values in all infants and children except children 1–3 yr of age with nitrous oxide and children 5–12 yr of age ($P < 0.05$). Systolic pressure returned toward awake values after skin incision but remained significantly less than awake values in the neonate and 6–12-month age groups ($P < 0.025$).

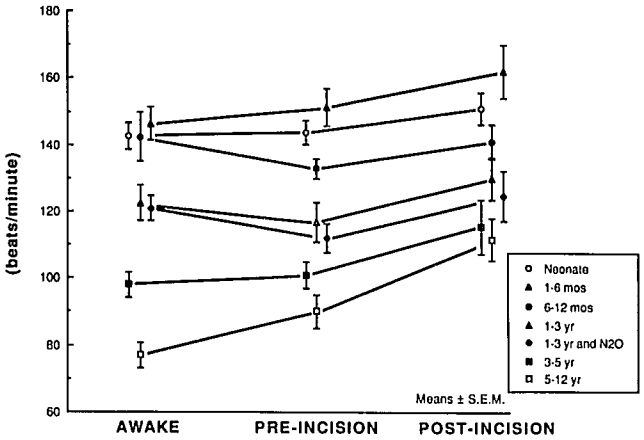

Fig. 4. Heart rate (mean ± standard error of the mean) for each of the six age groups while awake and at ≈ 1 MAC sevoflurane before and after skin incision. Heart rate was unchanged at ≈ 1 MAC compared with awake values in all infants and children except children 3–5 and 5–12 yr of age. In these two groups of children, heart rate increased significantly ($P < 0.017$) at ≈ 1 MAC compared with awake values.

min and twice in a second child in the 5–12-yr age group: first before the skin incision lasting 16 min and a second 18 min after skin incision lasting 13 min. Neither of these children required therapeutic intervention for the treatment of the arrhythmia. Sinus rhythm resumed spontaneously in both instances despite the continued use of sevoflurane. Bradycardia did not occur in any subjects.

During the maintenance period, systolic arterial pressure and heart rate were maintained within 20% of baseline measurements. There were no episodes of hypotension, hypertension, or arrhythmia.

Emergence from anesthesia was rapid (table 2). There were no airway reflex responses during emergence except for one episode of postextubation apnea in a neonate. The trachea was reintubated and then extubated shortly thereafter. The mean (± standard deviation) F_A/F_{AO} of sevoflurane for all age groups, measured at 2 and 5 min after discontinuation of sevoflurane were 0.23 ± 0.06 and 0.16 ± 0.05 respectively (table 2).

Nausea could not be assessed in infants and children < 3 yr of age. The incidence of nausea in children 3–5 yr was 17% and in children 5–12 yr was 50%. Vomiting was not assessed in neonates because all but one subject underwent gastrointestinal surgery for partial or complete bowel obstruction. The incidence of vomiting for all infants > 1 month old and children was 22% during the first 24 h after anesthesia (table 2).

The mean plasma concentrations of inorganic fluoride at induction of anesthesia ranged from 0–3.5 μM (fig. 5). The mean plasma concentrations of inorganic fluoride reached maximum values between 8.8 and 16.7 μM 30 min after discontinuation of sevoflurane (table 2) and decreased toward baseline concentrations during the subsequent 3.5 h (fig. 5). There was a poor correlation between the peak plasma concentration of inorganic fluoride and the MAC · h of sevoflurane (r^2 = 0.15).

Discussion

We investigated the pharmacology of sevoflurane in neonates, infants and children to determine whether this drug has a role in pediatric anesthesia. Sevoflurane facilitated a rapid induction of anesthesia, without irritating the airway, provided stable hemodynamics during maintenance and facilitated a rapid recovery from anesthesia. Although other ether inhalational anesthetics provide stable hemodynamics during maintenance and a rapid recovery in children, sevoflurane is the only ether anesthetic that also facilitates a smooth induction of anesthesia when it is administered by mask.

We found that the MAC of sevoflurane remained constant for neonates and infants < 6 months of age, 3.2–3.3%, and then decreased to 2.5% in infants > 6–12 months of age where it remained unchanged in children up to 12 yr (fig. 2). Our value for the MAC of sevoflurane in children 3–5 yr of age is consistent with the published data for the same age group, 2.49 ± 0.08%.[10] Previous studies have described the relationship between MAC and age for other inhalational agents.[4–7] For halothane, isoflurane and desflurane, MAC increased throughout infancy to a maximum value and decreased thereafter as age increased throughout childhood and adulthood. In the case of sevoflurane however, MAC is almost independent of age except for the 25% decrease in MAC during infancy (fig. 2). The explanation for the difference in the relationship between MAC and age for sevoflurane remains unclear.

We estimated the MAC of sevoflurane using the Up-and-Down technique described by Dixon.[13] Previous studies of the MAC of halothane[4,5] and isoflurane[6] were determined using the same technique, although more recently the MAC values of desflurane in children[7,15]

Table 2. Washout and Emergence Characteristics

Group	Duration of Maintenance Anesthesia* (min)	F_A/F_{AO} at 2 min of Washout	F_A/F_{AO} at 5 min of Washout	End of Sevoflurane to Extubation (min)	End of Sevoflurane to Eye Opening (min)	Time to Full Recovery† (min)	Sevoflurane (MAC · h)	Maximum Fluoride Concentration (μM)	Postoperative Vomiting (%)
Neonates	63.2 ± 36.9	0.23 ± 0.03	0.17 ± 0.04	12.3 ± 4.9	—	39.1 ± 13.1§	0.92 ± 0.58	12.9 ± 4.9	NA
Infants									
1–6 mo	42.1 ± 16.4	0.19 ± 0.07‡§	0.10 ± 0.05‡§¶**††	7.1 ± 1.1‡‡	9.6 ± 3.3	37.8 ± 11.7§	0.79 ± 0.26	8.8 ± 2.5††¶¶	12
6–12 mo	41.5 ± 13.4	0.19 ± 0.04‡§	0.11 ± 0.03‡§¶**††	5.8 ± 1.1‡‡	10.8 ± 3.0	32.4 ± 4.4§	0.83 ± 0.20	13.3 ± 3.5	8
Children									
1–3 yr	40.8 ± 8.0	0.28 ± 0.04	0.18 ± 0.04	6.2 ± 1.2‡‡	10.4 ± 3.6	37.2 ± 9.9§	0.75 ± 0.20	12.2 ± 2.4	8
1–3 yr (with 60% N_2O)	48.3 ± 11.2	0.20 ± 0.05‡§	0.16 ± 0.04	5.0 ± 1.3‡‡	8.5 ± 1.9§§	35.6 ± 4.7§	0.95 ± 0.20	14.1 ± 2.9	17
3–5 yr	42.6 ± 23.4	0.23 ± 0.05	0.19 ± 0.03	7.1 ± 1.9‡‡	11.6 ± 4.4	37.4 ± 7.5§	1.06 ± 0.71	15.8 ± 4.1§§	42
5–12 yr	37.1 ± 9.5¶	0.28 ± 0.07	0.21 ± 0.06	7.4 ± 1.2‡‡	16.5 ± 4.3	51.3 ± 9.8	0.72 ± 0.20	11.7 ± 2.0	42
Total	45.3 ± 20.5	0.23 ± 0.06	0.16 ± 0.05	7.2 ± 3.1	10.5 ± 3.2	38.7 ± 10.5	0.82 ± 0.25	13.0 ± 3.6	22

Values are mean ± SD except where indicated.

F_A = the alveolar fraction of sevoflurane during the washout of sevolfurane; F_{AO} = the alveolar fraction of sevoflurane at the time of discontinuation of anesthesia; NA = not applicable.

* From intubation to discontinuation of sevoflurane.

† Time from extubation until alert, oriented and vital signs stable.

‡ $P < 0.05$ *versus* 1–3 yr with 60% N_2O.

§ $P < 0.01$ *versus* 5–12 yr.

¶ $P < 0.025$ *versus* neonates.

** $P < 0.025$ *versus* 1–3 yr.

†† $P < 0.005$ *versus* 3–5 yr.

‡‡ $P < 0.001$ *versus* neonates.

§§ $P < 0.05$ *versus* 5–12 yr.

¶¶ $P < 0.025$ *versus* 1–3 yr with 60% N_2O.

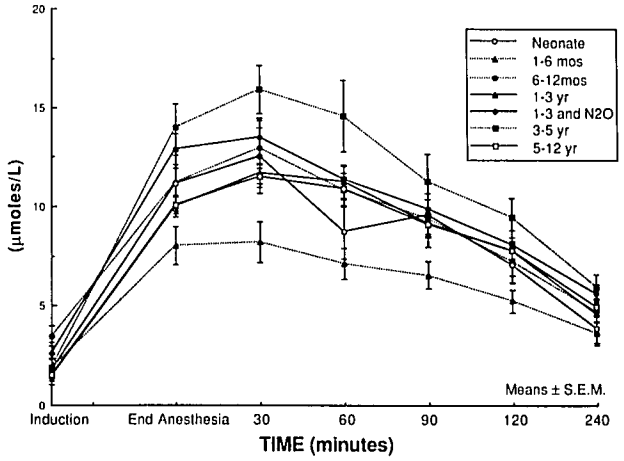

Fig. 5. The mean (± standard error of the mean) plasma concentration of inorganic fluoride for up to 4 h after discontinuation of sevoflurane for each age group. Inorganic fluoride reached a maximum plasma concentration (8.8–16.7 μM) after 0.82 MAC·h sevoflurane 30–60 min after discontinuation of the sevoflurane. The plasma concentration decreased rapidly, to ≤ 10 μM within 4 h.

and the elderly[16] were determined using both the technique of Dixon and logistic regression. In all three studies, the mean and variance of MAC as determined by logistic regression were similar to those determined by the technique of Dixon. We concluded that these data supported the continued use of Dixon's Up-and-Down technique.

Published studies have suggested that the MAC-reducing effect of nitrous oxide is proportional to the concentration of nitrous oxide. In adults, 60% nitrous oxide decreases the MAC of isoflurane and desflurane by approximately 60%.[17,18] Does this MAC-reducing effect of nitrous oxide also hold true for children? Sixty percent nitrous oxide decreases the MAC of halothane in children by 60%,[19] that of isoflurane by 40%[20] and that of desflurane by only 20%[15] compared with the respective MAC values in oxygen. In this study, 60% nitrous oxide decreased the MAC of sevoflurane in children 1–3 yr of age by only 24% (from 2.6% to 2.0%), an amount between its effects on isoflurane and desflurane.[15,20] These data suggest that the MAC-reducing effect of nitrous oxide in children is attenuated in the presence of less soluble inhalational anesthetics. Although the mechanism of this effect is unclear, it may represent competition between nitrous oxide and the insoluble anesthetics at the site of action. Age-related differences in the MAC of nitrous oxide cannot explain the different effect of nitrous oxide on the MAC of inhalational anesthetics as the age of the children was similar in these comparisons. Further studies are warranted to clarify this issue in children.

The hemodynamic responses to ≈ 1 MAC sevoflurane appear to be similar to those reported previously for ≈ 1 MAC halothane and ≈ 1 MAC desflurane.[5,7] In the presence of ≈ 1 MAC sevoflurane, the decreases in systolic arterial pressure were inversely related to age: greatest in the youngest subjects and least in the oldest subjects (table 1 and fig. 3). These decreases are less than those observed with desflurane in infants and children.[7] Heart rate was maintained at awake values even after 1 MAC in infants, although it decreased ≈ 20% in older children (fig. 1). Arrhythmia (nodal) was uncommon (3% incidence), and bradycardia was not observed. Hemodynamic homeostasis as reflected in the systolic arterial pressure and heart rate, appears to be maintained in infants and children up to ≈ 1 MAC sevoflurane.

The smooth induction characteristics of sevoflurane in 100% oxygen support its suitability for use as an induction agent in children.[1] Airway reflex responses during both induction of and emergence from sevoflurane anesthesia in the presence of oxygen are similar to those reported after halothane anesthesia in the presence of nitrous oxide.[21]

Although the speed of induction of anesthesia should be similar with all inhalational anesthetics when the overpressure technique is used, the rate of washout of anesthetics from the body varies inversely with the solubility of inhalational anesthetics in blood; that is, for anesthetics that are metabolized to similar extents, the greater the solubility, the slower the washout. This has been substantiated in adults in whom the washout of sevoflurane (blood–gas partition coefficient, 0.66) was between those of desflurane (blood–gas partition coefficient, 0.42) and isoflurane (blood–gas partition coefficient, 1.4).[22] In this study, the washout of sevoflurane was slower than that of desflurane, as evidenced by F_A/F_{A0} ratios in infants and children (table 2).[23] This is consistent with the relative speed of washout of sevoflurane and desflurane in adults.

Rapid emergence from sevoflurane anesthesia should follow the rapid washout of this anesthetic from the body. When the times to eye opening, response to commands and discharge from the recovery room were used to estimate the speed of emergence from sevoflurane anesthesia, we found that the emergence from sevoflurane anesthesia for all subjects was rapid, although not as rapid as after desflurane anesthesia.[23]

Several possible explanations may account for this difference between the two anesthetics. First, the solubilities of sevoflurane in blood and tissues are greater than those of desflurane.[2,3] With the duration of anesthesia lasting < 1 h, the anesthetic will be present primarily in the vessel-rich tissues and muscle. The magnitude of the differences in solubilities between the two anesthetics is substantial, (50% in the case of blood) and somewhat less in the case of the vessel-rich group and muscle. These differences will contribute to a delay in the washout of sevoflurane compared with desflurane. Second, a caudal block was administered to most of the subjects in this study whereas a regional block was not administered to the subjects in the desflurane study.[23] Afferent nociception is a potent stimulus for wakefulness and in its absence, emergence from anesthesia may be delayed. Thus, the slower recovery times after sevoflurane anesthesia may be explained in part, by differences in physicochemical properties between sevoflurane and desflurane although the magnitude of this difference may have been exaggerated by the difference in pain management in the two studies.

Sevoflurane is metabolized by the liver enzyme cytochrome P450IIE1 with the release of inorganic fluoride.[11,§] Small plasma concentrations of inorganic fluoride are probably not toxic to the renal tubules of healthy subjects, although concentrations in excess of 50 μM such as those reported after methoxyflurane anesthesia have been associated with a renal-concentrating defect in adults.[24] The range of peak plasma inorganic fluoride concentrations in our subjects was 8.8–16.7 μM. These values are less than those reported previously with methoxyflurane in children[25] but exceed those reported previously with enflurane in children after $\approx$ 1 MAC·h exposure.[26] Because the exposure to sevoflurane in this study was limited to a brief period ($\approx$ 1 MAC·h), we were unable to determine whether the peak concentration of inorganic fluoride varies directly with the duration of exposure to sevoflurane. Within the context of this study design, our data indicate that plasma concentrations of inorganic fluoride remain small and below any putative "nephrotoxic" threshold after a brief ($\approx$ 1 MAC·h) exposure to sevoflurane. Further studies are warranted to characterize the metabolism of sevoflurane to inorganic fluoride after extended exposure to sevoflurane in children.

In summary, the clinical pharmacology of sevoflurane was investigated in 80 neonates, infants and children. MAC in neonates and infants 1–6 months of age was 3.2–3.3% whereas that in infants 6 months to 12 yr of age was 2.5–2.6%. The smooth induction and recovery characteristics suggest that sevoflurane is suitable as an induction agent in infants and children. Circulatory stability was maintained at $\approx$ 1 MAC sevoflurane in all age groups. The peak plasma concentrations of inorganic fluoride in infants and children who were anesthetized with $\approx$ 1 MAC·h sevoflurane were one-third the purported nephrotoxic threshold reported for methoxyflurane in adults.[24]

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