Plasma Inorganic Fluoride Concentrations after Sevoflurane Anesthesia in Children


Background: Sevoflurane is degraded in vitro in adults yielding plasma concentrations of inorganic fluoride [F−] that, in some patients, approach or exceed the 50-μM threshold for nephrotoxicity. To determine whether the plasma concentration of inorganic fluoride [F−] after 1-5 MAC·h sevoflurane approaches a similar concentration in children, the following study in 120 children scheduled for elective surgery was undertaken.

Methods: Children were randomly assigned to one of three treatment groups before induction of anesthesia: group 1 received sevoflurane in air/oxygen 30% (n = 40), group 2 received sevoflurane in 70% N2O/30% O2 (n = 40), and group 3 received halothane in 70% N2O/30% O2 (n = 40). Mapleson D or F circuits with fresh gas flows between 3 and 6 l/min were used. Whole blood was collected at induction and termination of anesthesia and at 1, 4, 6, 12, and 18 or 24 h postoperatively for determination of the [F−]. Plasma urea and creatinine concentrations were determined at induction of anesthesia and 18 or 24 h postoperatively.

Results: The mean (± SD) duration of sevoflurane anesthesia, 2.7 ± 1.6 MAC·h (range 1.1-8.9 MAC·h), was similar to that of halothane, 2.5 ± 1.1 MAC·h. The peak [F−] after sevoflurane was recorded at 1 h after termination of the anesthetic in all but three children (whose peak values were recorded between 4 and 6 h postanesthesia). The mean peak [F−] after sevoflurane was 15.8 ± 4.6 μM. The [F−] decreased to <6.2 μM by 24 h postanesthesia. Both the peak [F−] (r² = 0.50) and the area under the plasma concentration of inorganic fluoride-time curve (r² = 0.57) increased in parallel with the MAC·h of sevoflurane. The peak [F−] after halothane, 2.0 ± 1.2 μM, was significantly less than that after sevoflurane (P < 0.0001) and did not correlate with the duration of halothane anesthesia (MAC·h; r² = 0.007). Plasma urea concentrations decreased 24 h after surgery compared with preoperative values for both anesthetics (P < 0.01), whereas plasma creatinine concentrations did not change significantly with either anesthetic.

Conclusions: It was concluded that, during the 24 h after 2.7 ± 1.6 MAC·h sevoflurane, the peak recorded [F−] is low (15.8 μM), F− is eliminated rapidly, and children are unlikely to be at risk of nephrotoxicity from high [F−]. (Key words: Anesthesia: pediatric. Anesthetics: volatile: halothane; sevoflurane. Ions: fluoride.)

SEVOFLURANE is a new polyfluorinated volatile anesthetic (fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether) that has been used extensively in Japan and was approved recently by the Food and Drug Administration for induction and maintenance of general anesthesia in adults and children undergoing inpatient and outpatient surgery. Approximately 5% of sevoflurane is metabolized in vivo,1 the primary route of metabolism being oxidative dehalogenation in the liver by the cytochrome isozyme, P450 2E1.2 Oxidative dehalogenation of the fluorinated ether anesthetics releases both inorganic and organic fluoride into the circulation. Published studies of methoxyflurane and its metabolites demonstrated that postoperative nephrotoxicity occurred only in those patients with high concentrations of inorganic fluoride.3,4 In adults, the blood concent
PLASMA FLUORIDE CONCENTRATIONS AFTER SEVOFLURANE IN CHILDREN

Measurement of plasma fluoride concentrations, as a measure of exposure to sevoflurane, has been performed in adults. The area under the concentration-time curve for sevoflurane and enflurane is less than that after an equivalent concentration of methoxyflurane. Published studies also demonstrated that the peak blood [F\textsuperscript{-}] after sevoflurane increases as the duration of anesthesia increases. In children, the blood concentration-time curve for inorganic fluoride after sevoflurane is understood incompletely. The plasma [F\textsuperscript{-}] time curve after a brief exposure to sevoflurane (0.82 minimum alveolar concentration \cdot h [MAC \cdot h]) in infants and children yielded a low peak fluoride value, 13.0 \pm 3.6 \mu M, but post-operative measurements were discontinued after only 4 h. The plasma [F\textsuperscript{-}] time curve after prolonged exposure to sevoflurane in children remains unknown. Accordingly, we undertook the following study, as part of a larger study already published, to determine the effect of time on the plasma [F\textsuperscript{-}] after exposure to sevoflurane for as long as 5 MAC \cdot h.

Methods

After Institutional Review Board approval at The Hospital for Sick Children, Toronto, and Children’s Hospital of Pittsburgh and approval by the federal regulatory agencies in both Canada and the United States, written consent was obtained from the parents of 120 children. ASA physical status 1 or 2 aged 1–12 yr who were scheduled for elective surgery. Because this study was conducted as part of a larger study, the methods outlined later have been reported in part.

Children scheduled for surgery with an anticipated loss of less than 10% of their blood volume and duration of 1–5 h were eligible for participation in the study. The surgical procedures included urologic (not involving the kidneys), general, plastic, orthopedic, or ear, nose, and throat surgery (excluding surgery of the tracheobronchial tree). Children with a history of pulmonary, cardiac, renal, or hepatic disease were excluded as were those with a history or family history of muscle disease (e.g., malignant hyperthermia) or those who had received any experimental drug in the preceding 28 days. Children who received medications known to be nephrotoxic, that increase hepatic enzyme activities or that affect MAC were also excluded from the study.

All children were fasted for approximately 4 h after clear fluids and none were premedicated. They were randomly assigned to one of three treatment groups before induction of anesthesia: group 1 received sevoflurane in air/oxygen 30% (n = 40), group 2 received sevoflurane in N\textsubscript{2}O 70%/oxygen 30% (n = 40), and group 3 received halothane in N\textsubscript{2}O 70%/oxygen 30% (n = 40). Anesthesia was induced by inhalation according to the treatment assignment using a Mapleson D or F anesthetic circuit. The fresh gas flow included nitrous oxide, air, and/or oxygen according to the treatment assignment, at a total fresh gas flow of 3–6 l/min. After tracheal intubation under deep inhalational anesthesia, ventilation was controlled mechanically to maintain the end-tidal carbon dioxide tension between 30 and 40 mmHg.

Anesthesia was maintained with 1.0–1.3 MAC sevoflurane or halothane. The MAC calculations, based on published data for sevoflurane and halothane, did not include the contribution of nitrous oxide: children 1–2 yr received sevoflurane 2.6% or halothane 1.0%, and patients 3–12 yr received sevoflurane 2.5% or halothane 0.9%. The end-tidal concentrations of sevoflurane and halothane were decreased to 1.0 MAC for at least 15 min before the termination of anesthesia. End-tidal concentrations of sevoflurane and halothane were monitored continuously using a calibrated Datex Capnomac Ultima (Helsinki, Finland). The monitor was calibrated immediately before administration of each anesthetic. Intravenous lactated Ringer’s solution was administered throughout the study to replace any fluid deficit and to provide maintenance fluids.

Immediately after loss of consciousness, an intravenous catheter was inserted into an arm vein to collect blood samples. Blood samples (5 ml) were collected for determination of the plasma [F\textsuperscript{-}] immediately after induction of anesthesia, at the termination of anesthesia, and at 1, 4, 6, 12, and at either 18 or 24 h after discontinuation of anesthesia. Two additional 3-ml blood samples were collected for complete blood count, liver function tests, and the plasma concentrations of electrolytes, urea, and creatinine immediately after induction of anesthesia and at 18 or 24 h after discontinuation of anesthesia. After these samples were collected in plastic syringes containing small quantities of heparin, they were centrifuged within 1 h of collection. The supernatant plasma was pipetted into plastic containers, sealed, and then stored at −20°C until analysis for [F\textsuperscript{-}].

Plasma inorganic fluoride concentrations [F\textsuperscript{-}] were determined using an Orion ion-specific ion analyzer (Orion Research, Boston, MA). The detection limit of
the assay was 1.0 μM. The within-batch percent coefficient of variation was 8.6%. The intergroup percent coefficient of variation was 7.9%. The plasma [F⁻] time profile for each child was plotted and the area under the plasma [F⁻] time curve (AUC_{C→}) determined using the trapezoidal rule from time 0 to the last blood sample (C₉). The AUC_{C→} was calculated using the ratio, C₉/B, where B is the elimination rate constant. The AUC_{C→} was the sum of the AUC_{C→} and the AUC_{C→}.

Data are presented as means ± standard deviation. Regression analysis was used to determine the relationship (expressed as the coefficient of determination (r²)) between the anesthetic exposure (MAC·h) and both the AUC for F⁻ and the peak plasma [F⁻], and to determine the relationship between the AUC and the peak [F⁻]. Parametric data were compared using the unpaired Student’s t-test. Statistical significance of P < 0.05 was accepted.

Results

Demographic data of the children in groups I and II within each center were similar. Accordingly, we combined the data from these two groups within each center. The duration of anesthesia for sevoflurane and halothane, respectively, in the two centers was similar. Here too, we combined the data of sevoflurane and halothane from the two centers, respectively.

The mean ages of the children and duration of anesthesia (in MAC·h) in the sevoflurane and halothane groups were similar (Table 1). The duration of sevoflurane anesthesia exceeded 5 MAC·h in six children, with the greatest exposure being 8.9 MAC·h.

The peak recorded plasma [F⁻] after sevoflurane was eightfold greater than that after halothane (P < 0.001; Table 1). The peak recorded plasma [F⁻] occurred 1 h after the termination of anesthesia in 77 of the 80 children. In the remaining three children, the peak value occurred between 4 and 6 h after anesthesia. The range of peak recorded [F⁻] after sevoflurane was 7–28 μM. The maximum recorded [F⁻] was 28 μM, occurred in a child who had received 7.0 MAC·h of sevoflurane. In all children who received sevoflurane, the plasma [F⁻] decreased to <6.2 μM by 24 h after termination of the anesthetic. The plasma [F⁻] after halothane was less than 10 μM throughout the entire 24-h study period.

The relationships between peak plasma [F⁻] and sevoflurane exposure (r² = 0.50; Fig. 2) and between AUC_{C→}, for inorganic fluoride and MAC·h sevoflurane (r² = 0.57; Fig. 3) were linear. The peak plasma [F⁻]

Table 1. Demographic Data and Laboratory Values

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<td>Plasma Creatinine Concentration (μM)</td>
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<tr>
<td>Plasma [F⁻] Concentration (μM)</td>
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Anesthesia. V 84, No 2. Feb 1996
after halothane was independent of the halothane exposure ($r^2 = 0.007$; fig. 2). The relationship between the peak plasma [$F^-$] and AUC$_{0-24}$ for sevoflurane was also linear ($r^2 = 0.66$). The AUC$_{0-24}$ after sevoflurane was $84 \pm 7.5\%$ of the AUC$_{0-24}$ for halothane (table 1). The AUC$_{0-24}$ for sevoflurane was ninefold greater than the AUC$_{0-24}$ for halothane (table 1).

The AUC$_{0-\infty}$ was determined accurately in 39 of the 80 children who received sevoflurane (fig. 3 and table 1). We could not determine an accurate AUC$_{0-\infty}$ in 41 of the children because of incomplete blood collection as a result of inadvertent removal of the intravenous cannula and/or patient or parental refusal to allow for the continued blood sampling in the recovery period. As a result, we could not accurately estimate the terminal elimination half-life of inorganic F and thus the AUC$_{0-\infty}$ for those 41 children.

The mean plasma concentration of urea 24 h after both sevoflurane and halothane anesthesia decreased significantly compared with preanesthetic values, respectively (table 1). In contrast, plasma creatinine level was unchanged after both anesthetics compared with preanesthetic values. One child developed pulmonary edema 48 h after surgery as a result of fluid overload that occurred during the postoperative period. His serum creatinine clearance increased from 39 mmol·1$^{-1}$·h$^{-1}$ preoperatively to 89 mmol·1$^{-1}$·h$^{-1}$ (normal < 60 mmol·1$^{-1}$·h$^{-1}$) 24 h after 4.8 MAC·h sevoflurane anesthesia.
thecia. The serum creatinine concentration returned to baseline concentrations 3 days postoperatively. The peak plasma $[F^-]$ in this patient was 25.5 $\mu M$. In this case, the investigator deemed the transient increase in plasma creatinine concentration to be unrelated to the administration of sevoflurane.

**Discussion**

The introduction of sevoflurane into clinical anesthesia has been clouded by concerns about the potential risk of nephrotoxicity after its use. Two theoretical sources for the nephrotoxicity after sevoflurane are the plasma concentration of inorganic fluoride, an *in vivo* metabolite of sevoflurane and compound A, an *in vitro* degradation product of sevoflurane in the presence of soda lime and baralyme. The purpose of this study was to address the possible role of inorganic fluoride in causing nephrotoxicity in children by characterizing the plasma $[F^-]$-time curve after 1–5 MAC·h sevoflurane. We found that the peak recorded plasma $[F^-]$ after 2.7 MAC·h (range of 1.1–8.9 MAC·h) sevoflurane in children aged 1–12 yr occurred approximately 1 h after discontinuation of sevoflurane, was 15.8 $\mu M$ and decreased rapidly to <6.2 $\mu M$ in all children by 24 h (fig. 1).

The plasma $[F^-]$-time relationship after inhalational anesthesia is determined by three variables: (1) the duration of anesthesia; (2) the lipid solubility of the anesthetic; and (3) metabolism of the anesthetic. Both the lipid solubility and metabolism of the anesthetic are properties of the anesthetic. The anesthetic (and estimated percent metabolized *in vitro* in the absence of enzyme induction) of the inhalational anesthetics follows the order: methoxyflurane (50%) > halothane (15–20%) > sevoflurane (5%) > enfurane (24%) > isoflurane (0.2%) > desflurane (0.02%).

Although published evidence suggests that the extent of metabolism of methoxyflurane, halothane, and enfurane may exceed these estimates, all ether anesthetics are de-fluorinated *in vitro* by the cytochrome P450 microsomal enzyme system and, quantitatively, the plasma $[F^-]$-time relationship parallels the relative metabolism of these anesthetics for a given duration of anesthesia. In contrast to the ether series of anesthetics however, the alkane anesthetic halothane is metabolized substantially *in vivo* but releases very little inorganic fluoride (figs. 1 and 2). Accordingly, the order of both the peak $[F^-]$ and the AUC for $[F^-]$ is: methoxyflurane > sevoflurane > enfurane > isoflurane = halothane > desflurane. On the basis of the pharmacokinetic curves, the terminal elimination of $F^-$ for sevoflurane is similar to that of enfurane.

The pharmacokinetics of $F^-$ in children have been investigated after only 2 ether anesthetics, enfurane and methoxyflurane. The peak $[F^-]$ after $\approx 1.5$ MAC·h enfurane, 6–10 $\mu M$, is similar to that obtained after sevoflurane when the latter was adjusted for the anesthetic dose, whereas the peak $[F^-]$ after methoxyflurane, 22 $\mu M$, is approximately 50% greater than that obtained after sevoflurane. Thus, the pharmacokinetics of inorganic fluoride after sevoflurane in children are similar to those after enfurane but less than those after methoxyflurane—a relationship similar to that reported in adults.

The pharmacokinetics of $F^-$ after inhalational anesthesia in children have not been compared directly with those in adults. In the case of methoxyflurane, the peak $[F^-]$ in children is approximately half that in adults for a similar duration of anesthesia. We calculated the AUCₐ₀₋₄₈h for $F^-$ based on published data and found that the AUCₐ₀₋₄₈h in children was half that in adults for the same MAC·h. For sevoflurane, the peak $[F^-]$ in children is less than half that reported after sevoflurane in adults although the dose of sevoflurane in children was 50% less than that in adults. The AUCₐ₀₋₄₈h in children, however, was only one fifth that in adults. These data suggest that in the case of both methoxyflurane and sevoflurane, peak $[F^-]$ and AUC for $F^-$ are less in children than they are in adults for a similar anesthetic exposure. This may be attributed to several differences between children and adults including decreased metabolism and lower solubility of the anesthetic in children, more rapid uptake by $F^-$ in tissues (such as bone) and more rapid renal elimination of $F^-$ in children than in adults.

None of the children in this study developed clinical or biochemical evidence of renal insufficiency postoperatively as evidenced by polyuria or an increase in plasma creatinine concentration. This is not surprising in view of the low plasma $[F^-]$ measured (maximum value of 28 $\mu M$). Although the plasma concentrations of urea after both sevoflurane and halothane anesthesia were significantly less than preoperative values (table 1), this isolated biochemical change is most likely explained by the intraoperative administration of large volumes of intravenous balanced salt solutions. Our assessment of renal function, however, was incomplete because we did not measure urine osmolality, renal concentrating ability, or urinary elimination of renal tubular enzymes. Despite this, it is unlikely that either sevoflurane or halothane at the doses used would result in renal insufficiency, obesity, or failure to produce evidence of renal insufficiency or nephrotoxicity, as recently questioned.

A second theoretical source of sevoflurane anesthesia is the interaction of the anesthetic with the metal ions in the kidneys. We used Mapleson D or circle systems and cardiopulmonally, the risk of nephrotoxicity in the current study was zero.

In conclusion, 2.7 MAC·h sevoflurane in children at that are low, similar plasma $[F^-]$-time curve to that in adults.
PLASMA FLUORIDE CONCENTRATIONS AFTER SEVOFLURANE IN CHILDREN

Multiple investigators have shown that fluoride is a potent inhibitor of tubular enzymes. Despite the incomplete testing performed, it is unlikely that nephrotoxicity will occur after sevoflurane in children, because similar studies in adult volunteers and patients even under conditions that are likely to yield increased plasma [F⁻] (i.e., after prolonged sevoflurane anesthesia (up to 11.5 MAC·h), renal insufficiency, obesity, and enzyme induction) failed to produce evidence of a renal concentrating defect or nephrotoxicity, although this has been questioned recently. A second theoretical cause of nephrotoxicity after sevoflurane anesthesia is compound A, an in vitro degradation product of sevoflurane in soda lime and baralyme. Compound A causes dose-dependent histologic changes in the kidneys of rats, although there has been no evidence of renal insufficiency attributable to compound A in humans to date. In the current study, we used Mapleson D and F circuits; we did not use circle circuits and carbon dioxide absorbers. Accordingly, the risk of nephrotoxicity from compound A in the current study was zero.

In conclusion, 2.7 MAC·h (range: 1.1–8.9 MAC·h) sevoflurane in children yields peak recorded plasma [F⁻] that are low, similar to those after enflurane and a plasma [F⁻]-time curve that has a small AUC compared with adults.

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References