Compound A Concentrations during Sevoflurane Anesthesia in Children

Edward J. Frink, Jr., M.D.,* William B. Green, Jr., Ph.D., M.D., †Elizabeth A. Brown, B.S.N., †
Mark Malcomson, M.S., § Leslie C. Hammond, § Francisco G. Valencia, M.D., ||
Burrnell R. Brown, Jr., M.D., Ph.D., F.R.C.A.##

Background: Sevoflurane is a new inhalation agent that should be useful for pediatric anesthesia. Sevoflurane undergoes degradation in the presence of carbon dioxide absorbents; however, quantification of the major degradation product (compound A) has not been evaluated during pediatric anesthesia. This study evaluates sevoflurane degradation compound concentrations during sevoflurane anesthesia using a 2-l fresh gas flow and a circle system with carbon dioxide absorbent in children with normal renal and hepatic function.

Methods: The concentrations of compound A were evaluated during sevoflurane anesthesia in children using fresh soda lime as the carbon dioxide absorbent. Nineteen patients aged 3 months–7 yr were anesthetized with sevoflurane (2.8% mean end-tidal concentration) using a total fresh gas flow of 2 l/min a circle absorption system. Inspiratory and expiratory limb circuit gas samples were obtained at hourly intervals, and the samples were analyzed using a gas chromatography-flame ionization detection technique. Carbon dioxide absorbent temperatures were measured in the soda lime during anesthesia. Blood samples were obtained before and after anesthesia for hepatic and renal function studies. Venous blood samples were obtained before anesthetization, at the end of anesthesia, and 2 h after anesthesia for plasma inorganic fluoride ion concentration.

Results: The maximum inspiratory concentration of compound A was 5.4 ± 4.4 ppm (mean ± SD), and the corresponding expiratory concentration was 3.7 ± 2.7 ppm (mean ± SD). The maximum inspiratory compound A concentration in any patient was 15 ppm. Mean concentrations of compound A peaked at intubation and remained stable, declining slightly after 120 min of anesthesia. The duration of anesthesia was 240 ± 139 min (mean ± SD). Maximum soda lime temperature ranged between 23.1°C and 40.9°C. There was a positive correlation between maximum absorbent temperature and maximum compound A concentration (r² = 0.58), as well as between the child's body surface area and maximum compound A concentration (r² = 0.59). Peak plasma inorganic fluoride ion concentration was 21.5 ± 6.1 μmol/l. There were no clinically significant changes in hepatic or renal function studies performed 24 h postanesthesia.

Conclusions: Sevoflurane anesthesia of 4 h in normal children using a 2-l flow circle system produced concentrations of compound A of 15 ppm or less. There was no evidence of abnormality of renal or hepatic function up to 24 h after anesthesia; however, larger studies will be required to confirm the absence of organ toxicity. (Key words: Anesthesia; pediatric. Anesthetics, volatile; sevoflurane. Equipment: carbon dioxide absorbents. Toxicity: hepatic; renal.)

SEVOFLURANE is a newly approved inhalation anesthetic with a low blood/gas solubility coefficient and nonpungent properties that make it attractive for use in pediatric patients. Studies have shown that sevoflurane provides rapid and smooth inhalation induction in children, with more rapid emergence compared to halothane.2 A concern with the delivery of sevoflurane in clinical practice has been its instability in carbon dioxide absorbents and resultant degradation products in the anesthetic circuit. The degradation compound produced in greatest amount with potential for toxic effect is fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether, termed "compound A." In rats, concentrations of compound A greater than 50–100 ppm are capable of producing renal toxicity.3-5 Several investigators studied the production of the degradation products of sevoflurane with carbon dioxide absorbents in adults under various conditions without evidence of nephrotoxicity6-8; however, production of compound A in pediatric patients has not been evaluated.

* Associate Professor, Department of Anesthesiology.
† Assistant Professor, Department of Anesthesiology.
‡ Research Nurse.
§ Research Assistant.
|| Assistant Professor, Section of Orthopedic Surgery.
## Professor and Head, Department of Anesthesiology.

Received from the University of Arizona Health Sciences Center, Tucson, Arizona. Submitted for publication March 7, 1995. Accepted for publication November 30, 1995. Supported in part by a grant from Abbott Laboratories. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 15–19, 1994.

Address reprint requests to Dr. Frink, Department of Anesthesiology, University of Arizona Health Sciences Center, P.O. Box 245114, Tucson, Arizona 85724-5114.
Concentrations of compound A in the anesthetic circuit of pediatric patients might differ from adults for several reasons: (1) higher sevoflurane concentrations used because of high minimum alveolar concentration in children, (2) lower total carbon dioxide production in children, or (3) smaller lung surface area for compound A exposure or absorption. In this study, we evaluate the concentrations of compound A and inorganic fluoride in children using a circle system with soda lime as the carbon dioxide absorbent.

Methods and Materials

With approval from the University of Arizona Human Subjects Committee, 19 ASA physical status 1 or 2 pediatric patients (aged 3 months–7 yr) received sevoflurane for anesthesia of anticipated duration of 1 h or longer. Written informed consent was obtained from the parent or guardian of all participants.

Patients with a history of renal or hepatic disease were excluded. Clinical laboratory tests were performed before anesthesia or immediately after loss of consciousness with intubation or anesthesia end and the end of anesthesia before discharge (outpatient candidates) or 24 h after anesthesia. Before anesthetic induction, patients received no premedication (n = 10) or received either oral midazolam (n = 5) or rectal methohexital (n = 4). Anesthesia was induced via face mask using sevoflurane in 50–70% N₂O and 30–50% O₂. After inhalation induction and loss of consciousness, an intravenous infusion of 5% dextrose with Ringer’s lactate solution was initiated. Tracheal intubation was performed after neuromuscular blockade using 0.1–0.15 mg·kg⁻¹ vecuronium intravenously. Sevoflurane was delivered during induction using 1–2% increases in inspiratory concentration every three to five breaths as required or tolerated by the patient. Intravenous fentanyl in 1–2 μg·kg⁻¹ doses was administered as desired by the anesthesiologist. Total fresh gas flow during anesthetic maintenance was 2 L min⁻¹ (50–60% N₂O and 40–50% O₂). Anesthetic gases were delivered using a North American Dräger Narkomed II (Telford, PA) machine with circle system. The ventilatory rate was adjusted to maintain end-tidal carbon dioxide concentrations between 30 and 35 mmHg. Sevoflurane concentration during anesthetic maintenance ranged from 1.9% to 3.2%, depending on age and stimulation related requirements. End-tidal anesthetic concentrations were monitored using a Datex Capnomac Ultima Monitor (Helsinki, Finland). MAC-h values were determined by using the mean end-tidal concentrations to age-appropriate MAC value per time in 5-min intervals.

The carbon dioxide absorbent used in the circle system was soda lime (Sodasorb, W.R. Grace, Lexington, MA). The soda lime was replaced before each anesthetic administration. Soda lime temperature was monitored within the carbon dioxide absorbent canisters using temperature probes placed in the central area of the upper, middle, and lower thirds of the upper canister (three sites) and in only the upper one-third of the lower carbon dioxide absorbent canister (one site). Probe temperatures were measured using two temperature monitors (Mon-A-Therm model 6500, Mon-A-Therm, St. Louis, MO). Soda lime temperature readings were obtained from all sites 30 min after intubation, every 1 h during anesthetic maintenance, and at anesthetic end.

Gas samples were obtained from the inspiratory and expiratory limbs of the anesthetic circuit distal to the one-way valves via a capped stopcock port, using gastight glass syringes (Supelco, Bellefonte, PA) for compound A analysis. Samples were obtained from each limb during mask intubation at 30 min and then every 1 h after intubation and at anesthetic end.

Venous blood samples were obtained for fluoride ion concentration determination from a second intravenous catheter in the arm opposite from that for fluid administration. Samples were obtained after loss of consciousness, at hourly intervals during anesthesia, at anesthesia end, and 1 and 2 h after anesthesia. Plasma fluoride ion concentrations were determined using an ion selective electrode (Orion, Cambridge, MA) calibrated against standard sodium fluoride solution (1–100 μmol/l).

Blood samples were obtained before anesthesia or immediately after loss of consciousness, at anesthesia end, and immediately before discharge (same-day surgery patients) or 24 h after anesthesia (hospitalized patients) for serum creatinine, blood urea nitrogen, bilirubin, aspartate aminotransferase, alanine, aminotransferase, and alkaline phosphatase.

Pre- and postoperative hepatic and renal function tests were compared using repeated-measures analysis of variance with Student’s paired t-test when appropriate. Regression analysis was used to evaluate correlation of compound A concentration with soda lime temperature and body surface area (BSA). All values are repeated as mean ± SD. A P value of less than 0.05 was considered significant.
Table 1. Patient Demographics, Anesthetic Concentration, and Duration

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>3.0 ± 2.6</td>
<td>0.25–7.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14 ± 6.5</td>
<td>4.1–27.6</td>
</tr>
<tr>
<td>Sevoflurane duration (min)</td>
<td>240 ± 139</td>
<td>52–521</td>
</tr>
<tr>
<td>Mean end-tidal sevoflurane concentration (%)</td>
<td>2.8 ± 0.9</td>
<td>1.9–3.2</td>
</tr>
<tr>
<td>MAC-h</td>
<td>5.6 ± 3.5</td>
<td>1–9</td>
</tr>
</tbody>
</table>

Gas Sample Handling and Degradation Compound Analysis

Inspiratory and expiratory limb gas samples (4 ml) for compound A analysis were collected using gas-tight locking syringes (Supelco) and injected into a sealed 20-ml sample bottle with stopper and aluminum crimp cap. (Samples maintained stable concentrations by this method for 48 h.) Analyses of samples were performed on a Hewlett Packard gas chromatograph (HP 5710; Palo Alto, CA) with flame ionization detection and integrated using a Spectra Physics Integrator (model 4100; Fremont, CA). Standards for sevoflurane, compound A, and the internal standard (n-butyl chloride) were prepared. The peak area of sevoflurane and compound A from patient samples to the internal standard was determined with injection of a total volume of 1 ml (sample + internal standard). Calibration curves were linear in the range of 1.5–59 ppm.

Results

Demographics for the study population and anesthetic exposure data are shown in table 1. Inspiratory and expiratory concentrations of compound A are shown in figure 1. The maximum inspiratory concentration obtained was 5.4 ± 1.4 ppm (mean ± SD). The maximum concentration measured in any patient circuit was 15 ppm. The maximum expiratory concentration of compound A was 3.7 ± 2.7 ppm (mean ± SD). Maximum soda lime temperatures were obtained in the upper or middle third of the upper absorbent canister. Maximum absorbent temperatures ranged between 23.1°C and 40.9°C. The mean soda lime temperature value was 30.0°C ± 4.8°C.

A positive correlation was found between maximum carbon dioxide absorbent temperature and maximum compound A concentration ($r^2 = 0.58$; fig. 2). A correlation also was present between maximum soda lime temperature and patient BSA, as well as maximum compound A concentration and the child’s BSA ($r^2 = 0.59$; fig. 3). Plasma fluoride ion concentrations increased during sevoflurane anesthesia, with peak concentrations of 21.5 ± 6.1 µmol/l occurring at 2 h. The highest recorded inorganic fluoride ion concentration was 57.2 µmol/l.

Pre- and postanesthetic renal and hepatic function studies are shown in table 2. There were no significant changes in clinical laboratory studies other than a mild decrease in aminotransferase concentration at anes-

Anesthesiology. V 84, No 3, Mar 1996
COMPOUND A CONCENTRATIONS IN CHILDREN

![Graph](image)

Fig. 3. Correlation between child's body surface area and maximum inspiratory compound A concentration. A positive correlation was found: \( r^2 = 0.59 \) (\( y = 0.04x + 0.3 \); \( P < 0.01 \)).

Discussion

Although the concentration of the sevoflurane degradation products from carbon dioxide absorbents have been documented during higher-flow, low-flow, and closed-circuit anesthesia conditions in adults, there is no information on concentrations generated in children. Several factors have been shown to influence the concentration of degradation product occurring within the anesthesia circuit, which include: (1) absorbent temperature, (2) type of absorbent (soda lime vs. Baralyne), (3) sevoflurane concentration, (4) fresh versus used absorbent, and (5) fresh gas flow within the circuit.\(^{11}\)

We used a 2-L total fresh gas flow for all patients after intubation. Flow rates lower than those used in our study during pediatric anesthesia should result in higher concentrations of compound A than we obtained. Therefore, our results may underestimate the maximum concentration that could be achieved with the use of low-flow or closed-circuit techniques.

Fresh soda lime was used for each anesthetic administration. This was done in an effort to obtain higher concentrations of compound A, which have been shown to occur when fresh, rather than used, absorbent is exposed to sevoflurane.\(^{11}\) Our results show that compound A inspiratory concentrations in this study achieved a mean maximum value of 5.4 ppm, with the highest value obtained in any child to be 15 ppm. These concentrations are less than those shown to produce a histologic lesion in rats (50–100 ppm) exposed to compound A.\(^{4,5}\)

An interesting finding in our investigation was the range of maximum carbon dioxide absorbent temperatures obtained (23–41°C). On further analysis, maximum soda lime temperatures correlated with both maximum compound A concentration and child’s BSA. An increasing child’s BSA also correlated with increasing compound A concentrations. A deficiency in our correlation between absorbent temperature and compound A concentration may be present because absorbent temperature was not recorded until 30 min after intubation. In some patients, the maximum compound A concentration occurred after intubation; the highest mean concentration of compound A occurred immediately after intubation. Thus, in some patients, data

### Table 2. Hepatic and Renal Function Studies in Children with Sevoflurane Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Preanesthesia (n = 19)</th>
<th>End of Anesthesia (n = 19)</th>
<th>Same-day Discharge (before discharge) (n = 6)</th>
<th>24 h After Anesthesia (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (SGOT) (IU/l)</td>
<td>36 ± 16</td>
<td>30 ± 12</td>
<td>15 ± 4*</td>
<td>55 ± 47</td>
</tr>
<tr>
<td>ALT (SGPT) (IU/l)</td>
<td>19 ± 12</td>
<td>15 ± 7*</td>
<td>35 ± 10*</td>
<td>26 ± 14</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l)</td>
<td>179 ± 57</td>
<td>152 ± 52</td>
<td>168 ± 25</td>
<td>148 ± 56</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>0.41 ± 0.2</td>
<td>0.41 ± 0.2</td>
<td>0.42 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>11 ± 3</td>
<td>11 ± 4</td>
<td>13 ± 5</td>
<td>5 ± 2*</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD. In seven patients, postanesthesia blood samples were unobtainable because of sampling catheter failure.

* Differs from preanesthesia values (\( P < 0.05 \) for same group of patients).

AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); BUN = blood urea nitrogen.

Anesthesiology. V 84, No 3, Mar 1996
for temperature was not recorded during the times when maximum compound A concentration occurred. This absence of data may have altered our correlation between temperature and maximum compound A concentration. It is possible that some of the high concentrations recorded at intubation may have been due to the higher sevoflurane concentration used during induction.

Total carbon dioxide produced by each child is to some degree dependent on the size of the child. It is probable, therefore, that we are observing that the quantity of carbon dioxide applied to the absorbent relates to the temperature obtained, and hence the quantity of compound A, and that this is dependent on the child's body weight. However, for anesthetized infants and children, carbon dioxide production has some variation dependent on child size. Previous investigations, by Nightingale and Lambert and Bain and Sporrell, showed a higher carbon dioxide production per kilogram body weight in smaller children compared to older children and adults. Although carbon dioxide production per kilogram weight increases slightly, an increased total amount of carbon dioxide will be produced with an increase in the size of the child. If carbon dioxide production did not vary on a per weight basis, it is possible that our correlation between compound A concentration and BSA would have been greater. Our results suggest that lower concentrations of compound A should be produced in the younger child if similar circuit flows, anesthetic concentration, and absorbent type are used.

Plasma fluoride ion concentration with sevoflurane anesthesia in children produced a mean peak concentration of 21.5 μmol/l. This concentration is consistent with other reported values in children and is less than that after a comparable 2 h of sevoflurane anesthesia in adults. It is unlikely that this plasma fluoride ion concentration would be capable of producing a renal concentrating function deficit given data from previous studies in adults.

We observed no changes in postanesthetic renal or hepatic function studies in our patients. A limitation of our study was the short period of postoperative evaluation for renal and liver function tests. Our length of testing was limited by constraints of outpatient procedures and early discharge of hospitalized patients. However, 24 h may be sufficient to detect abnormalities due to possible renal injury from compound A, because in animals given high concentrations of compound A, injury was present 1 day after exposure and had undergone repair of injury by 4 days after anesthesia. Our study used blood urea nitrogen and creatinine as measures of renal function. These measures might not change with more subtle degrees of renal abnormality because of the functional reserve of the kidney. However, other tests, such as urinary enzymes, are not well established as diagnostic markers of changes in renal physiology or pathophysiology; thus we elected to use a change in serum creatinine as evaluation of renal function, which is clinically relevant. It is unlikely that the low concentration of compound A obtained in this study would be capable of producing even a nonfunctional renal injury, given data previously obtained in animals.

In summary, our results show that the concentrations of compound A measured in pediatric patients during sevoflurane anesthesia using approximately 2 l fresh gas flow are low. There is a correlation between the child’s size and maximum compound A concentration obtained, which is likely due to the varying total mass of carbon dioxide produced based on child size.

References