Closed-circuit Anesthesia with Sevoflurane in Humans

Effects on Renal and Hepatic Function and Concentrations of Breakdown Products with Soda Lime in the Circuit

Hiromichi Bito, M.D.,* Kazuyuki Ikeda, M.D.

Background: Sevoflurane reacts with CO₂ absorbents, resulting in the generation of breakdown products. The concentrations of sevoflurane breakdown products in a low-flow system within 5 h have been reported, but concentrations in low-flow anesthesia exceeding 5 h or in closed-circuit anesthesia have not. In this study, the breakdown products of sevoflurane in closed-circuit anesthesia exceeding 5 h were examined.

Methods: Closed-circuit sevoflurane anesthesia was administered to ten patients. Laboratory tests of hepatic and renal function were performed before and after anesthesia. Gas samples were obtained from the inspiratory limb of the anesthesia circuit, and breakdown products were analyzed by gas chromatography. The temperature of the soda lime was measured during anesthesia.

Results: Among the breakdown products of sevoflurane, two products, CF₂ = C(CF₃)-O-CH₂F (compound A) and CH₂OCF₂CH(CF₃)OCH₂F (compound B), were detected. Compound A was detected in all measurements, and its concentration reached 19.5 ± 5.4 ppm 1 h after anesthesia and decreased after 5 h. The highest concentration observed for compound A was 30.0 ppm. Compound B was detected in seven of the ten patients; its concentration was 0.17 ± 0.37 ppm after 0.5 h of anesthesia and remained at similar concentrations thereafter. The highest mean temperature of the soda lime was 46.0 ± 1.7°C. Postanesthetic clinical laboratory tests showed no abnormalities in hepatic or renal function associated with anesthesia.

Conclusions: Two breakdown products were detected in the patients anesthetized with sevoflurane using a closed-circuit technique. No abnormalities were observed during anesthesia, and no evidence of hepatic or renal dysfunction was noted in postoperative laboratory tests. (Key words: Anesthetics, volatile: sevoflurane. Carbon dioxide, absorption: soda lime. Equipment, anesthetic system: closed-circuit.)

SEVOFLURANE was approved for clinical use in Japan in 1990. One serious drawback of this anesthetic is the generation of potentially toxic breakdown products resulting from reaction with CO₂ absorbents. Wallin et al. detected two breakdown products of sevoflurane by heating liquid sevoflurane with soda lime at 70°C for 3 h in a glass vial. The two substances detected were CF₂ = C(CF₃)-O-CH₂F (compound A) and CH₂OCF₂CH(CF₃)OCH₂F (compound B). Hanaki et al. detected five breakdown products of sevoflurane by heating sevoflurane with soda lime at 120°C in a test tube.

As of April 1993, sevoflurane anesthesia has been administered to 800,000 patients in Japan with no reports of associated hepatotoxicity or nephrotoxicity. In Japan, however, the most commonly used anesthesia circuit is a semiclosed system with relatively high flow rates of fresh gas; low-flow systems and closed-circuit systems are not used. In a closed circuit, the concentrations of sevoflurane breakdown products are higher than in a high-flow system in vitro. Therefore, questions remain concerning the safety of sevoflurane when used in closed-circuit anesthesia.

Concentrations of sevoflurane breakdown products have been examined using a low-flow system of less than 1 l for 3–5 h, and neither hepatotoxicity nor renal toxicity was seen. In that study, however, the anesthesia time was limited to 5 h or less, and the sevoflurane concentration in the circuit was approximately 1%. Therefore, the safety of sevoflurane anesthesia in a closed-circuit or low-flow system has not yet been clarified.

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Anesthesiology, V 80, No 1, Jan 1994
In a closed circuit, there is greater contact between CO₂ and the CO₂ absorbent than in a low-flow system, and an increase in the temperature of the absorbent can be expected. Moreover, since the washout of gas within the system is reduced in a closed circuit, it is speculated that the concentrations of breakdown products would be higher than in a low-flow system. The purpose of this study was to assess the concentrations of sevoflurane breakdown products in a closed circuit during exposures exceeding 5 h. The intracircuit concentrations of the sevoflurane breakdown products reported by Hanaki et al.³ were measured, and the effects of closed-circuit anesthesia with sevoflurane on hepatic and renal function were evaluated.

**Materials and Methods**

This study was approved by the institution's Committee on Human Research, and informed consent was obtained from all patients. Ten ASA physical status 1 or 2 patients for whom surgery of at least 5 h was planned were studied. Patients who were to undergo hepatic surgery were excluded from the study group, as were patients with hepatic cirrhosis, hepatitis, or chronic renal failure. These exclusion criteria were confirmed by laboratory tests of hepatic and renal function carried out preoperatively. Any patients who might have been expected to exhibit a postoperative decrease in liver or renal function (e.g., due to hepatectomy, the postoperative administration of anticancer drugs, or aneurysm of the renal artery) also were excluded. The patients in the study group ranged in age from 23 to 63 yr (48.8 ± 14.9 yr), in height from 150 to 170 cm (160.4 ± 6.2 cm), and in weight from 46 to 63 kg (55.9 ± 5.5 kg). The duration of anesthesia ranged from 3.83 to 11.58 h (6.90 ± 2.53 h).

Premedication was 50 mg hydroxyzine and 0.5 mg atropine sulfate injected intramuscularly 45 min before induction of anesthesia. Anesthesia was induced by administration of 100% O₂ for 5 min followed by 5 mg·kg⁻¹ thiopental and 0.12–0.15 mg·kg⁻¹ vecuronium. Tracheal intubation was performed, and the flow rate of air was set to 6 l·min⁻¹. When the O₂ concentration in the circuit reached 40%, the flow rate of air was set to zero; the flow rate of O₂ was set to 200 ml·min⁻¹; and the pop-off valve was closed. Anesthesia was maintained with O₂ and sevoflurane. The lungs were ventilated with a tidal volume of 10–12 ml·kg⁻¹, with the ventilatory rate adjusted to maintain an end-tidal CO₂ concentration of 30–40 mmHg. The flow rates of air and O₂ were then adjusted to maintain a constant volume of gas in the circuit and a 40% O₂ concentration. Liquid sevoflurane was intermittently injected into the circuit with a glass syringe attached to a metal three-way stopcock connected to the inspiratory limb. The injected volume and interval of injection were adjusted to maintain the adequate anesthetic concentration.

After termination of anesthesia, O₂ was administered at 6 l·min⁻¹. After the patient regained an adequate level of consciousness, the tracheal tube was removed. Clinical laboratory tests for hepatic and renal function were performed preoperatively and 1 and 2 days after anesthesia.

An Aika AM200 (Tokyo, Japan) anesthesia machine and a Bear AV500 (Riverside, CA) ventilator were used. Anesthesia machine hoses and ventilator circuitry were made of polyester elastomer, and fittings were made of silicone rubber. The canister was filled with 2 kg fresh soda lime (Sodasorb, W. R. Grace & Co., Lexington, MA). Before the induction of anesthesia, the rates of leakage from the anesthesia machine and the circuit were confirmed⁵ to be less than 10 ml·min⁻¹. The circuit volume, including the volume in the ventilator, was 8.8 l.

To permit measurement of the temperature of the soda lime, two holes were made in the canister, and thermal probes (temperature probe model 9182, Hioki Electric, Nagano, Japan) were inserted. Gas in the canister of the anesthesia machine flows from the bottom of the canister upward, so that the soda lime is heated from the bottom. Therefore, we measured the temperature in the lower compartment of the two-compartment canister. The probes were inserted at points above and below the center of the lower compartment of the canister. The temperature of the soda lime was measured at 15-min intervals. The room temperature was maintained at 24°C, and the humidity was maintained at 50%.

The end-tidal concentrations of sevoflurane and CO₂ were measured using a Capnomac anesthetic gas monitor (Datex, Helsinki, Finland), and the sampled gas was returned to the circuit. The oximeter of the Capnomac requires fresh air as a reference gas. This results in the introduction of gas into the circuit, which presents a problem in closed-circuit anesthesia. Therefore, the O₂ measurement function of the Capnomac was disabled. Instead, the O₂ concen-
CLOSED-CIRCUIT ANESTHESIA WITH SEVOFLURANE IN HUMANS

Table 1. Individual Patient Maximum Compound A and B Concentrations and MAC Hour

<table>
<thead>
<tr>
<th>Patient</th>
<th>Maximum Concentration (ppm)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Compound A</td>
</tr>
<tr>
<td>1</td>
<td>19.7</td>
</tr>
<tr>
<td>2</td>
<td>30.0</td>
</tr>
<tr>
<td>3</td>
<td>25.1</td>
</tr>
<tr>
<td>4</td>
<td>24.9</td>
</tr>
<tr>
<td>5</td>
<td>26.9</td>
</tr>
<tr>
<td>6</td>
<td>17.8</td>
</tr>
<tr>
<td>7</td>
<td>23.1</td>
</tr>
<tr>
<td>8</td>
<td>19.3</td>
</tr>
<tr>
<td>9</td>
<td>17.9</td>
</tr>
<tr>
<td>10</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Compound A and B maximum concentrations = maximum compound A and B concentration, respectively, in the circuit on samples of each patient; MAC hour = sevoflurane MAC hour exposure for each patient.

Fig. 1. Concentration of breakdown products in the anesthesia circuit. Open circles = the concentration of compound A; filled circles = the concentration of compound B. All values are expressed as mean ± SD; n = 10.

The concentrations of breakdown products in the circuit were measured using a gas chromatography apparatus (model GC-9A, Shimadzu, Kyoto, Japan) equipped with a gas sampler (model MGS-5, Shimadzu) 0.5 and 1 h after the initiation of anesthesia and at 1-h intervals thereafter. A glass column of length 5 m and internal diameter 3 mm, packed with 20% diocetyl phthalate on a Chromosorb white acid-washed (Technolab S. C., Osaka, Japan) 80/100 mesh, was maintained at 100°C in a Shimadzu gas chromatography apparatus (model GC-9A). The injection port was maintained at 140°C. A carrier stream of N₂ flowing at 50 ml · min⁻¹ was delivered through the column to a hydrogen flame ionization detector. Gas in the circuit was collected from the inspiratory limb using a glass syringe (20 ml). Nonabsorbent grease was applied to ensure that the syringe was airtight.

Measured values were expressed as mean ± SD. The data were analyzed using analysis of variance and t tests and, when indicated, using the F test.

Results

Compound A was detected in the anesthesia circuit at all measurement times. Its mean concentration reached 19.5 ± 5.4 ppm after 1 h and tended to decrease after 5 h, decreasing to 14.7 ± 3.0 ppm after 7 h (fig. 1 and table 1). The concentration of compound A after 11 h in the patient with the longest anesthesia time was 11.4 ppm. Compound B was detected in seven of ten patients. Its mean concentration was 0.17 ± 0.37 ppm after 0.5 h and did not change significantly thereafter.

The temperature of the soda lime at the upper measurement point in the lower compartment of the canister was 45.8 ± 1.5°C after 3 h and did not change thereafter (fig. 2). The temperature at the lower measurement point was 46.0 ± 1.7°C after 2 h and did not change until after 5 h, decreasing to 43.5 ± 1.8°C after 7 h.

The mean sevoflurane exposure was 7.38 ± 2.68 MAC h. The hourly mean end-tidal sevoflurane concentra-

Fig. 2. The temperature of soda lime. Open circles = the temperature of soda lime at the upper point in the lower compartment of the canister; filled circles = the temperature at the lower point in the lower compartment of the canister. All values are expressed as mean ± SD; n = 10.
tions were $2.22 \pm 0.27\%$, $2.10 \pm 0.26\%$, $2.14 \pm 0.26\%$, $2.13 \pm 0.24\%$, $2.24 \pm 0.26\%$, $1.99 \pm 0.27\%$, $2.04 \pm 0.24\%$, and $2.05 \pm 0.30\%$ at $0.5$, $1$, $2$, $3$, $4$, $5$, $6$, and $7$ h after anesthesia, respectively.

Postoperative clinical laboratory tests showed no abnormalities in hepatic or renal function associated with anesthesia (table 2).

Discussion

The concentrations of breakdown products resulting from reaction between soda lime and sevoflurane were measured during closed-circuit anesthesia. Safe levels for the concentration and exposure time of these breakdown products (especially compound A) have not been clarified in humans. Frink et al. measured the concentrations of these breakdown products during low-flow anesthesia of $3$–$5$ h. In their study, the anesthesia time was limited to $5$ h or less, and the sevoflurane concentration was about $1\%$ because it was used in combination with fentanyl and nitrous oxide. Because major surgery often requires an anesthesia time of more than $5$ h and even less serious surgery requires a sevoflurane concentration of greater than $1\%$, it is necessary to examine the breakdown products and adverse effects of sevoflurane anesthesia in which the concentration of sevoflurane is greater than $1\%$ and the anesthesia time is more than $5$ h.

In this study, the concentrations of breakdown products during closed-circuit anesthesia were measured for exposure times exceeding $5$ h. The highest mean concentration of compound A in our study was $19.5 \pm 5.4$ ppm, whereas Frink et al., when also using soda lime as the absorbent, reported a maximum mean concentration of $8.2 \pm 2.7$ ppm. A variety of factors are believed to be responsible for these differences.

First, the sevoflurane concentrations were different. End-tidal concentration in our study was approximately $2\%$, whereas Frink et al. used a concentration of approximately $1\%$. Use of a higher sevoflurane concentration results in a higher concentration of breakdown products, as has been demonstrated by Hanaki et al. using a model lung and closed and semiclosed circuits. This is in agreement with our results, which show higher concentrations of breakdown products at higher sevoflurane concentrations than those used by Frink et al.

Second, the temperature of the soda lime in our study was $46.0 \pm 1.7^\circ$ C, compared with $37.8 \pm 1.14^\circ$ C in the study by Frink et al. When absorbent temperatures are high, the generation of sevoflurane breakdown products is increased *in vitro*. Because the temperature of the soda lime in our study was higher than that in the study by Frink et al., it is understandable that the observed concentrations of breakdown products were higher. The temperature difference may be due to greater contact between the absorbent and CO$_2$ in a closed circuit than in a low-flow system or due to increased production of CO$_2$ by the patients in our study.

Third, gas washout in the circuit is reduced in a closed circuit. This is believed to be another reason for the higher concentrations of breakdown products in our study.

According to Frink et al., when Baralyme absorbent (Chemtron, Allied Healthcare, St. Louis, MO) was used *in vivo*, the concentration of compound A was $2.5$ times higher than when soda lime was used. It is not possible to predict what the concentration of compound A would be for closed-circuit anesthesia using Baralyme. This is because experiments *in vitro* have shown that sevoflurane is taken up more readily by Baralyme than by soda lime, but no published studies have compared soda lime and Baralyme with regard to concentrations of breakdown products in closed-circuit systems. According to Frink et al., who used low-flow anesthesia, the temperature of Baralyme was $46.4 \pm 1.31\%$ C, but that of soda lime was $37.8 \pm 1.14\%$ C. In studies using model circuits, however, almost no difference was seen in the temperatures of soda lime and Baralyme. It is possible that the different temperatures resulting in different concentrations of compound A, as reported by Frink et al., in experiments using two different absorbents, were not due to differences in the composition of these absorbents. It is speculated that the difference in temperature may be due to lower CO$_2$ rates of exhalation in the studies using soda lime absorbents than in those using Baralyme absorbents.

In our study, the highest measured concentration of compound A was $30.0$ ppm. In the study by Frink et al. using Baralyme, one patient with a concentration of $60$ ppm was observed. However, this value was much greater than the average and was considered exceptional. It also is not clear why the concentration of compound A increased in this manner. The increase could not be attributed to an increase in the temperature of the Baralyme or to a high concentration of sevoflurane.

Anesthesiology, V 80, No 1, Jun 1994
Table 2. Renal and Hepatic Functions with Sevoflurane

<table>
<thead>
<tr>
<th></th>
<th>Preanesthesia</th>
<th>1 Day Postanesthesia</th>
<th>2 Days Postanesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq)</td>
<td>140.2 ± 1.9</td>
<td>138.7 ± 2.5</td>
<td>138.8 ± 3.4</td>
</tr>
<tr>
<td>Potassium (mEq)</td>
<td>3.93 ± 0.43</td>
<td>3.86 ± 0.41</td>
<td>3.91 ± 0.44</td>
</tr>
<tr>
<td>Chloride (mEq)</td>
<td>104.6 ± 1.9</td>
<td>102.2 ± 2.2*</td>
<td>102.0 ± 2.6*</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>14.21 ± 3.45</td>
<td>11.93 ± 5.95</td>
<td>10.54 ± 4.65</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.74 ± 0.17</td>
<td>0.73 ± 0.15</td>
<td>0.69 ± 0.16</td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (mg/dl)</td>
<td>0.51 ± 0.10</td>
<td>0.76 ± 0.31*</td>
<td>0.59 ± 0.17</td>
</tr>
<tr>
<td>Direct (mg/dl)</td>
<td>0.19 ± 0.06</td>
<td>0.24 ± 0.05*</td>
<td>0.21 ± 0.06</td>
</tr>
<tr>
<td>AST (SGOT) (IU/l)</td>
<td>15.8 ± 7.0</td>
<td>21.9 ± 6.8</td>
<td>23.4 ± 7.2*</td>
</tr>
<tr>
<td>ALT (SGPT) (IU/l)</td>
<td>12.0 ± 8.4</td>
<td>13.9 ± 9.6</td>
<td>14.3 ± 8.9</td>
</tr>
<tr>
<td>ALP (IU/l)</td>
<td>8.31 ± 1.92</td>
<td>6.84 ± 1.54</td>
<td>6.45 ± 1.48</td>
</tr>
<tr>
<td>LDH (IU/l)</td>
<td>268.2 ± 42.4</td>
<td>339.6 ± 35.9*</td>
<td>351.9 ± 29.5*</td>
</tr>
</tbody>
</table>

Values shown as mean ± SD.

BUN = blood urea nitrogen; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ALP = alkaline phosphatase; LDH = lactic dehydrogenase.

* Differs from preanesthesia value (P < 0.05).

In our study, the average concentration of compound A in the circuit reached a peak after 1 h. In the study by Frink et al., using low-flow anesthesia, the average concentration of compound A in the circuit reached a peak after 4 h. It is probable that the gradual increase in the concentration of compound A was due to a slower increase in the temperature of the CO₂ absorbent than in a closed circuit. Another factor may have been the slight increase in the average concentration of sevoflurane during the course of the experiment. In our study, the average concentration of compound A showed a tendency to decrease after 5 h. Similarly, according to Frink et al., the concentration of compound A tended to decrease in experiments using Baralyme absorbents for more than 5 h. This is believed to be due to the production of water resulting partly from the reaction between CO₂ and the absorbent and partly from exhaled moisture, which affects the soda lime. Even in closed-circuit systems, in which gas washout is least, the concentration of compound A probably reaches a plateau, rather than continuing to increase, and may decline after 5 h.

The median lethal concentration (LC₅₀) of compound A in Wistar rats after exposure for 1 h was 1,090 ppm for male rats and 1,050 ppm for female rats. After exposure for 3 h, the LC₅₀ was 350–490 ppm for male rats and 340–460 ppm for female rats. The LC₅₀ of compound A has not been examined for exposures of more than 3 h. It is believed that the LC₅₀ decreases with an increase in exposure time. The mean concentration of compound A after 7 h of exposure in our study was 14.6 ± 3.0 ppm. The mean concentration after 11 h in the patient with the longest anesthesia time was 11.4 ppm. This latter value may approach the estimated LC₅₀ of compound A after 7 or 11 h of exposure in Wistar rats, but the LC₅₀ value in rats cannot be directly applied to humans. One reason for this is that in the rat experiments, breathing was spontaneous, whereas in clinical practice, breathing is always assisted. No patient in our study showed clinical or laboratory evidence of organ toxicity, and no abnormal values were seen in tests of liver or kidney function.

The highest concentration of compound B measured in our study was 1.5 ppm. Because of the low toxicity of compound B, this value was not considered to present a risk of organ damage.

In conclusion, two breakdown products were detected in closed-circuit sevoflurane anesthesia. The concentrations observed in closed-circuit anesthesia were higher than those in low-flow anesthesia. In none of our patients was there evidence of organ damage during anesthesia or in postoperative laboratory tests.

References


