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Compound A concentration and the temperature of CO_2 absorbents during low-flow sevoflurane anesthesia in surgical patients

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Abstract: Sevoflurane, a new inhalational anesthetic, is metabolically broken down into several decomposition products in the presence of CO_2 absorbents. One of the products, $CF_2 = C (CF_3) OCH_2F$ (compound A), which appears to be the most toxic, was quantitated in 20 surgical patients subjected to more than 3 h of anesthesia using a low-flow anesthesia circuit. To minimize the variables in the reaction velocity between sevoflurane and the CO_2 absorbents, we maintained the sevoflurane concentration at 2%. Wakolime-A, one type of soda lime, resulted in the highest increase in compound A concentration. The peak concentration was 27.1 ± 3.1 ppm, less than one-tenth of the LC_{50} (50% lethal concentration) of compound A, which was previously reported as 420 or 400 ppm in rats. We also measured the temperature in CO_2 absorbents, which had been reported to influence compound A production. The elevation in the temperature was 27.9 ± 1.3°C in Wakolime-A, 29.4 ± 8.4°C in Baralyme, and 31.0 ± 5.0°C in Sodasorb II. Further studies are needed to assess the safety and efficacy of sevoflurane.

Key words: Anesthetics, Volatile sevoflurane, Low-flow anesthesia, Compound A, Co_2 absorbents

Introduction

Sevoflurane (flurormethyl–2, 2, 2-trifluoro-1 (trifluoromethyl) ethyl ether), a potent inhalational anesthetic agesthetic, has a low blood-gas partition coefficient and nonpungent character that enables smooth induction and recovery from anesthesia [1,2]. Sevoflurane is currently in clinical use in Japan and is under investigation in the USA.

Research has shown that sevoflurane is degraded in the presence of CO_2 absorbents to yield several decomposition products [3]. Hanaki et al. identified five degradation products that occur when sevoflurane reacts with CO_2 absorbents at high temperatures [4]. One of the major products is fluoromethyl–2, 2-difluoro-1 (trifluoromethyl) vinyl ether [$CF_2 = C (CF_3) OCH_2F$], abbreviated as compound A, which is the most toxic decomposition product [5].

The safety of sevoflurane administration has been questioned, especially when the low-flow or closed-circuit technique is used, because the production of compound A is expected to be higher in these circuits than in conventional high-flow anesthesia. The low-flow or closed-circuit technique relies mainly on the CO_2 absorbents for CO_2 disposal, and the reaction of CO_2 with hydroxy alkali produces heat. There are a few clinical reports on low-flow anesthesia using sevoflurane [6,7], and in these reports the sevoflurane concentrations varied. In the present study, we measured compound A concentrations and temperature during low-flow anesthesia in surgical patients, using three different types of absorbents. We maintained a constant sevoflurane concentration at a clinically acceptable value to limit the variables affecting the results.

Methods and materials

Following approval by the Kyoto University Committee on Human Research, a total of 20 ASA physical status 1 and 2 patients were scheduled to receive sevoflurane anesthesia anticipated to be 3 h or more in duration. Informed consent was obtained from each patient. Patients with a history or laboratory evidence of hepatic, renal, or significant cardiovascular diseases were excluded.

All patients were premeditated with diazepam (5 mg p.o.) 1 h before anesthesia and atropine sulfate (0.5 mg i.m.) 30 min prior to anesthesia. They were then given an intravenous line of lactated Righer's solution and an

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intraarterial line was set up in a radial artery. Anesthesia was induced with thiopental 4 mg·kg^{-1} and fentanyl 1–3 μg·kg^{-1}, and neuromuscular blockade was obtained using vecuronium 0.12 mg·kg^{-1}. Following tracheal incubation, the total flow rate was fixed at 1 l·min^{-1}. Oxygen and nitrous oxide flows were adjusted to give 50% oxygen/50% nitrous oxide. After taking an initial sample to confirm the absence of residual compound A, anesthesia was maintained with 2% sevoflurane and 50% oxygen/50% nitrous oxide. The concentrations of each agent were monitored by continuous observation using a Rascal anesthetic gas monitor (Ohmeda, Madison, WI, USA).

The lungs were ventilated with a tidal volume of 10–12 ml·kg^{-1}, and ventilatory rates were adjusted to maintain an end-tidal CO_2 concentration of 30–40 mmHg. Vecuronium was added to provide neuromuscular blockade. Blood pressure was maintained within ±20% of basline and pressors (dopamine) or vasodilators (nicardipine) were used as needed.

Anesthetic gases were delivered using a Modulus II Anesthesia System (Ohmeda). Two types of soda lime and one type of baralyme were used. The first seven study subjects were anesthetized using soda lime, Wakolime-A (Wako Pure Chemical Industries, Osaka, Japan) as the absorbent. In the second group, Baralyme (Chemtron Medical Division, Allied Healthcare Products, St. Louis, MO, USA) was used. A second type of soda lime, Sodasorb II (W. R. Grace, Lexington, MA, USA), was employed in the last group. Fresh CO_2 absorbents were unpacked and put in the canisters immediately prior to anesthesia to avoid deterioration.

Temperatures of the soda limes and Baralyme were observed using two temperature monitors (Terumo, Tokyo, Japan) and the two accompanying probes. A single probe was inserted into the middle of each of vertically connected absorbent canisters. Temperature readings were recorded at 30 min intervals during anesthesia.

Samples of inhalation gases were taken from the anesthetic circuit through a three-way stop-cock during the anesthesia. Gas-tight glass syringes, equipped with a Louer lock port, were used to obtain 100 ml samples. Each sample was then transferred to an air-tight bottle (155 ml), in which the pressure was reduced to 70 mmHg before use. The samples were kept in the bottle until measurement. For each patient, samples were taken every hour during the 3 or 4 h of sevoflurane administration. After the last sampling, the total anesthetic gas flow was increased to 6 l·min^{-1}. Sevoflurane and nitrous oxide were discontinued at the end of surgery. Then atropine sulfate and neostigmine were administered intravenously to reverse neuromuscular blockade. Patients were extubated after signs of awakening were confirmed.

Compound A analysis

Compound A was analyzed and quantitated using a gas chromatography (model GC-9A and model C-R4A, Shimadzu, Kyoto, Japan). A glass column of 5 m × 3 mm ID, packed with 20% dioctyl phthalate on a Chromosorb (WAWR Technolab S. C. Corp., Osaka, Japan) with 80/100 mesh, was maintained at 110°C. The injection port was maintained at 130°C. A carrier stream of nitrogen, 35 ml·min^{-1}, was delivered through the column to a hydrogen flame ionization detector.

Statistical analysis

All values are shown as the mean ± SD. Student's *t*-test was applied to comparisons of pre- and postoperative blood chemistry. The repeated measures analysis of variance (ANOVA) was employed to compare the amount of compound A production among the three CO_2 absorbents. A value of $P < 0.05$ was considered significant.

Results

Table 1 shows the age, height, body weight, and duration of anesthesia of the three groups of patients. The patients who received Wakolime-A as the CO_2 absorbent were younger than the patients in the other groups. The difference was significant at $P < 0.05$. The other variables displayed no significant difference among the groups.

Compound A concentrations in each of the three groups, at individual time points, are depicted in Fig. 1.

Table 1. Patient characteristics

	Age (years)	Height (cm)	Body weight (kg)	Anesthesia time (min)	Operation time (min)
Wakolime-A	27.5 ± 11.2	161.3 ± 6.1	64.9 ± 13.0	289.3 ± 82.9	225.4 ± 81.5
Sodasorb II	47.0 ± 14.1*	163.5 ± 4.2	62.0 ± 9.2	340.2 ± 95.9	269.6 ± 81.1
Baralyme	44.6 ± 14.5*	164.4 ± 10.7	65.6 ± 15.8	331.9 ± 163.1	250.1 ± 164.4

* $P < 0.05$ *vs* Wakolime-A.

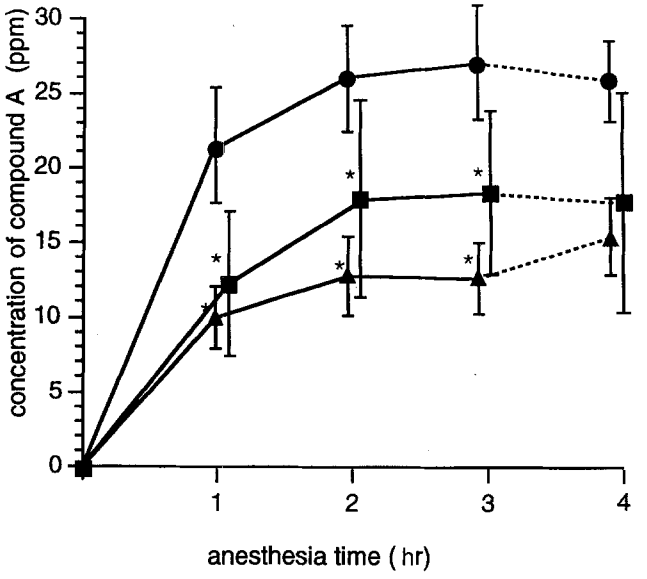

Fig. 1. Concentrations of compound A over time. *Circles*, Wakolime-A; *squares*, Baralyme; *triangles*, Sodasorb II

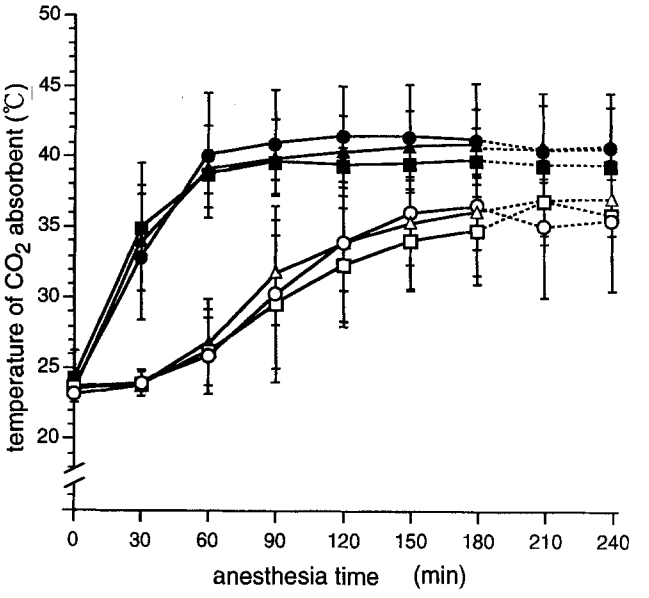

Fig. 2. Mean temperatures of CO_2 absorbents in the upper (*closed symbols*) and lower (*open symbols*) canisters. *Squares*, Wakolime-A; *circles*, Baralyme; *triangles*, Sadasorb II

In the Wakolime-A group, compound A increased to 21.5 ± 3.9 ppm at 1 h after administration of 2% sevoflurane. The maximum inhalational concentration of compound A in the presence of Wakolime-A was 27.1 ± 3.8 ppm. In the Baralyme group, the concentration was 12.3 ± 4.8 ppm at 1 h and the maximum value was 18.6 ± 5.4 ppm at 3 h. When sodasorb II was used, the concentration was 9.9 ± 2.1 mmp at 1 h and the peak value was 14.5 ± 2.6 ppm at 4 h. Compound A was not detectable in any of the samples taken prior to sevoflurane administration.

A comparison of the inhalational concentrations of compound A at hourly intervals in the three groups shows that Wakolime-A produced a significantly larger amount of compound A than Baralyme or Sodasorb II ($P < 0.05$). A comparison between the compound A production of Baralyme and Sodasorb II showed no statistically significant difference. Data for the concentration at 4 h were in insufficient because the anesthetic time was less than 4 h in four patients of the Wakolime-A group, three of the Baralyme group and one of the Sodasorb II group.

Figure 2 shows the mean temperatures of the individual CO_2 absorbents in the upper and lower canister at 30 min intervals. The maximum temperatures in the upper canisters were 39.7 ± 1.09°C in Wakolime-A, 41.2 ± 1.2°C in Baralyme, and 41.9 ± 1.09°C in Sodasorb II. In the lower canisters, the rate of elevation was slow and temperatures were always lower than those in the upper canisters. There was no statistically significant difference in temperature in canisters among the three absorbents. The oxygen flow required to maintain 50% oxygen in a 1 l·min^{-1} flow system was 535 ± 31 ml·min^{-1} at 1 h and 577 ± 32 ml·min^{-1} at 2 h. Only two patients in the Sodasorb II group required inotropics or vasodiator. Arterial blood gas analyses obtained at 1 h intervals showed no abnormality during anesthesia.

Table 2. Blood chemistry data

	Preoperatively	2 days postoperatively
GOT (IU/l)	20.3 ± 6.7	18.7 ± 8.6
GPT (IU/l)	23.2 ± 10.8	21.3 ± 12.7
LDH (IU/l)	319 ± 63.3	276 ± 83.2
UA (mg/dl)	5.5 ± 1.5	4.6 ± 1.5
Cre (mg/dl)	0.68 ± 0.18	0.65 ± 0.18
BUN (mg/dl)	14.3 ± 4.1	13.6 ± 4.7

GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; LDH, lactate dehydrogenase, UA, uric acid; Cre, creatinine; BUN, blood urea nitrogen.
Values are shown as the mean ± SD.

Both pre- and postoperative blood chemistry data revealed no evidence of hepatic or renal damage as shown in Table 2. Postoperative urinalysis revealed abnormalities in two patients which were not caused by the inhalational anesthesia technique. In one case the urine sugar was due to diabetes mellitus; in the other case, occult blood was due to a history of difficulty in inserting Foley catheter.

Discussion

The present study confirmed that the compound A concentrations and the canister temperatures are elevated in surgical patients receiving 2% sevoflurane and 50%

oxygen/50% nitrous oxide anesthesia in a 1 l min^{-1} low-flow system. The largest increase in compound A concentration was produced by Wakolime-A.

Five different sevolfurane degradation products have been identified [4]. Of the five products, compound [5]. A and B ($CH_3OCF_2CH(CF_3)OCH_2F$) were detected in the closed anesthesia circuits. It has also been reported that only compound A was detected in semiclosed circuits with a flow rate of 6 l·min^{-1} [4,7]. Compound A has been reported to cause pulmonary, hepatic, and renal damage [5]. In contrast, the concentration of compound B has been reported to be low in the anesthetic circuit and it is not toxic.

Several factors are involved in sevoflurane degradation with the CO_2 absorbent [4,7,8]: use of closed- or low-flow circuit, use of high concentrations of sevoflurane, freshness of CO_2 absorbent, constituent of CO_2 absorbent, and high temperature in the canisters. Frink et al. [7], who used a low-flow technique, reported similar elevation of canister temperatures, but their concentration of sevoflurane was not consistent in different patients. For a precise evaluation of the interaction between sevolfurance and CO_2 absorbents, maintenance of a constant rate of its degradation is essential, and employment of a single concentration of sevoflurane is preferable. Thus, we used a fixed concentration of 2% sevolfurane in our study.

Compound A production is also influenced by the composition of CO_2 absorbents. Liu et al. reported that Bralyme produced a higher concentration than soda lime [6]. In addition, Kudo et al. showed that one type of soda lime, Wakolime-A, resulted in a greater production than another soda lime, Wakolime [8]. Table 3 shows the composition of the absorbents we tested. The major difference between the two soda limes is in the content of KOH, which is small in Wakloime-A. Kudo et al. reported that KOH was the major factor contributing to the increase of compound A production, and attributed the increased production to the greater content of KOH [9]. However, in another in vitro study, greater concentrations of compound A were produced by Wakolime-A than by conventional soda lime [8]. The latter observation supports our results.

Table 3. Composition of CO_2 absorbents

	Wakolime-A	Baralyme	Sodasorb II
Ca $(OH)_2$	79.2	74	76.5
KOH	0.1	5	2.25
NaOH	4.2	—	2.25
Ba $(OH)_2$	—	11	—
Sodium silicate	0.4	—	—
H_2O	13.6	10	18.9
Mg $(OH)_2$	0.5	—	—
Al $(OH)_3$	0.3	—	—

Values are shown as % (wt/wt).

Furthermore, Morio et al. reported that the compound A concentration in the flasks decreased slowly in the presence of Wakolime-A, suggesting that Wakolime-A had a low affinity for compound A [5]. Thus, the increased concentration of compound A, produced in the Wakolime-A group, may be due to the lower affinity of Wakolime-A to compound A.

Baralyme produced greater heat than soda lime in a model circuit supplied with sevoflurane and CO_2 [6]. In our study, the peak value of canister temperature was not statistically different among the three types of CO_2 absorbents. These findings suggest that a model circuit supplied with a constant flow of CO_2 does not necessarily represent the clinical case.

Frink et al. reported that Baralyme produced a greater amount of compound A than Sodasorb during the low-flow technique, the peak level of which was 20.3 ± 8.6 ppm [7]. This concentration approximately agrees with our observation of 18.6 ± 5.4 ppm at 3 h. However, in the case of Sodasorb, the concentration was 8.2 ± 2.7 ppm, which was lower than our concentration of 14.5 ± 4.6 ppm. The difference may be due to the fact that the peak temperatures in canisters of Baralyme and Sodasorb in their study were different or that the sevoflurane concentration was not fixed [7].

Morio et al. described an acute toxicity of compound A in rats [5]. The LC_{50} was calculated to be 1090 ppm in males and 1050 ppm in females following 1 h exposure. When rats were exposed to compound A for 3 h, the LC_{50} was 420 ppm in males and 400 ppm in females. In our study, the peak concentration was 27.1 ± 3.8 ppm, which was less than one-tenth of the LC_{50} in a 3 h exposure to rats. In one case, the highest value reached 34.9 ppm.

In our postoperative follow-up, blood chemistry and urinalysis revealed no abnormalities in the heaptic and renal functions which could be attributed to sevoflurane administraiton. However, the degradation products of sevoflurane have a potential to damage the vital organs such as the lungs, liver, and kidney. At this time we cannot determine the usefulness of sevoflurane as an anesthetic or suggest that it be used to replace isoflurane or halothane. Further experimental and clinical studies are required to fully ensure the safety of sevoflurane.

In conclusion, we demonstrated that Wakolime-A produced the largest amount of compound A in the low-flow anesthesia circuits in which concentration of sevoflurane was kept constant.

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