Carbon Dioxide Absorbents Containing Potassium Hydroxide Produce Much Larger Concentrations of Compound A from Sevoflurane in Clinical Practice

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We investigated the concentrations of degraded sevoflurane Compound A during low-flow anesthesia with four carbon dioxide (CO_2) absorbents. The concentrations of Compound A, obtained from the inspiratory limb of the circle system, were measured by using a gas chromatograph. In the groups administered 2 L/min fresh gas flow with 1% sevoflurane, when the conventional CO_2 absorbents, Wakolime™ (Wako, Tokyo, Japan) and Drägersorb™ (Dräger, Lübeck, Germany), were used, the concentrations of Compound A increased steadily from a baseline to 14.3 ppm (mean) and 13.2 ppm, respectively, at 2 h after exposure to sevoflurane. In contrast, when the other novel types of absorbents containing decreased or no potassium hydroxide/sodium hydroxide, Medisorb™ (Datex-Ohmeda, Louisville, CO) and Amsorb™ (Armstrong, Coleraine, Northern Ireland), were used, Compound A remained at baseline (<2 ppm) throughout the study. In the groups administered 1 L/min fresh gas flow with 2% sevoflurane, Wakolime™ and Drägersorb™ produced much larger concentrations of Compound A (35.4 ppm and 34.2 ppm, respectively) at 2 h after exposure to sevoflurane. Medisorb™ showed measurable concentrations of Compound A (8.6 ppm at 2 h), but they were significantly smaller than those produced by the two conventional absorbents. In contrast, when Amsorb™ was used, Compound A concentrations remained at baseline throughout the study period.

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Currently used carbon dioxide (CO_2) absorbents can degrade sevoflurane to fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether ($CF_2 = C(CF_3)–O–CH_2F$, Compound A) (1,2). Compound A has a dose-dependent nephrotoxic effect in rats (3–5), although clinically significant renal effects of this degradation in surgical patients have rarely been found (6–9). Because of the environmental pollution and costs of volatile anesthetics, low-flow anesthesia <2.0 L/min of fresh gas flow has been widely used (10). Concentrations of Compound A in inspired gas given to patients could be significantly larger in low-flow anesthesia than in high-flow anesthesia because the washout of the degraded sevoflurane decreases and the temperature of the canister increases during low-flow anesthesia (11–13). Although the clinical effect of Compound A on renal function under low-flow anesthesia is still controversial (14), patients probably should not be exposed to a large concentration of degraded sevoflurane. Recently, Neumann et al. (15) showed the importance of potassium hydroxide (KOH) and sodium hydroxide (NaOH) in a laboratory model to the formation of Compound A, and some novel CO_2 absorbents, which reduce strong bases such as KOH and NaOH, have become available for clinical use (16). We therefore compared the concentrations of Compound A in the inspired gas breathed by patients from anesthetic circuits containing absorbents with and without these strong bases.

Methods

This study was approved by the our university ethical committee on human research, and informed consent was obtained from each patient. Forty-eight ASA physical status I and II adult patients who had been scheduled to receive sevoflurane for general anesthesia anticipated to last 4 h or longer were enrolled in this study. Patients with a history of, or with laboratory evidence or physical examination indicating, hepatic, renal, or significant cardiovascular disease were

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Table 1. Compositions of Calcium Dioxide Absorbents Tested (%)

	Wakolime™ A	Drägersorb™800Plus	Medisorb™	Amsorb™
$Ca(OH)_2$	Approximately 80	Approximately 80	70 –80	>75
NaOH	1.3	2.0	1.0 –2.0	0
KOH	2.6	3.0	0.003	0
Water	Approximately 13	Approximately 14	16 –20	14.5
Other materials	SiO_2, $Mg(OH)_2$, $Al(OH)_3$	SiO_2, $Mg(OH)_2$, $Al(OH)_3$	SiO_2, $Mg(OH)_2$, $Al(OH)_3$	$CaCl_2$, $CaSO_4$, PVP

PVP = polyvinylpyrrolidine.
Wakolime™ A (Wako, Tokyo, Japan), Drägersorb™800Plus (Dräger, Lübeck, Germany), Medisorb™ (Datex-Ohmeda, Louisville, CO), Amsorb™ (Armstrong, Coleraine, Northern Ireland).

excluded from the study. Atropine (0.5 mg) and midazolam (2.0–3.0 mg) were given IM 1 h before the surgery and anesthesia administration.

Anesthesia was induced by an IV injection of 3–4 mg/kg thiamylal, 1–2 μg/kg fentanyl, and muscle paralysis facilitated with 0.10–0.12 mg/kg vecuronium. After tracheal intubation, anesthesia was maintained with sevoflurane and 50% nitrous oxide/50% oxygen along with 1–2 μg/kg fentanyl in incremental doses as required to maintain systolic arterial blood pressure within ±20% of the baseline value. Ventilation was controlled with a tidal volume of 10–12 mL/kg with the ventilatory rate adjusted to maintain P_{ETCO_2} between 34 and 38 mm Hg. The anesthetic machine used was a Modulus SE Anesthetic System (Datex-Ohmeda, Louisville, CO). The circle system hoses were made of polyester elastomer, and fittings were made of silicone rubber. The Y-piece was made of polypropylene. The other components of the circle system (valves, fresh gas inlet, canister, etc) were the standard components used in the Modulus SE Anesthesia System.

The patients were randomly divided into eight groups according to the fresh gas flow rate and the type of CO_2 absorbent. When the fresh gas flow rates were 2.0 and 1.0 L/min, the inspired sevoflurane concentrations were adjusted as indicated by the calibrated gas monitor (5250 RGM; Datex-Ohmeda) to 1.0% and 2.0%, respectively. The CO_2 absorbents were Wakolime™ A (Wako, Tokyo, Japan), Drägersorb™800Plus (Dräger, Lübeck, Germany), Medisorb™ (Datex-Ohmeda), and Amsorb™ (Armstrong, Coleraine, Northern Ireland) (16). Compositions of the CO_2 absorbents used are listed in Table 1. Fresh CO_2 absorbents and new circle systems were used for each patient.

Gas samples for measurement of degradation products were obtained from the inspiratory limb of the circle system at 0, 1, 2, and 4 h after exposure to sevoflurane. The concentrations of Compound A were measured by using a gas chromatograph (model GC-7AG; Shimadzu, Kyoto, Japan) equipped with a gas analyzer (model MGS-5; Shimadzu). The gas chromatograph column was 5 m in length and 3.0 mm in internal diameter, and it was filled with 20% dioctyl phthalate and chromosorb WAW (Technolab, Osaka, Japan) with 80/100 mesh. The injection port temperature was 130°C, and the column temperature was 110°C. The carrier gas was nitrogen, and the carrier gas flow rate was 28 mL/min. The gas chromatograph was calibrated with standard calibration gas prepared from a stock solution of Compound A (Maruishi Pharmaceutical, Osaka, Japan).

All data were presented as mean ± SD. The concentrations of Compound A were compared by using one-way analysis of variance followed by Scheffe's *post hoc* test to evaluate statistical significance between any two groups. A P value <0.05 was considered statistically significant.

Results

All eight groups were comparable with respect to sex, age, weight, body mass index, ASA physical status, and P_{ETCO_2} (Table 2). In the groups administered 2.0 L/min fresh gas flow, analysis of the gas samples taken from the inspired circuit when the conventional CO_2 absorbents, Wakolime™ A and Drägersorb™800Plus, were exposed to 1.0% sevoflurane showed that the mean ± SD concentrations of Compound A increased steadily from the baseline values (<2 ppm) to 13.2 ± 4.2 ppm and 14.3 ± 3.4 ppm, respectively, at 2 h after exposure to sevoflurane and became constant (Fig. 1A). In contrast, when the other novel types of absorbents, Medisorb™ and Amsorb™, were used, Compound A remained at the baseline concentrations throughout the study period.

In the groups administered 1.0 L/min fresh gas flow (2.0% sevoflurane), Wakolime™ A and Drägersorb™ 800Plus produced much larger concentrations of Compound A (34.2 ± 5.6 ppm and 35.4 ± 7.6 ppm, respectively) at 2 h after the exposure to sevoflurane than did the groups administered 2.0 L/min fresh gas flow (Fig. 1B). Medisorb™ produced measurable concentrations of Compound A (8.6 ± 1.3 ppm at 2 h), but they were significantly smaller than those produced by the two conventional absorbents Wakolime™ A and Drägersorb™800Plus. In contrast, when Amsorb™ was used, Compound A concentrations remained at baseline values throughout the study period.

Table 2. Demographics and P_{ETCO_2} for the Eight Groups

	Wakolime™ A	Drägersorb™800Plus	Medisorb™	Amsorb™
2.0-L/min groups with 1.0% sevoflurane				
Sex (F/M)	3/3	2/4	3/3	3/3
Age (yr)	46 ± 12	49 ± 9	51 ± 11	48 ± 12
Weight (kg)	56 ± 13	53 ± 11	52 ± 13	50 ± 9
Body mass index	21 ± 5	19 ± 6	22 ± 6	21 ± 4
ASA physical status I	5	4	5	5
P_{ETCO_2} (mm Hg)	35 ± 3	36 ± 3	35 ± 2	35 ± 3
1.0-L/min groups with 2.0% sevoflurane				
Sex (F/M)	2/4	2/4	2/4	3/3
Age (yr)	47 ± 11	45 ± 11	46 ± 9	48 ± 11
Weight (kg)	54 ± 11	55 ± 10	57 ± 11	52 ± 9
Body mass index	20 ± 6	21 ± 5	23 ± 7	22 ± 6
ASA physical status I	4	5	5	4
P_{ETCO_2} (mm Hg)	36 ± 2	35 ± 2	36 ± 3	35 ± 2

Values are mean ± SD.
$n = 6$ for each group.
Wakolime™ A (Wako, Tokyo, Japan), Drägersorb™800Plus (Dräger, Lübeck, Germany), Medisorb™ (Datex-Ohmeda, Louisville, CO), Amsorb™ (Armstrong, Coleraine, Northern Ireland).

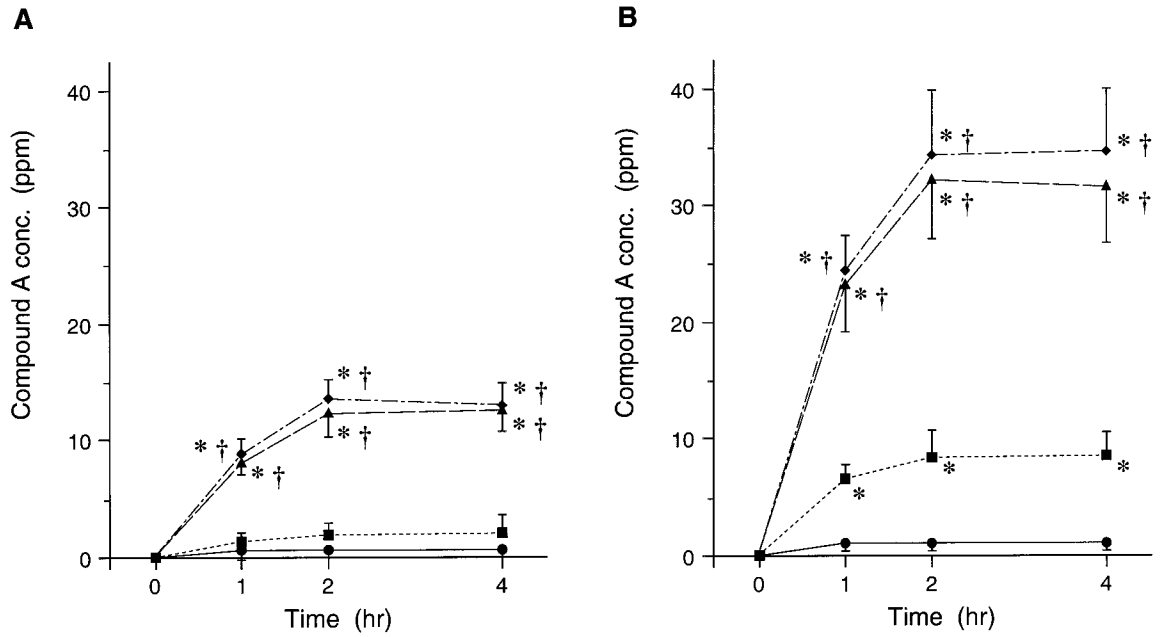

Figure 1. Comparison of concentrations of Compound A at fresh gas flow of (A) 2.0 L/min with 1.0% sevoflurane and of (B) 1.0 L/min with 2.0% sevoflurane with four kinds of carbon dioxide absorbents, Amsorb™ (Armstrong, Coleraine, Northern Ireland) (closed circle, solid line), Medisorb™ (Datex-Ohmeda, Louisville, CO) (closed square, dotted line), Wakolime™ A (Wako, Tokyo, Japan) (closed triangle, dashed line), and Drägersorb™800Plus (Dräger, Lübeck, Germany) (closed diamond, dot-dashed line). Data are presented as mean ± SD. *$P < 0.05$ versus Amsorb™ at each point. †$P < 0.05$ versus Medisorb™ at each point. $n = 6$ in each group.

The inspired concentrations of CO_2 remained at unmeasurable levels throughout anesthesia in all patients, demonstrating the effectiveness of the new absorbents in removing CO_2.

Discussion

Compound A is nephrotoxic in rats, causing proximal tubular necrosis (3,5,7,17). Although the threshold for renal toxicity in rats is generally thought to be 300–340 ppm/h Compound A (4,5,18), we still do not know the threshold in humans. Eger et al. (19) reported profound postanesthesia albuminuria, glucosuria, and increased a-glutathione-*S*-transferase (GST) excretion in humans after an eight-hour administration of 3% sevoflurane at 2 L/min of fresh gas flow. Similar results have been shown by Higuchi et al. (8) in volunteers and Goldberg et al. (20) in patients. In contrast, a multicenter investigation that duplicated the eight-hour 3% sevoflurane (2 L/min of fresh gas flow)

protocol found no significant differences in the same measurements of renal function (21). Therefore, Compound A formation and renal effects are still areas of intense controversy. Compound A is formed as a result of an elimination reaction initiated by proton abstraction, and the presence of strong bases NaOH and/or KOH is fundamental to this reaction (15,22). Additional factors that influence formation of Compound A include absorbent water content and temperature, CO_2 production, sevoflurane concentration, and fresh gas flow rates, with greater formation of Compound A at lower flow rates (13).

The conventional CO_2 absorbents Wakolime™ A and Drägersorb™800Plus, which include large concentrations of NaOH/KOH (Table 1), produced high concentrations of Compound A, depending on the fresh gas flow rate and sevoflurane concentration (Fig. 1). In contrast, Amsorb™ did not produce Compound A at all because it does not include strong bases. The incorporation of calcium chloride as a humectant allows the calcium hydroxide to remain damp at all times without resorting to the hygroscopic properties conferred by NaOH or KOH in standard soda lime (16). Medisorb™, which includes small concentrations of NaOH (1%–2%), produced small concentrations of Compound A at a low fresh gas flow rate (1 L/min) with a large concentration of sevoflurane (2%). Although the CO_2 scavenging capacities of the novel absorbents Amsorb™ and Medisorb™ are 85%–90% of those currently used absorbents (16), these new absorbents are thought to be potentially safer than current absorbents when used with low-flow anesthesia.

Although we did not measure the degradation of isoflurane or desflurane carbon monoxide (CO), the generation of CO with low-flow breathing systems is also an important subject (23–25). CO is neurotoxic and cardiotoxic, and the ill patient is especially vulnerable (26). Although the mechanism by which CO formation from volatile anesthetics occurs remains unclear, Baxter et al. (27) postulated that base-catalyzed difluoromethoxy proton abstraction was an initial step in CO formation and that this base-catalyzed reaction was greater with KOH than with NaOH. Murray et al. (16) reported that Amsorb™ did not produce CO or Compound A. We can easily speculate that Medisorb™, which includes little KOH (0.003%), can produce a substantially smaller concentration of CO than that produced by conventional CO_2 absorbents.

In conclusion, our clinical study shows that novel CO_2 absorbents without strong bases, especially Amsorb™, are effective absorbents because little, or no, Compound A was detected during low-flow anesthesia with sevoflurane.

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