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Quantification of the Degradation Products of Sevoflurane in Two CO₂ Absorbants during Low-flow Anesthesia in Surgical Patients

Edward J. Frink, Jr., M.D.,* T. Philip Malan, M.D., Ph.D.,* Scott E. Morgan, B.S.,† Elizabeth A. Brown, R.N.,‡
Mark Malcomson, M.S.,† Burnell R. Brown, Jr., M.D., Ph.D., F.F.A.R.C.S.§

Sevoflurane, a new inhalational anesthetic agent has been shown to produce degradation products upon interaction with CO₂ absorbants. Quantification of these sevoflurane degradation products during low-flow or closed circuit anesthesia in patients has not been well evaluated. The production of sevoflurane degradation products was evaluated using a low-flow anesthetic technique in patients receiving sevoflurane anesthesia in excess of 3 h. Sevoflurane anesthesia was administered to 16 patients using a circle absorption system with O₂ flow of 500 ml/min and average N₂O flow of 273 ml/min. Preoperative and postoperative hepatic and renal function studies were performed. Gas samples were obtained from the inhalation and exhalation limbs of the anesthetic circuit for degradation product analysis and analyzed by gas chromatography/mass spectrometry for four degradation products. The first eight patients received sevoflurane anesthesia using soda lime, and the following eight patients received anesthesia using baralyme as the CO₂ absorbant. CO₂ absorbant temperatures were measured during anesthesia. Of the degradation products analyzed, only one compound [fluoromethyl-2, 2-difluoro-1-(trifluoromethyl) vinyl ether], designated compound A, was detectable. Concentrations of compound A increased during the first 4 h of anesthesia with soda lime and baralyme and declined between 4 and 5 h when baralyme was used. Mean maximum inhalation concentration of compound A using baralyme was 20.28 ± 8.6 ppm (mean ± SEM) compared to 8.16 ± 2.67 ppm obtained with soda lime, a difference that did not reach statistical significance. A single patient achieved a maximal concentration of 60.78 ppm during low-flow anesthesia with baralyme. Exhalation concentrations of compound A were less than inhalation concentrations, suggesting patient uptake. Peak CO₂ absorbant temperatures were greater with baralyme (46.4 ± 1.31° C) than soda lime (37.8 ± 1.14° C) (*P* < .001). No abnormal changes in hepatic or renal function testing were detectable up to 48 h after anesthesia. Sevoflurane when used in a low-flow anesthetic circuit for 3-5 h duration

generally produced low levels of a single degradation product, though in one case a higher concentration of compound A was produced. Although the concentrations of compound A obtained in this study are well below those reported to cause toxicity in animals, further studies will be needed to evaluate potential variability in compound A production. No patient in our study had clinical or laboratory evidence of organ toxicity following low-flow sevoflurane anesthesia. (Key words: Anesthetics: volatile, sevoflurane. Equipment: CO₂ absorbers. Toxicity: hepatic; renal.)

SEVOFLURANE, A NEW inhalational anesthetic currently under clinical investigation, possesses a low blood gas partition coefficient and non-pungent character allowing rapid induction^{1,2} and recovery from anesthesia.^{2,3} Regardless of these advantages questions have been generated regarding the extent of sevoflurane degradation in the presence of CO₂ absorbants and the potential toxicity of degradation products produced.⁴ This in turn raises the question of the safety of administration of sevoflurane to humans using low-flow or closed circuit anesthesia. Additionally, *in vitro* studies show that degradation of sevoflurane may be greater in the presence of baralyme compared to that of soda lime.^{*4} Wallin *et al.*¹ exposed soda lime to sevoflurane (5%) with CO₂ in a glass vial and detected two compounds: fluoromethyl-2, 2-difluoro-1-(trifluoromethyl) vinyl ether (compound A) and fluoromethyl-2-methoxy-2,2-difluoro-1-(trifluoromethyl) ethyl ether (compound B). Hanaki *et al.*⁵ identified five decomposition products when sevoflurane is reacted with soda lime in the presence of high temperature (120° C). The purpose of this study was to evaluate the concentrations of sevoflurane degradation products produced using a low-flow anesthesia circuit with CO₂ absorbants in patients receiving sevoflurane anesthesia for greater than 3 h duration. We measured the inhalation and exhalation limb concentration of four of the five sevoflurane degradation compounds identified by Hanaki *et al.*⁵ These compounds have been labeled A, B, C, and D and are shown in figure 1. In this study we sought to determine whether production of degradation compounds differed when either soda lime or baralyme was used as the CO₂ absorbant. Additionally,

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* Assistant Professor of Anesthesiology.

† Research Assistant.

‡ Research Nurse.

§ Professor and Chairman of Anesthesiology.

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Address reprint requests to Dr. Frink: Department of Anesthesiology, University of Arizona Health Sciences Center, Tucson, Arizona 85724.

Tanifuji Y, Takagi K, Kobayashi K, Yasuda N, Eger EI II: The interaction between sevoflurane and soda lime or baralyme (abstract). *Anesth Analg* 68:S285, 1989.

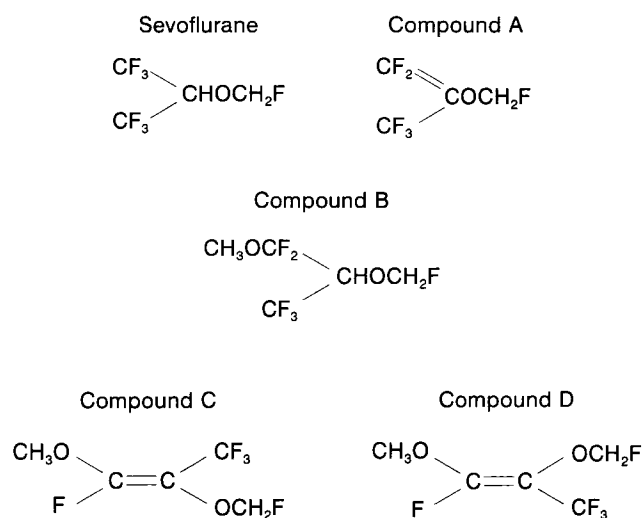


FIG. 1. Diagram of sevoflurane and four degradation products evaluated in this study. Sevoflurane = fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether); compound A = [fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether]; compound B = [fluoromethyl-2-methoxy-2,2 difluoro-1-(trifluoromethyl) ethyl ether] compound C, D(isomers)-[fluoromethyl-2-methoxy-2 fluoro-1-(trifluoromethyl) vinyl ether].

each absorbant was used for more than one anesthetic administration to compare degradation compound production in both fresh and used absorbant material.

Methods

With approval from the University of Arizona Human Subjects Committee, 16 ASA physical status 1 and 2 patients were scheduled to receive sevoflurane for anesthesia anticipated to be of 3 h duration or greater. Written informed consent was obtained from all participants.

Patients were excluded from the study with a history, laboratory, or physical examination evidence of hepatic, renal, or significant cardiovascular disease. Clinical laboratory studies were performed preoperatively and repeated 24 h after anesthesia and when possible 48 hr after anesthesia.

Prior to anesthesia an intravenous infusion of lactated Ringer's solution was started and patients received 1–2 mg midazolam iv prior to anesthetic induction. Anesthesia was induced by iv injection of 2–4 mg/kg thiopental, 1–3 µg/kg fentanyl, and muscle paralysis facilitated with either 1–2 mg/kg succinylcholine or 0.1 mg/kg vecuronium. Subsequent paralysis was provided with incremental doses of vecuronium. Following tracheal intubation anesthesia was maintained with sevoflurane and 50% nitrous oxide/50% oxygen along with 1–2 µg/kg fentanyl in incremental doses as desired by the anesthesiologist. Oxygen flow rate was fixed at 500 ml/min and nitrous oxide flow rate reduced from an initial flow of 500 ml/min to maintain a 50% concentration (average N₂O flow = 273 ml/min). The lungs were ventilated with a tidal

volume of 10–12 ml/kg with ventilatory rate adjusted to maintain end tidal CO₂ concentration between 30 and 35 mmHg. Sevoflurane end tidal concentration during maintenance anesthesia ranged from 0.30 to 2.0% in our group of 16 patients. Sevoflurane concentration was adjusted by the anesthesiologist throughout the anesthetic to maintain systemic arterial blood pressure within ±20% of baseline. Anesthetic gases were delivered with an Ohio medical anesthetic machine (Model 50, Madison, WI) using a circle system.

For the first eight study subjects, soda lime (Sodasorb W. R. Grace, Lexington, MA) was used as the CO₂ absorbant. In the following eight subjects, baralyme (Chemtron Medical Division, Allied Healthcare Product, St. Louis, MO) was the CO₂ absorbant. Soda lime was changed in the upper and lower canisters following the fourth anesthetic case (*i.e.*, patient 5 received fresh soda lime). Baralyme was changed following the fourth, sixth, and seventh anesthetic cases in the baralyme absorbant group.

Soda lime or baralyme temperature was monitored throughout the anesthetic using two temperature monitors (Mon-A-Therm Model 6500, Mon-A-Therm, St. Louis, MO) and four temperature probes inserted in the upper, middle, and lower thirds of the upper absorbant canister and the upper third of the lower canister. Temperature readings were recorded every 30 min during anesthesia.

Inhalation limb gas samples were obtained from the anesthetic circuit prior to each anesthetic to analyze for possible residual degradation compounds from the previous anesthetic case. Inhalation and exhalation limb gas samples were obtained at hourly intervals during the anesthesia using gas tight glass syringes equipped with side port needles (Supelco, Bellefonte, PA) for degradation compound analysis. Sevoflurane and nitrous oxide were continued at surgical anesthetic concentrations until wound closure. Residual muscle paralysis was reversed using iv glycopyrrolate and neostigmine. Oxygen flow rate was increased to 6 L/min and spontaneous ventilation allowed to return. Following eye opening to command the tracheas were extubated.

SEVOFLURANE DEGRADATION PRODUCT ANALYSIS

Analyses of sevoflurane degradation products were performed using a gas chromatography/mass spectrometry system (Hewlett Packard, Palo Alto, CA; model 5890 gas chromatograph, model 5970 mass selective detector, and RTE-6 data system). The GC column was HP-5 fused silica capillary column (Hewlett Packard) with a 5% phenyl methyl silicone stationary phase. The carrier gas was helium with column head pressure of 18 psig. The GC oven temperature was 35° C, injector temperature 250° C, and gas chromatography/mass spectrometry transfer line temperature 250° C. Samples were injected using a gas-

tight syringe and 0.4-ml sample volume into a split injector operating with a 60:1 split ratio.

A stock calibration standard was prepared by weighing quantities of degradation compounds obtained from Maruishi Pharmaceutical (Osaka, Japan; compounds A, B, C, and D; fig. 1) into a volumetric flask of toluene (reagent grade, Aldrich Chemical, Milwaukee, WI) to obtain a concentration of 5 $\mu\text{g}/\text{ml}$. A standard for the fifth degradation compound [2-methoxy-2, 2-difluoro-1-(difluoromethylene) ethylether] was unavailable at the time of this study. Gas standards were prepared by injecting 0.5–15 ml of the stock solution into 125 ml gas sampling bulbs to obtain gas standards with degradation compound concentrations ranging from 2 to 50 ppm.

The gas chromatography/mass spectrometry system was programmed for analysis in the electron ionization (70 eV), selected ion monitoring mode. For compound A, the ions monitored were 69.0, 129.0, 161.0, and 180.0. For compound B, the ions monitored were 81.0, 113.0, 163.0, and 193.0. For compounds C and D, the ions monitored were 69.0, 131.0, 159.0, and 192.0. Quantitation was performed with external standard calibration using the chromatographic area of the most abundant ion. Detection limits were 1 ppm for compound A, 2 ppm for compound B, and 4 ppm for compounds C and D.

Preoperative and postoperative renal and hepatic function tests were compared using Student's *t* test. Concentrations of degradation compounds and CO₂ absorbant temperatures were compared at hourly time intervals using repeated measures ANOVA where appropriate and Student's *t* tests. All results are expressed as mean \pm SEM. *P* values less than .05 was considered significant.

Results

Of the potential sevoflurane degradation products analyzed for in this study, only one compound [fluoromethyl-

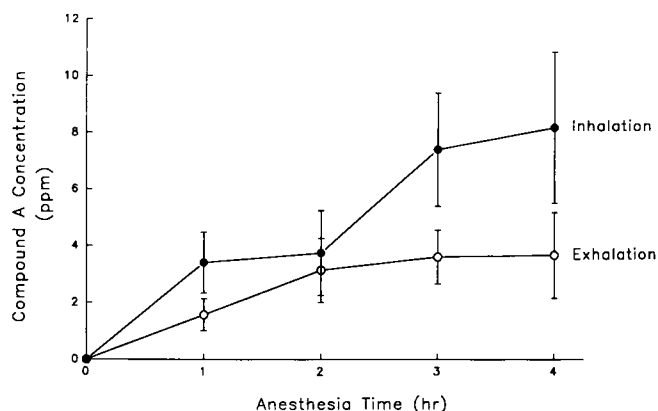


FIG. 2. Graph showing inhalation and exhalation concentrations of compound A during sevoflurane low-flow anesthesia with soda lime used as CO₂ absorbant, *n* = 8 for all time points other than 4 h where *n* = 4. Data are shown as mean \pm SEM. No significant differences occurred.

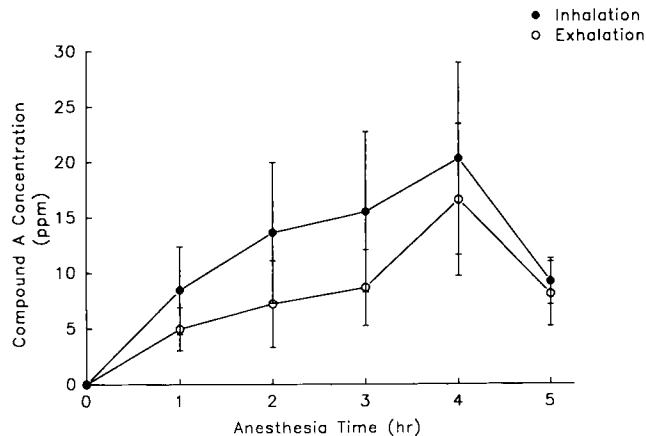


FIG. 3. Inhalation and exhalation concentrations of compound A during low-flow anesthesia using baralyme CO₂ absorbant, *n* = 8 for 1 h, 2 h, 3 h; *n* = 4 for 4 h and 5 h time points. Data are shown as mean \pm SEM. No significant differences occurred.

2, 2-difluoro-1-(trifluoromethyl) vinyl ether], designated compound A, was detectable in our low-flow anesthetic circuit. The mean maximal inhalational concentration of compound A when soda lime was utilized was 8.16 ± 2.67 ppm occurring at 4 h (fig. 2). The mean exhalational limb concentration at this time point was 3.55 ± 1.51 ppm (fig. 2). The mean maximal inhalational compound A concentration in anesthesia circuits when baralyme was used was 20.28 ± 8.67 ppm with an exhalational concentration of 8.16 ± 2.67 ppm (fig. 3). A comparison of inhalational and exhalational concentrations of compound A at hourly intervals for baralyme or soda lime groups did not attain a statistical difference. Compound A concentrations using new baralyme (25.12 ± 10.91 ; *n* = 4) were not statistically greater than those present when the baralyme had been used for at least one previous anesthetic case (6.05 ± 2.33 ; *n* = 4; table 1). Residual compound A was not detectable in the anesthetic circuit prior to anesthetic administration in any analysis.

Concentrations of compound A increased over the first 4 h of anesthesia when baralyme was the CO₂ absorbant used. The inhalation concentration of compound A with baralyme then decreased between 4 and 5 h from 20.3 ± 8.7 to 9.2 ± 2.1 ppm (fig. 3). Compound A inhalation limb concentration also increased during the first 4 h of anesthesia to a concentration of 8.2 ± 2.7 ppm when soda lime was used. Data for 5-h compound A concentration with soda lime were insufficient since only one patient in this group received anesthesia in excess of 5 h. However, the inhalation concentration of compound A in this subject was 1.85 ppm, suggesting that compound A concentrations may also decrease after 4 h of anesthesia if soda lime is utilized as the absorbant in a low-flow anesthetic circuit.

Peak temperatures produced in CO₂ absorbant when baralyme was used in the anesthetic circuit were higher

TABLE 1. Individual Patient Maximal Compound A Concentrations and Number of Absorbant Utilizations

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Soda lime group								
Compound A maximal concentration (ppm)	15.2	3.56	2.17	11.14	3.89	14.18	1.72	3.76
Prior absorbant utilizations	0	1	2	3	0	1	2	3
MAC hour	2.23	1.39	1.75	1.30	2.98	2.39	1.85	0.84
	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16
Baralyme group								
Compound A maximal concentration (ppm)	60.78	14.07	3.34	2.63	5.61	4.14	9.21	24.89
Prior absorbant utilizations	0	1	2	3	0	1	0	0
MAC hour	2.01	1.50	2.10	1.66	1.38	0.76	3.30	5.37

Compound A maximal concentration = maximum inhalational limb compound A concentration obtained in the patient anesthetic circuit based on hourly samples. Prior absorbant utilizations = the number

of prior absorbant utilizations for anesthesia with sevoflurane. MAC hour = sevoflurane MAC hour exposure for each patient.

than when soda lime was used. Mean peak temperatures with baralyme were $46.4 \pm 1.31^\circ\text{C}$ and with soda lime $37.8 \pm 1.14^\circ\text{C}$ ($P < .001$). Additionally temperatures tended to be greater if new CO_2 absorbant was used. Temperatures produced with new baralyme ($48.35 \pm 0.33^\circ\text{C}$) were greater than with baralyme, which had been used for at least one prior anesthetic case ($42.05 \pm 3.36^\circ\text{C}$; $P < .05$). Temperatures for fresh compared to used soda lime did not attain statistical difference.

The mean MAC-hour sevoflurane exposure for the baralyme group was 2.2 ± 0.5 and for the soda lime group 1.8 ± 0.2 MAC hours. The hourly mean end tidal sevoflurane concentrations for the baralyme group were 0.88 ± 0.09 , 0.91 ± 0.09 , 1.00 ± 0.13 , 1.14 ± 0.22 , and $1.09 \pm 0.24\%$ for 1, 2, 3, 4, and 5 h of anesthesia, respectively. Mean end tidal sevoflurane concentrations for the soda lime group were 0.8 ± 0.09 , 0.92 ± 0.08 , 0.92 ± 0.09 , and $1.08 \pm 0.15\%$ for hours 1, 2, 3, and 4, respectively. Mean end tidal concentrations for hourly intervals 1-4 did not differ between groups. The mean hourly fentanyl dose for the baralyme group ($1.05 \pm 0.16 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) did not differ from that in the soda lime group ($1.17 \pm 0.15 \mu \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$).

Clinical laboratory investigations obtained prior to and

after anesthesia showed no evidence of renal or hepatic dysfunction (table 2).

Discussion

To evaluate the interaction of sevoflurane with CO_2 absorbants, we studied accumulation of degradation by-products in an anesthetic circuit with total flow rate under 1 L during anesthesia in surgical patients. Because of an increased contact of exhaled gas with CO_2 absorbant during a low-flow anesthetic technique, we would predict that degradation compounds should accumulate to a greater degree using low-flow anesthesia than techniques using higher flow rates. The interaction of sevoflurane with CO_2 absorbants and production of degradation products with potential toxicity has been an area of uncertainty in the development of the drug for clinical use. To a limited extent our results show the degree to which these compounds accumulate during a low-flow anesthetic technique.

In our investigation we did not change the CO_2 absorbant with each anesthetic administration. Instead we chose to evaluate degradation product concentrations as might occur in usual anesthetic practice where CO_2 absorbant is changed only after several anesthetics. This allowed

TABLE 2. Renal and Hepatic Functions with Sevoflurane

	Preanesthesia (n = 16)	24 h Postanesthesia (n = 16)	48 h Postanesthesia (n = 11)
Sodium (mmol/L)	140 ± 1	138 ± 1*	138 ± 1*
Chloride (mmol/L)	105 ± 1	105 ± 1	104 ± 1
Osmolality (serum) (mosm/kg)	289 ± 1	282 ± 4	280 ± 2*
BUN (mg/dL)	13 ± 1	9 ± 1*	10 ± 1*
Creatinine (mg/dL)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.04
Total bilirubin (mg/dL)	0.60 ± 0.1	0.70 ± 0.1	.75 ± 0.1
Direct bilirubin (mg/dL)	0.23 ± 0.02	0.23 ± 0.02	.25 ± 0.03
AST (SGOT) (IU/L)	26 ± 2	32 ± 3	34 ± 4
ALT (SGPT) (IU/L)	22 ± 3	23 ± 4	21 ± 4
Alkaline phosphatase (IU/L)	73 ± 5	61 ± 5	64 ± 6

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

shown as mean ± SEM.

* Differs from preoperative value ($P < .05$)

TABLE 3. CO₂ Absorbant Compositions Utilized in Sevoflurane Low-flow Anesthetics

	Sodasorb	Baralyme
Calcium hydroxide [Ca(OH) ₂] (%)	76.5	69.0
Potassium hydroxide (KOH) (%)	2.25	4.6
Sodium hydroxide (NaOH) (%)	2.25	—
Barium hydroxide [Ba(OH) ₂] (%)	—	10.4
Sodium silicate (%)	—	2.1
Water (%)	18.9	13.75
pH indicator (%)	0.06	0.15

evaluation of degradation product production with both fresh and used CO₂ absorbant as well as analysis of gases for possible residual accumulated degradation products within the anesthetic circuit. No compound A was detectable within the anesthetic circuit prior to the next anesthetic administration.

Another important aspect of this study is the concentration of sevoflurane used. We delivered sevoflurane in 50% oxygen and 50% nitrous oxide. The concentrations of sevoflurane used were those required for surgical anesthesia in our patients and ranged from 0.3 to 2.0% end tidal concentrations (MAC = 2.05%).⁶ The mean hourly end tidal anesthetic concentrations and MAC-hour exposure between the two absorbant groups did not differ. Therefore, although end tidal concentrations varied and were frequently adjusted during the anesthetic, the groups were comparable in terms of amount and concentrations of sevoflurane to which they were exposed.

Higher degradation product levels can be obtained using higher sevoflurane concentrations. This has been shown by Hanaki *et al.*⁵ in both a closed or semi-closed anesthetic circuit using a model lung with soda lime. They found approximately 14 ppm compound A produced in a closed anesthetic circuit using 2.7% sevoflurane compared to 5 ppm produced when 1.7% sevoflurane was used. Compound A is a contaminant of sevoflurane produced during the manufacturing process. The sevoflurane utilized in our study contained 1–2 ppm concentration of compound A.

Our results are comparable in several aspects to those from initial studies by other investigators studying sevoflurane degradation with CO₂ absorbants *in vitro*. Liu *et al.*⁴ found that when sevoflurane was combined with soda lime or baralyme a greater loss of sevoflurane occurred when exposed to baralyme, suggesting greater degradation. They interpreted their results to suggest a greater (fourfold) rate of degradation by baralyme than soda lime. Our results suggest this difference but to a much lesser degree. Our concentrations of compound A in baralyme were slightly greater than twice those occurring in the presence of soda lime. The two studies also agree that higher absorbant temperatures occurred when sevoflurane was exposed to baralyme compared to those produced when soda lime was utilized. In addition, in the present

study, fresh baralyme produced higher temperatures and tended to produce higher concentrations of compound A. A recent *in vitro* investigation by Wong and Lerman⁷ also showed that the disappearance of sevoflurane was greater in the presence of fresh as compared to used baralyme suggesting that sevoflurane degradation is enhanced with fresh absorbant. Sevoflurane is also absorbed by soda lime and baralyme in addition to the process of degradation.⁴ Though we did not attempt to measure absorption in our study, the results of Lui *et al.*⁴ suggest most absorption occurs within the first 20 min of anesthetic administration.

In our study, as in that of Lui *et al.*,⁴ Sodasorb (W. R. Grace) was the brand of soda lime used. It should be noted however, that several brands of soda lime are available that vary somewhat in their constituents and may differ in their ability to produce sevoflurane degradation. In addition there may be minor variations in the ingredient percentiles for any given brand from one absorbant lot to another. These differences generally occur in water percentile or minor variations in calcium hydroxide content as a result of incomplete conversion from calcium oxide. The ingredient percentiles for both Sodasorb and baralyme utilized in this study are shown in table 3.

Although inhalation concentrations of compound A with baralyme tended to be higher than those with soda lime, we were unable to show a statistical difference. This likely resulted from our small population size (n = 8, each group) which may have produced a type II or β error. One patient (9) in the baralyme group (table 1) had a high concentration of compound A, producing a large standard error. Additionally inhalation concentrations had a large range of values since both fresh and used absorbant studies were included. Our inability to detect a difference between fresh and used absorbant compound A concentrations likely resulted from similar hindering circumstances. Thus, although our results suggest compound A concentrations are higher when fresh absorbant is present, a larger population would be required to establish those results.

The concentrations of compound A in the exhalation limb of the anesthetic circuit were generally lower than those of the inhalation limb. This result suggests that some compound A is removed from the inhalation gases and absorbed by the patient during sevoflurane anesthesia.

Another interesting aspect of our results was that after 4 h of exposure of sevoflurane to baralyme the concentration of compound A declined. This result has also been noted by Hanaki *et al.*⁵ in a closed anesthetic circuit using a model lung and Morio *et al.*¹¹ in a similar anesthetic circuit with soda lime. Therefore, throughout a sevoflurane anesthetic administration using low-flow or closed circuit technique, a patient is exposed to a rising and potentially

¹¹ Personal communication. October 1991.

declining concentration of compound A dependent on the length of the anesthetic. The cause of declining degradation product concentration is not known. However, it possibly results from change in absorbant composition or interactive surface available for formation of compound A. Our data suggest degradation compound concentration may vary depending on whether new or used absorbant is present. This lends further credence to the hypothesis that a change in the absorbant may occur over time leading to a lower compound A concentration.

Results from this investigation combined with those of previous investigations allow us to predict that the following factors may lead to increased compound A concentrations during sevoflurane anesthesia: 1) low flow or closed circuit anesthetic techniques, 2) the use of baralyme rather than soda lime, 3) higher concentrations of sevoflurane in the anesthetic circuit, 4) higher absorbant temperatures, and 5) fresh absorbant. Other factors such as a longer anesthetic administration may lead to a greater mass exposure but not necessarily higher maximal concentrations of degradation compounds.

In our study using a low-flow system we found only one degradation product produced (compound A). This compound has been noted by other investigators to be produced in the highest concentrations of any potential breakdown product. Now that we have evaluated the concentrations of this compound in a low-flow anesthetic circuit we require information regarding concentrations required to produce toxic effects and organs affected by compound A toxicity. Recently Morio *et al.*⁸ investigated the toxicity of compound A was studied in Wistar rats. They found the inhalation toxicity (LC₅₀) of compound A was 1,050–1,090 ppm after a 1-h exposure. They determined the 3 h LC₅₀ to be 340–490 ppm. Toxicity noted was renal tubular degeneration and necrosis as well as lung congestion and hyperemia in the rats following lethal doses of compound A. Chronic toxicity was studied using 3-h exposures, 3 days per week for 8 weeks, using 30, 60, or 120 ppm. No effects occurred in these chronic exposures other than a loss of body weight in females exposed to 120 ppm on the final days of study. Although toxicity requirements in animals and humans are not directly comparable, concentrations of compound A required for acute toxicity in rats exposed for 3-h duration were 40 times (soda lime) or 17 times (baralyme) greater than the mean maximal concentrations produced in our low-flow circuits. The highest concentration used in chronic exposure studies by Morio *et al.* that produced no effect was six times higher than the mean maximal concentration found in the anesthetic circuit in our study and two times higher than the maximal compound A concentration achieved in any of our patient circuits. Although we did not specifically investigate the possibility of pulmonary toxicity, there was no clinical evidence of any respiratory abnormality in any patient. We observed no organotox-

icity in any of our patients studied. There were no elevations of hepatocellular enzymes and no changes in BUN or creatinine levels.

As noted in table 1, the maximal inhalational concentration of compound A varied among the patients studied. This was because of the use of two different absorbants as well as fresh and used absorbant material. Patient 9 achieved a maximal concentration of compound A in the anesthetic circuit that was higher than values seen with other subjects. The reasons for the higher level in this patient are not clear. Fresh baralyme was utilized during the anesthesia for this patient which may lead to greater degradation. However, sevoflurane concentrations in the circuit and absorbant temperature (47.6° C) were not disproportionately greater when compared to other study cases. It is unknown how the variable of patient uptake of compound A affects the levels of compound A in the anesthetic circuit. All hourly compound A concentrations in the inhalation circuit were somewhat elevated in this patient (1 h = 37.3 ppm, 2 h = 59.4 ppm, 3 h = 60.7 ppm, 4 h = 46.6 ppm, 5 h = 14.2 ppm), and therefore we have no evidence the maximal concentration achieved was spurious. This patient displayed no evidence of toxicity from this concentration of compound A. Theoretic calculations indicate that the mean 3-h duration level of compound A for this patient (56 ppm) was 16% of LC₅₀ in rats. This concentration produces no pathologic changes in animals even when delivered in multiple dosing. However, because of this single observation, larger studies may be required to investigate the possibility of sporadically high compound A concentrations occurring with low-flow sevoflurane anesthesia.

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