

Effects of the Water Content of Soda Lime on Compound A Concentration in the Anesthesia Circuit in Sevoflurane Anesthesia

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Background: Sevoflurane anesthesia is usually performed with fresh gas flow rates greater than 2 l/min due to the toxicity of compound A in rats and limited clinical experience with sevoflurane in low-flow systems. However, to reduce costs, it would be useful to identify ways to reduce compound A concentrations in low-flow sevoflurane anesthesia. This goal of this study was to determine if compound A concentrations can be reduced by using soda lime with water added.

Methods: Low-flow sevoflurane anesthesia (fresh gas flow of 1 l/min) was performed in 37 patients using soda lime with water added (perhydrated soda lime) or standard soda lime as the carbon dioxide (CO₂) absorbent. The soda lime was not changed between patients, but rather was used until CO₂ rebreathing occurred. The perhydrated soda lime was prepared by spraying 100 ml distilled water onto 1 kg fresh soda lime, and water was added only when a new bag of soda lime was placed into the canister. Compound A concentrations in the circle system, soda lime temperatures, inspired and end-tidal CO₂ and end-tidal sevoflurane concentrations, and CO₂ elimination by the patient were measured during anesthesia.

Results: Compound A concentrations were significantly lower for the perhydrated soda lime (1.9 ± 1.8 ppm; means \pm SD) than for the standard soda lime (13.9 ± 8.2 ppm). No differences were seen between the two types of soda lime with regard to the temperature of the soda lime, end-tidal sevoflurane concentrations, or CO₂ elimination. Compound A concentration decreased with the total time of soda lime use for both types of soda lime. The CO₂ absorption capacity was significantly less for perhydrated soda lime than for standard soda lime.

Conclusions: Compound A concentrations in the circuit can

be reduced by using soda lime with water added. The CO₂ absorption capacity of the soda lime is reduced by adding water to it, but this should not be clinically significant. (Key words: Low-flow anesthetic circuit; carbon dioxide absorbent; degradation product; exhaustion of soda lime.)

SEVOFLURANE reacts with soda lime, resulting in the generation of fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether (compound A),¹ which has been reported to be toxic in rats.²⁻⁶ Because the compound A concentration in the anesthesia circuit is higher in low-flow sevoflurane anesthesia than in relatively high-flow anesthesia at flow rates of 3 to 6 l/min,^{7,8} there has been some controversy regarding the safety of low-flow sevoflurane anesthesia. Current US Food and Drug Administration recommendations state that fresh gas flow rates less than 2 l/min in a circle absorber system are not recommended. However, the use of inhalational anesthetics at low flow rates is economically desirable. Thus it would be useful to identify ways to minimize the concentration of compound A during low-flow sevoflurane anesthesia.

It has been suggested that the factors affecting the compound A concentration in the anesthetic circuit are the sevoflurane concentration^{2,9}; carbon dioxide (CO₂) elimination by the patient⁸; ventilation⁸; the fresh gas flow rate^{7,8}; and the temperature,^{10,11} type,^{9,12} freshness,^{12,13} and the water content of the CO₂ absorbent.^{10,13,14} Of these factors, decreasing the water content of the CO₂ absorbent is associated with an increase in compound A formation.^{10,13,14} Conversely, increasing the water content of the CO₂ absorbent (adding water) might be expected to decrease the compound A concentration in the anesthesia circuit.

Our purpose of this study was to determine whether adding water to the soda lime might serve as a simple and effective method to reduce the compound A concentration in low-flow sevoflurane anesthesia, and to determine whether the CO₂ absorption capacity of soda lime is affected by the addition of water. Because the

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experimental conditions used in the study were chosen to accurately reflect routine clinical anesthesia, the soda lime was not changed for every patient, but rather was used until it was exhausted and CO₂ rebreathing occurred.

Materials and Methods

This study was approved by the Committee on Human Research of our institution, and informed consent was obtained from all patients. Thirty-seven patients classified as American Society of Anesthesiologists physical status I or II who were scheduled for general anesthesia were studied.

Premedication included 50 mg hydroxyzine and 0.5 mg atropine, injected intramuscularly 45 min before the anesthesia was induced by administration of 100% oxygen followed by 4–5 mg/kg thiopental, 50–100 µg fentanyl, and 0.10–0.15 mg/kg vecuronium. After tracheal intubation, the flow rates of oxygen and nitrous oxide were set to 300 ml/min and 700 ml/min, respectively. Anesthesia was maintained with sevoflurane (usually 1%–3%) in oxygen and nitrous oxide. The fresh gas flow rate was set to 1 l/min, and the ratio of the oxygen and nitrous oxide flow rates was adjusted to maintain the oxygen concentration in the inspiratory limb above 30%. The sevoflurane concentration was adjusted to maintain systolic blood pressure within $\pm 20\%$ of baseline. Hypertensive responses that were not controlled at the maximum concentration of inhaled sevoflurane were treated by bolus injection of 50–100 µg fentanyl. The lungs were ventilated mechanically with a tidal volume of 10–12 ml/kg, with the ventilatory rate adjusted to maintain an end-tidal CO₂ concentration (partial pressure) of 30–40 mmHg. After completion of the surgical procedure, sevoflurane and nitrous oxide were discontinued and 100% oxygen was administered at 8 l/min. After the patient regained an adequate level of consciousness, the tracheal tube was removed.

The anesthesia machine used was a Modulus CD Anesthesia System (Ohmeda, Madison, WI), and this system was used exclusively for this study. Soda lime (Sodasorb II; W.R. Grace, Lexington, MA), to which additional water was added (perhydrated soda lime) or without water added (standard soda lime), was used as the CO₂ absorbent. The type of soda lime to be used (perhydrated or standard) was selected by drawing lots, and the soda lime selected was used repeatedly until exhaus-

tion. One kilogram fresh soda lime (weight before the addition of water for perhydrated soda lime) was placed into the upper canister, and glass balls were placed into the lower canister as filler. Soda lime was not changed for each patient but was left in the canister until the first anesthesia during which CO₂ rebreathing was observed was completed, at which time the soda lime was replaced with either fresh perhydrated or standard soda lime, selected by drawing lots. This procedure was repeated six times in total to obtain data for three trials each for perhydrated and standard soda lime in a randomized manner. The study was performed on consecutive days, excluding weekends. The perhydrated soda lime was prepared by spraying 100 ml distilled water onto 1 kg fresh soda lime as evenly as possible using a sprayer before the soda lime was placed into the canister. Water spraying was performed only when a new bag of soda lime was added to the canister (not for anesthesia of each patient). The water content in each batch of soda lime was determined before the experiment by calculating the change in weight after drying.

To monitor the temperature of the soda lime, two temperature probes (temperature probe model 9182; Hioki Electric, Nagano, Japan) were inserted into the centers of the top and bottom of the upper canister. The temperature was recorded every 15 min.

During anesthesia, inspired and end-tidal CO₂ concentrations and inspired and end-tidal sevoflurane concentrations were monitored by mass spectrometry (Medical Gas Analyzer 1100; Perkin-Elmer, Pomona, CA). The volume of CO₂ eliminated by the patient was calculated as minute expired volume times mean expired CO₂ concentration. Minute expired volume was measured using a linearized electronic Wright respirometer (BOC Medishield, Essex, UK). Mean expired CO₂ concentration was obtained using a bypassed minimixing chamber and then measured by mass spectrometry.¹⁵ These data were recorded at 1-min intervals.

Sample gas for the measurement of compound A was collected from the inspiratory limb of the circle system and analyzed immediately at our hospital. The concentration of compound A was measured every hour in each patient using a gas chromatograph (model GC-9A; Shimadzu, Kyoto, Japan) equipped with a gas sampler (model MGS-5, Shimadzu). For gas chromatography, the column temperature was maintained at 100°C and the injection inlet temperature was maintained at 140°C. Nitrogen was used as the carrier gas at a flow rate of 50 ml/min. The detector was a hydrogen flame ion detector. The glass column was 5 m long and 3 mm in

internal diameter and filled with 20% DOP Chromosorb WAW (Technolab S.C. Corp., Osaka, Japan) 80/100 mesh. The gas chromatograph was calibrated with standard calibration gas prepared from stock solutions of compound A (Maruishi Pharmaceutical Co., Osaka, Japan).

Statistical Analysis

All values are expressed as means \pm SD. The compound A concentration, as well as the temperature of the soda lime, the end-tidal sevoflurane concentration, and the volume of CO₂ elimination at the corresponding time points were compared between perhydrated and standard soda lime using the unpaired Student's *t* test.

The CO₂ absorption capacity of each type of soda lime was evaluated by the sum of low-flow anesthesia time (CO₂ absorption capacity [h]) and the sum of the volume of CO₂ eliminated by the patients (CO₂ absorption capacity [l/kg absorbent]) until 1 mmHg of CO₂ was detected in the inspiratory limb (the occurrence of CO₂ rebreathing). The CO₂ absorption capacity was compared between the two types of soda lime using Mann-Whitney's *U* test. Probability values less than 0.05 were considered significant.

Results

Among the degradation products of sevoflurane, only compound A was detected. The compound A concentration at all data points was significantly lower for the perhydrated soda lime than for the standard soda lime (table 1). No significant difference in the temperature of the soda lime was observed between the two types of soda lime (table 1). The end-tidal sevoflurane concentration and patient CO₂ elimination did not differ significantly between the two types of soda lime (table 1). There was no correlation between the compound A concentration and the end-tidal sevoflurane concentration for the perhydrated soda lime, but there was positive correlation for the standard soda lime (fig. 1). There was positive correlation between the compound A concentration and the temperature of the soda lime for both types of soda lime (fig. 2). There was a negative correlation between the compound A concentration and the total time of soda lime use for both types of soda lime (fig. 3). There was no correlation between the compound A concentration and patient CO₂ elimination or between patient CO₂ elimination and the temperature of the soda lime (data not shown).

Table 1. Compound A Concentration, Temperature of the Soda Lime, End-tidal Sevoflurane Concentrations, and CO₂ Elimination

	Perhydrated Soda Lime (n = 67)	Standard Soda Lime (n = 71)
Compound A concentration (ppm)	1.9 \pm 1.8* (0.1–7.4)	13.9 \pm 8.2 (1.0–28.3)
Temperature of soda lime (°C)	38.4 \pm 3.2 (30.8–43.1)	39.5 \pm 4.6 (29.6–47.2)
End-tidal sevoflurane concentration (%)	2.0 \pm 0.7 (0.8–4.3)	2.0 \pm 0.7 (0.7–4.1)
CO ₂ elimination (ml/min)	122 \pm 24 (66–179)	127 \pm 23 (81–192)

"n" represents the number of data points. Data shown were obtained every 1 h beginning 1 h after the start of anesthesia in each patient. Values shown are mean \pm SD (range).

* Significantly lower than for the standard soda lime.

The perhydrated soda lime in trials 1, 2, and 3 was used for 8, 7, and 5 patients, respectively (table 2). The standard soda lime in trials 1, 2, and 3 was used for 5, 7, and 5 patients, respectively (table 2). The CO₂ absorption capacity (h) was significantly shorter for the perhydrated soda lime than for the standard soda lime (table 2). The CO₂ absorption capacity (l/kg absorbent) was significantly lower for the perhydrated soda lime than for the standard soda lime (table 2). The water content of the perhydrated soda lime measured before the experiment was 25.2% \pm 0.6%, and that of the standard soda lime was 18.1% \pm 0.1%.

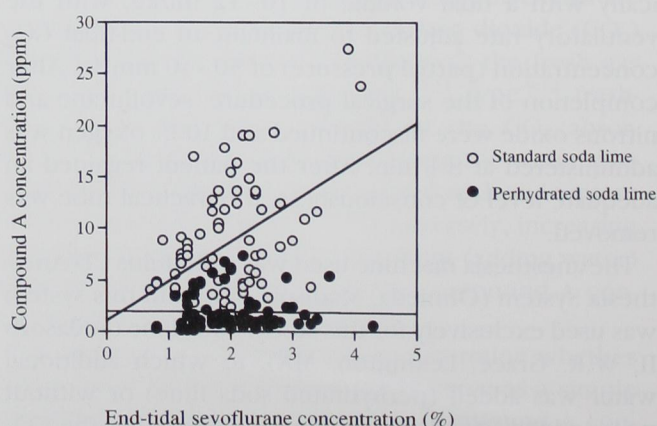


Fig. 1. Relation between compound A concentration and end-tidal sevoflurane concentration for perhydrated soda lime ($r^2 = 0.000$; $P = 0.885$) and for standard soda lime ($r^2 = 0.227$; $P < 0.001$).

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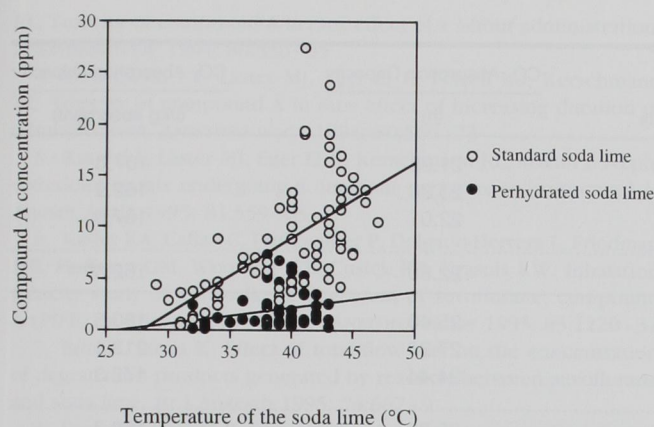


Fig. 2. Relation between compound A concentration and the temperature of the soda lime for perhydrated soda lime ($r^2 = 0.072$; $P = 0.027$) and for standard soda lime ($r^2 = 0.370$; $P < 0.001$).

Discussion

In sevoflurane anesthesia, the factors that have been suggested to affect the concentration of compound A in the anesthesia circuit are (1) the sevoflurane concentration,^{2,9} (2) CO₂ elimination by the patient,⁸ (3) ventilation,⁸ (4) the fresh gas flow rate,^{7,8} (5) the temperature of the CO₂ absorbent,^{10,11} (6) the type of CO₂ absorbent,^{9,12} (7) the freshness of the CO₂ absorbent,^{12,13} and (8) the water content of the CO₂ absorbent.^{10,13,14} Considering the utility of each of these factors in reducing the concentration of compound A in clinical anesthesia, factors 1–3 are determined by the patient; factor 4 is

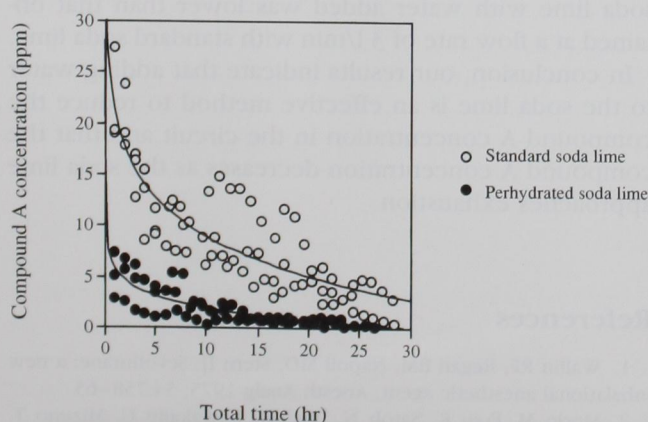


Fig. 3. Relation between compound A concentration and the total time of soda lime use for perhydrated soda lime ($r^2 = 0.639$; $P < 0.001$) and for standard soda lime ($r^2 = 0.750$; $P < 0.001$).

limited if anesthesia is to be performed at low flow rates; factor 5 has been investigated by cooling the canister in an ice-water bath¹¹ but has been found to be impractical; factor 6 is limited because even Sodasorb, which produces the least amount of compound A, increases the compound A concentration to more than 20 ppm^{9,16,17}; factor 7 is unrealistic because it is not possible to use exhausted soda lime at all times; and factor 8 is worthy of serious investigation.

There have been no studies of the effects of the water content of the CO₂ absorbent on the compound A concentration in the anesthesia circuit in clinical practice. It has been reported that CO₂ absorbent with a higher water content is less reactive with sevoflurane *in vitro*.¹⁰ Our results showed that the concentration of compound A in the circuit is reduced when water is added to the soda lime, and they correspond with the findings of *in vitro* studies.^{10,13,14} Spraying water onto the soda lime may reduce the structural integrity of the soda lime (e.g., surface dissolution of the alkali salt and occlusion of pores). These physical alterations of the soda lime could inhibit the increase in compound A concentration in the anesthesia circuit.

In previous studies, we reported that the concentration of compound A decreased after 10 h of sevoflurane anesthesia,^{9,16,17} suggesting that the production of compound A decreases as the soda lime approaches exhaustion. In the present study, figure 3 also indicates that the compound A concentration decreased as the soda lime approached exhaustion. This may be because depletion of the total base content by CO₂ absorption leads to lower levels of compound A in exhausted soda lime. Further, this is thought to be due to the production of water resulting partly from the reaction between the CO₂ and the absorbent and partly from exhaled moisture, which affects the soda lime.^{10,13,14}

Fresh soda lime contains 15–20% water, which provides the maximum CO₂ absorption capacity and rate of CO₂ absorption. The perhydrated soda lime we prepared in this study contained 25% water. To evaluate the differences in CO₂ absorption capacity of the two types of soda lime (perhydrated and standard), we calculated the sum of low-flow anesthesia time and the sum of the volume of CO₂ eliminated by the patients until the occurrence of CO₂ rebreathing. The latter reflects the CO₂ volume that the soda lime could absorb in a closed circuit and serves as a good reference value for low-flow systems. Our data showed that the CO₂ absorption capacity of soda lime is decreased by adding water, but that this decrease is trivial and appears to

Table 2. CO₂ Absorption Capacity

	Soda Lime Trial	Number of Patients	CO ₂ Absorption Capacity	CO ₂ Absorption Capacity
			(h)	(l/kg absorbent)
Perhydrated soda lime	1	8	21.93	157.6
	2	7	23.86	162.9
	3	5	22.01	167.0
	mean		22.60*	162.5*
Standard soda lime	1	5	25.46	180.6
	2	7	27.36	213.1
	3	5	24.44	172.3
	mean		25.75	188.7

Number of patients = the number of patients for which the same soda lime was used. CO₂ absorption capacity (h) = the sum of low-flow anesthesia times until the occurrence of CO₂ rebreathing. CO₂ absorption capacity (l/kg absorbent) = the sum of the volume of CO₂ eliminated by the patients until the occurrence of CO₂ rebreathing.

* Significantly less than for the standard soda lime.

be outweighed by the decrease in the compound A concentration in the circuit. In addition, the method used to add water was simply to spray the soda lime with water using a sprayer when the soda lime was exchanged, and this procedure did not need to be repeated for each patient. Taking all these factors into consideration, we conclude that this method should prove practical in clinical use. However, it cannot be assumed that soda lime manufactured with a high water content will provide the same results as the soda lime we prepared in this study, and further studies are required to clarify this point.

In the present study, the soda lime was not changed for every patient because our objective was to measure the compound A concentration under experimental conditions mimicking routine clinical anesthesia and because no studies have measured the compound A concentration when the same soda lime was used for more than 5 patients. One possible risk that we anticipated was an increase in the degradation products of compound A over time, resulting in increases in the compound B, C, D, and E concentrations in the anesthesia circuit. However, this phenomenon was not observed in our study. Compounds B, C, D, and E were not detected, and the compound A concentration in the circuit decreased as the soda lime was used for a prolonged period.

Glass balls were placed into the lower canister as filler in this study. This was because exhaustion of the soda lime could be achieved more readily if only a single canister was used. The compound A concentration is

essentially unaffected by the amount of soda lime used.¹⁰ Therefore, we expect that similar results would have been obtained even if soda lime had been placed into both canisters.

The Food and Drug Administration recommends that sevoflurane anesthesia be performed at flow rates greater than 2 l/min. When fresh soda lime is used, the compound A concentration at a fresh gas flow rate of 3 l/min is 8.1 ± 2.7 ppm.⁷ In the present study, even at a low flow rate of 1 l/min, when water was added to the soda lime, the compound A concentration was 1.9 ± 1.8 ppm, with a maximum value of 7.4 ppm for all measurement points. Therefore, the compound A concentration at a fresh gas flow rate of 1 l/min using soda lime with water added was lower than that obtained at a flow rate of 3 l/min with standard soda lime.

In conclusion, our results indicate that adding water to the soda lime is an effective method to reduce the compound A concentration in the circuit and that the compound A concentration decreases as the soda lime approaches exhaustion.

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