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Inhibition of Volatile Sevoflurane Degradation Product Formation in an Anesthesia Circuit by a Reduction in Soda Lime Temperature

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Background: **Sevoflurane reacts with carbon dioxide absorbents, such as soda lime, to release the volatile products compounds A and B. These two products, which have been detected in anesthesia circuits, are among five formed when sevoflurane is degraded by soda lime at increased temperature; the others, compounds C, D, and E, have been detected only in heated sealed systems. The current study attempted to determine the influence of soda lime temperature on compounds A and B generation in an anesthesia circuit and whether a decrease in soda lime temperature could eliminate product formation in the circulating gases.**

Methods: **Sevoflurane (1.5% in oxygen) was circulated (6 l/min) in a partially closed, low-flow (215 ml/min fresh gas) anesthesia circuit that included a canister containing 1.2 kg fresh soda lime. Carbon dioxide was introduced into the circuit at 200 ml/min, and gas samples for analysis of sevoflurane, compounds A, B, C, and D, and carbon dioxide were taken at the opening of an attached artificial lung. The circuit was operated for 8 h under conditions whereby the soda lime temperature could increase freely or the soda lime was chilled with ice.**

Results: **A maximum core soda lime temperature of about 46°C was measured when the experiment was run under conditions whereby the soda lime temperature was allowed to increase. Compounds A and B increased with time to a maximum of 23 and 9 ppm, respectively. At 4.5 h of circuit operation, compound C/D was found. Chilling of the soda lime canister, which produced a maximum core soda lime temperature of 26°C, resulted in neither compound B nor C/D being detected during the 8-h period. Compound A was present in the circuit at all times at approximately 10 ppm; however, its concentration did not increase as occurred when the experiment was conducted under nonchilled conditions. Carbon dioxide levels at the opening of the lung remained at a constant 5% for 8 h with or without soda lime chilling.**

Conclusions: **This study demonstrates that the release of volatile sevoflurane degradation products in an anesthesia circuit is highly dependent on soda lime temperatures. A reduction of the temperature of soda lime may be a feasible method of preventing the release of significant levels of sevoflurane degradation products without interfering with carbon dioxide absorption or altering the sevoflurane concentration. (Key words: Anesthetics, volatile. Compound A. Compound B. Degradation. Sevoflurane.)**

THE use of sevoflurane in anesthesia rebreathing circuits is associated with the production of small concentrations of volatile sevoflurane degradation products (fig. 1) that are potentially toxic to the patient if present in sufficiently high concentrations.[1–5] Morio *et al.* indicate that compound A has an LC_{50} of 420 ppm in male rats exposed for 3 h, whereas compound B appears to be much less toxic.[2] These compounds are released in the circuit when sevoflurane contacts the highly basic carbon dioxide absorbents, such as soda lime or Baralyme, and undergoes base-dependent degradation. The product formed to the greatest degree is compound A, and that formed to the second greatest degree is compound B[4]: Up to 61 ppm compound A[1] and up to 2 ppm compound B have been detected in anesthesia circuits.[2,4] Other products have not been reported in anesthesia circuits; however, heating (40–50°C) of sealed systems containing sevoflurane and soda lime for several hours produces, in addition to compounds A and B, the *cis*- and *trans*-isomers compounds C and D and compound E.[4,6]

The release of compounds A and B in anesthesia circuits is an undesirable consequence of sevoflurane administration. Although the use of high fresh gas-flow rates can facilitate their removal to lower circulating levels, no practical methods of preventing their formation or effecting their removal from a circuit in low-flow systems have been developed. The chemical reactions of sevoflurane with base are influenced to various degrees by sevoflurane concentration, duration of sevoflurane exposure to the absorbent, quantity of ab-

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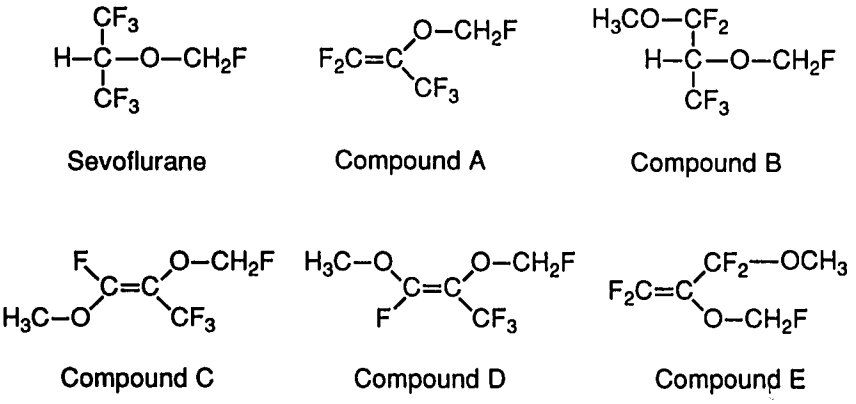

Fig. 1. Chemical structures of sevoflurane and the volatile sevoflurane degradation products.

sorbent used, absorbent temperature,[7,8] and absorbent water content.[9,10] Among these factors, only carbon dioxide absorbent temperature can be controlled independently as a means of inhibiting sevoflurane degradation when sevoflurane is administered to patients from conventional anesthesia machines.

The possibility that absorbent temperature plays a significant role in sevoflurane degradation, and that this may be a point of intervention, is suggested by two relevant facts. In sealed flasks containing sevoflurane and soda lime, increasing temperatures from ambient to as great as 120°C markedly increases the quantities of products generated.[2,4,6] Second, temperatures of the absorbents in anesthesia circuits normally increase to well above ambient.[1,2] In anesthesia circuits, mean peak temperatures in the carbon dioxide absorbing canisters are reported to be 38–48°C when they contain soda lime.[1,2,8,10]

In view of the influence of temperature on sevoflurane degradation, the objective of this study was to determine whether a reduction in carbon dioxide absorbent temperature can significantly reduce circulating sevoflurane degradation products in anesthesia circuits. To accomplish this, the quantity of products released in a low-flow anesthesia circuit with soda lime was compared to that in the same circuit in which soda lime was maintained at reduced temperatures by external cooling. Soda lime chilling was performed by immersing the soda lime canister on the anesthesia machine in an ice bath. The effects of reduced absorbent temperature on carbon dioxide absorption also were determined.

Materials and Methods

Chemicals

Sevoflurane was a gift from Abbott Laboratories (Abbott Park, IL). Soda lime (Sodasorb, 14%–19% moisture content), the carbon dioxide absorbent, was obtained from W. R. Grace (Atlanta, GA). Lithium bis(trimethylsilyl) amide (1.0 M in tetrahydrofuran) was purchased from Sigma Chemical Co. (St. Louis, MO), and sodium methoxide was from Aldrich Chemical Co. (Milwaukee, WI).

Preparation of Compounds A and B

Compounds A and B were synthesized from sevoflurane essentially as described by Huang *et al.*[11] Compound A was synthesized starting with 3.0 g (15 mmol) sevoflurane, which was reacted with lithium bis(trimethylsilyl) amide (17 mmol) in tetrahydrofuran to produce crude compound A. The crude pot-to-pot distillation product (approximately 10% compound A) was fractionally distilled at atmospheric pressure to afford four fractions ranging from 30% to 45% compound A. The highest purity fraction, obtained at 46°–48.5°C, was further purified by preparative gas chromatography. The partially purified fraction containing compound A was injected into a gas chromatograph, and the eluted compound A fraction was collected from the column (through the inactive detector) at approximately 17 min. The compound was collected in a customized Teflon tube trap immersed in liquid nitrogen. Compound A was obtained in >98% purity.

Preparative gas chromatography for compound A was performed on a Hewlett Packard (Palo Alto, CA) 3830A gas chromatograph using a glass column (6 m × 4 mm ID) packed with Carbopack C/0.1% SP-1000 (Supelco, Bellefonte, PA). The injector temperature was 100°C, the oven was 55°C, the (unlit FID) detector was 75°C, and the carrier gas (helium) flow rate was 22 ml/min.

Compound B was synthesized by the reaction of sevoflurane with methanolic sodium methoxide.[11] The crude product was vacuum-distilled to afford com-

pound B in 92% purity with a 51% yield. Trapping of the distillate was improved by immersing the collection flask in liquid nitrogen.

Reaction of Sevoflurane with Soda Lime in Sealed Vials

To generate the additional sevoflurane degradation products, soda lime (0.5 g) was placed in a 10-ml hypovial. The vial was sealed and evacuated. Sevoflurane (40 μl) was injected into the vial, and atmospheric pressure was restored using a syringe. The vial was heated in a 120°C oven for 40 min. After cooling to room temperature, samples of headspace gas (100 μl) were withdrawn and analyzed by gas chromatography or by gas chromatography/mass spectrometry.

Anesthesia Circuit

An anesthesia circuit was set up and operated with a constant sevoflurane concentration and no patient in the system. An anesthesia machine (Foregger model F500, Hauppauge, NY) was outfitted with a 3-l rubber bag, which served as a model lung, and polypropylene corrugated connecting tubing (hyperinflation bag system, Marquest, Englewood, CO). Fresh Sodasorb (1.2 kg) was used in each experiment. The temperature inside the carbon dioxide absorbent was monitored with a Digi-Sense model 8528-40 thermocouple (Cole-Parmer, Chicago, IL). The probe was identically placed for each experiment in the center of the canister midway between the upper and lower canister chambers. Carbon dioxide concentrations were continuously monitored with a Datex (Helsinki, Finland) model 254 Airway Gas Monitor, which sampled the gas (minimum rate, 200 ml/min) from a port immediately atop the rubber lung. The gas exiting the monitor served as the vent for the circuit, which was otherwise sealed. The gas was circulated using the attached Foregger ventilator. Gas samples (400 μl) for sevoflurane and sevoflurane degradation product determinations were withdrawn *via* a gas-tight syringe through a septum covering a port at the neck of the rubber lung.

To initiate each experiment, the circuit was flushed thoroughly with 100% O_2 until no residual compounds A or B were present from prior trials. Sevoflurane vapor in oxygen (~40 ml/min) was introduced from a copper kettle and further mixed with oxygen to give a total flow input of 215 ml/min. The anesthetic gases were circulated at a rate of 6 l/min (500 ml per stroke, 12 strokes/min). A stable concentration of 1.5% sevoflurane (vol/vol) in oxygen, as determined by gas chromatographic analysis, was attained in about 35 min. A flow of 200 ml/min carbon dioxide (100%) was started. Initiation of carbon dioxide flow was taken as time 0. To determine sevoflurane degradation in a nonchilled circuit, the temperature of the soda lime was allowed to rise freely. For experiments to determine the effect of reduced soda lime temperature on product formation, the carbon dioxide absorbent canister was immersed in an ice bath (2°C) to within 2 inches of the top of the canister, a position that placed all soda lime below the surface of the ice water. Chilling of the canister was started after sevoflurane concentrations were stabilized, and it was chilled for 10 min before the initiation of the carbon dioxide flow. The ice bath was maintained in place throughout the 8-h experiment. Gas samples were taken every 30 min in all experiments. As controls, similar experiments using nonchilled circuits were performed without the introduction of carbon dioxide into the circuit or without soda lime in the canister.

Analysis of Sevoflurane Degradation Products

Gas chromatographic analysis of sevoflurane and sevoflurane degradation products was performed with a Hewlett Packard 5890 Series II gas chromatograph equipped with an FID detector and an Alltech (Deerfield, IL) AT-624 cyanopropylphenyl dimethylpolysiloxane (30 m × 0.53 mm I.D.) column. The injector temperature was 125°C, the detector was 255°C, and the oven was operated isocratically at 35°C. Helium (17 ml/min) served as the carrier gas. Concentrations of sevoflurane and compounds A and B were determined by comparison to standard curves constructed with authentic compounds A and B and sevoflurane. Levels of compounds C and D were estimated using the standard curve constructed with compound B. Limits of detection were 0.8 ppm for compound A and 0.5 ppm for compound B.

Mass Spectral Analyses

Mass spectral analyses were performed on a Nermag (Paris, France) R10-10C mass spectrometer operated in the electron impact mode. The Alltech AT-624 capillary column was used for sample introduction.

Results

Gas chromatographic/mass spectral analysis of the headspace in vials containing sevoflurane heated in the

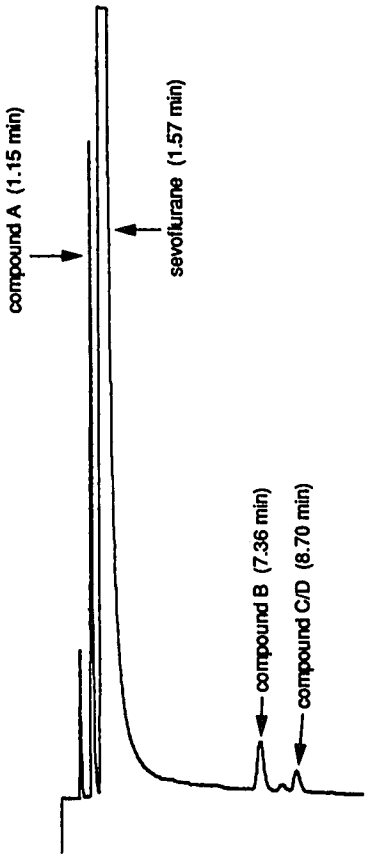

Fig. 2. Sample chromatogram obtained by gas chromatography analysis of the gas in a nonchilled circuit showing injection of a sample (400 μl) taken 7 h after the initiation of carbon dioxide flow (canister temperature, 46°C). Chromatographic conditions are given in materials and methods.

presence of soda lime provided positive identification of peaks corresponding to sevoflurane and five degradation products (figs. 1 and 2).4–6 Key mass spectral fragments for the degradation products, listed in their order of elution from the gas chromatograph, included: compound A (retention time 1.2 min); m/z 180 (M^+), 161 (M^+-F), 128 ($F_2CC(O)CF_2$), 78 (F_2CCO), 69 (CF_3, base peak); compound E (5.6 min), m/z 192 (M^+), 161 (M^+-CH_3O), 159 (M^+-CH_2F), 140 ($CH_3OCFC(O)CF_2$), 111 (M^+-CH_3OCF_2), 97 (CF_3CO), 81 (M^+-CF_2COCH_2F), 69 (CF_3, base peak); compound B (7.4 min), m/z 193 (M^+-F), 163 ($CH_3OCF_2CHCF_3$), 113, 81 (CH_3OCF_2, base peak); and compounds C and D (8.1 and 8.7 min), m/z 192 (M^+), 173 (M^+-F), 159 (M^+-CH_2F), 131 ($CH_2FOCHCF_3$), 69 (CF_3, base peak). Compounds C and D, structural isomers, cannot be distinguished by mass spectrometry. Identification of the compounds detected in gas samples taken from the anesthesia circuit was made on the basis of their identical chromatographic retention times with those products produced in the heated vials and with synthesized compounds A and B.

Introduction of 200 ml/min carbon dioxide into the nonchilled anesthetic circuit resulted in a gradual but pronounced increase in temperature inside the soda lime canister. During the initial 2 h, the core temperature increased from ambient (approximately 23°C) to a maximum of about 46°C, where it remained for the duration of the 8-h experiment (fig. 3). Chromatography of gas samples taken from the nonchilled anesthesia circuit at different time included compounds that were identified as sevoflurane and compounds A, B, and C, and D (fig. 2). One of the C/D isomers was detected in only trace quantities (that chromatographing immediately after compound B), whereas the other was found in measurable amounts. The measurable isomer in this study is referred to as compound C/D.

When the nonchilled circuit was operated without soda lime in the canister, compound A was present at

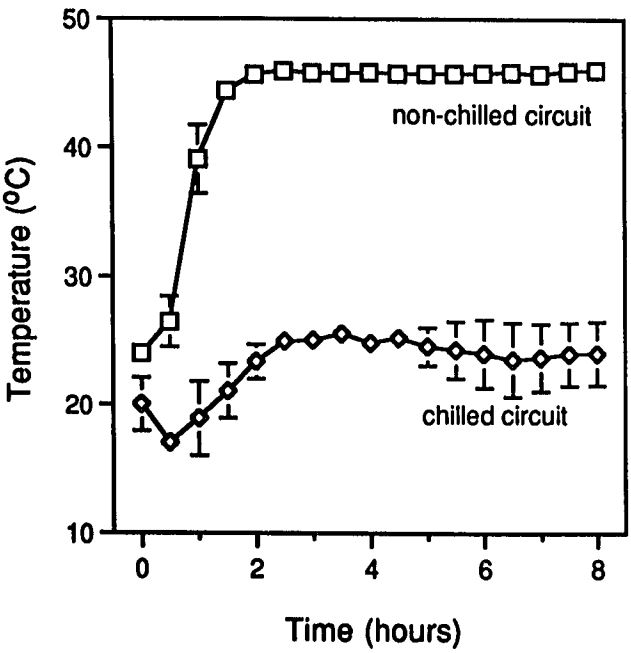

Fig. 3. Temperatures of the soda lime canister core measured in nonchilled circuits (open squares) and in circuits in which the soda lime canister was chilled in an ice-water bath (open diamonds). Measurements were made as described in materials and methods. Graph depicts readings taken at 30-min intervals for 8 h. Each point represents the average of the values (±SEM) obtained in three experiments.

concentrations of about 1 ppm. This level of compound A is likely due to its presence as a manufacturing contaminant, in accord with previous reports.[1,4] In the nonchilled circuit containing soda lime, compound A was detected in the circuit at a concentration of approximately 10 ppm before the addition of carbon dioxide and the rise in soda lime temperature. The increase in soda lime canister temperature that followed was accompanied by increases in compound A and the appearance of the other volatile compounds. Unlike compound A, compounds B and C/D were not detectable in the nonchilled circuit containing no soda lime, nor were they detectable at the start of the experiments with soda lime. However, continued operation of the circuit led to a steady increase in concentration of compound A, which reached a level of 23 ppm at the end of 8 h (fig. 4). Compound B was first detected 2 h into the experiment, and its concentration also rose steadily, reaching 8.5 ppm (fig. 5). After 4.5 h, compound C/D was detected, its concentration rising slowly to a maximum level of 3.5 ppm (fig. 5).

Immersion of the soda lime canister into an ice bath provided effective cooling of the canister, the core of

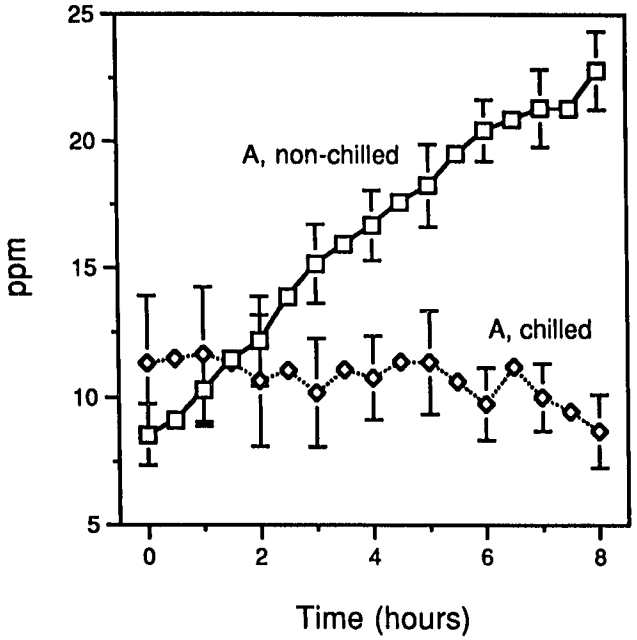

Fig. 4. Concentrations of compound A in nonchilled circuits (open squares) and in circuits in which the soda lime canister was chilled (open diamonds). Samples of circulating circuit gas (400 μl) were removed every 30 min for 8 h and analyzed by gas chromatography. Each point represents the average of the values (±SEM) obtained in three experiments.

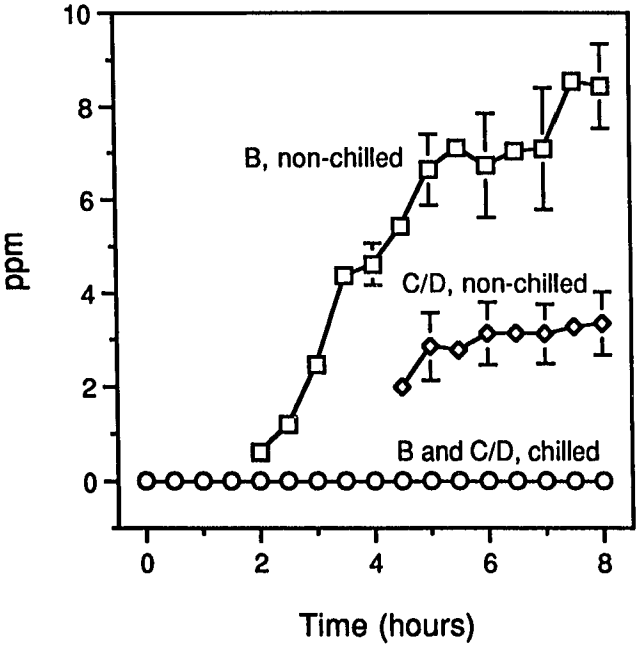

Fig. 5. Concentrations of compound B (open squares) and estimated concentrations of compound C/D (open diamonds) in nonchilled circuits and in circuits in which the soda lime canister was chilled (open circles). No compound B or C/D was detected in circuits employing chilled soda lime. Each point represents the average of the values (±SEM) obtained in three experiments.

which only reached a maximum of 26°C at any time during the 8-h period (fig. 3). As in the nonchilled circuit, compound A was detected immediately in the circulating gases; however, operation of the circuit with the soda lime canister chilled eliminated any increase in compound A in the circuit. Further, at no time in the 8-h experiment was compound B or C/D detected.

Although cooling of the soda lime led to a pronounced reduction in the rate of sevoflurane degradation, it had no apparent effect on the ability of the soda lime to absorb carbon dioxide. Introduction of carbon dioxide into the circuit at 200 ml/min produced a stable circulating concentration of 5% CO_2, regardless whether the soda lime was chilled (fig. 6). In a scaled-down system (5.0 g soda lime in a tube through which 200 ml/min oxygen/carbon dioxide (95%/5%) was introduced), soda lime chilling was determined to modestly shorten the time during which soda lime completely absorbed carbon dioxide. The time during which it absorbed carbon dioxide to nondetectable levels was shortened by 17%, and the time during

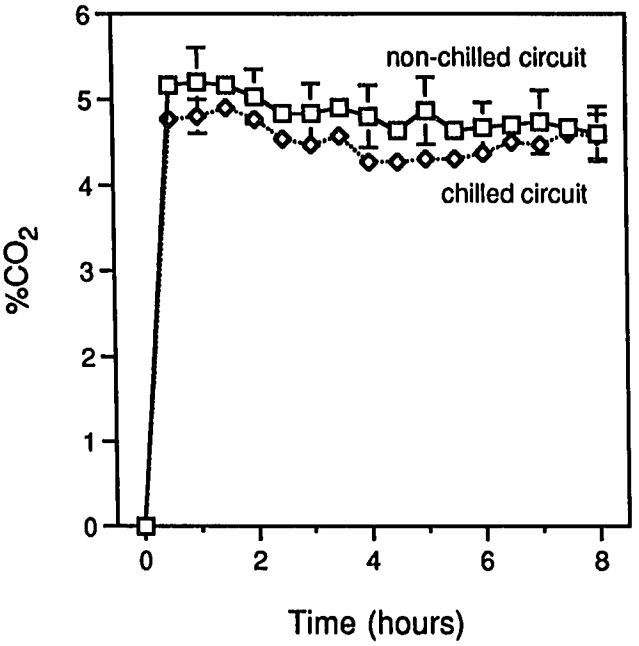

Fig. 6. Concentrations of carbon dioxide observed in nonchilled circuits (open squares) and in circuits in which the soda lime canister was chilled in an ice-water bath (open diamonds). Carbon dioxide was monitored as described in materials and methods. Each point represents the average of the values (±SEM) recorded at 30-min intervals from three experiments.

which it absorbed carbon dioxide until a 3.5% CO_2 end-point was reached in the eluting gas was shortened 25% (data not shown).

An ability to modulate sevoflurane degradation in an anesthetic circuit by reducing the temperature of the soda lime was illustrated by experiments in which the canister was not cooled and no carbon dioxide was introduced into the circuit. Elimination of carbon dioxide flow from the nonchilled circuit resulted in no increase in soda lime canister temperature. In this case, the temperature inside the canister remained essentially at room temperature (22–24°C) for 8 h. This had the same net effect on sevoflurane degradation as did cooling of the soda lime canister, *i.e.*, no increase in compound A from background concentrations of approximately 10 ppm, and no detectable quantities of compound B or C/D.

Discussion

As previously demonstrated, operation of a partially closed, nonchilled anesthesia circuit with sevoflurane as the anesthetic and soda lime as the carbon dioxide absorbent results in the appearance of sevoflurane degradation products in the circulating gases. Compound A, which is formed from a one-step reaction of sevoflurane with base and is a sevoflurane contaminant,[1] is found in the greatest quantity. Compound B, which results from the reaction of compound A with methanol, is generated to the next greatest degree; and compound C/D, which is thought to be formed as a result of the reaction of compound B with base, is present in only low amounts and only after 4.5 h of circuit operation.

Based on the relationships of soda lime temperature to the presence of the sevoflurane products in the circuit, it is apparent that increased temperature of the soda lime in the anesthesia machine is critical to their release in the circuit. There are no detectable quantities of compound B in the circuit until the soda lime temperature increases to greater than ambient (about 2 h). No increases in compound A and no detectable amounts of compound B or C/D occurred if carbon dioxide was not introduced into the circuit. Lastly, when the soda lime canister was chilled, no increase in compound A and no detectable quantities of compound B or C/D occurred.

The effect of reduced temperatures to inhibit sevoflurane degradation is due to the effects of temperature on chemical reactions. These include inhibited interactions of sevoflurane molecules with the soda lime granules and reduced rates at which the reactions proceed. Although the possibility exists that the degradation products are condensed in the soda lime canister and only released with increasing soda lime temperatures, it is clear that the production of each is very low or nonexistent when the soda lime is near room temperature. This can be inferred from the steady, flat circulating concentration (9–11 ppm) of the highly volatile compound A (boiling point 43°C[2]) in the chilled circuit. Were compound A susceptible to extensive condensation within the canister, its measured concentration would be expected to decrease with soda lime chilling. Similarly, the circulating concentration of sevoflurane (boiling point 58.5°C) was not significantly diminished after immersion of the canister in the ice bath. Any reduction of compound A formation, by necessity, also reduces that of compounds B and C/D because compound A is the precursor to compounds B and C/D.

Although chilling had a pronounced effect on the quantities of circulating degradation products, it had

no discernable effect on the ability of soda lime to remove carbon dioxide from the circuit. The reactions of carbon dioxide with soda lime granules resulting in carbon dioxide absorption are reactions that are designed to go to completion in anesthesia machine canisters under a variety of conditions (*e.g.*, flow rates, gas mixtures, moisture content).[12] The rapidity of the key reactions that remove carbon dioxide from the circuit are such that the degree of cooling necessary to inhibit product formation did not adversely affect carbon dioxide absorption.

Although patients were not connected to the circuit in these experiments, the results show that patients may inhale, in addition to compound A, compound B, and under longer periods of anesthesia (>4.5 h), compounds C and D, if very low flow circuits are used. The inability of other investigators to detect compounds B, C, and D in the circuit to which a patient is connected[1] may have been due to the fact that patients act as absorbers of each of the products with the result that circulating levels of compounds B, C, and D decreased to less than the level of detectability. Patients also add moisture to the circuit, which inhibits the degradation of sevoflurane.[10] The circuit, as operated here, with a constant sevoflurane concentration, no patient, and with no additional water added, therefore represents a circuit in which the circulating product concentrations will be maximized and clearly demonstrates the effectiveness of chilled soda lime in inhibiting product formation.

In conclusion, this study demonstrates that the carbon dioxide-dependent increase in temperature of soda lime is a necessary factor for the appearance of detectable sevoflurane degradation products in circuit gases. Because the detrimental effects of these degradation products to the patient are unclear, a reduction of soda lime temperature appears to offer a simple and economical means of preventing release of significant levels of sevoflurane degradation products in anesthesia circuits while not altering carbon dioxide absorption or affecting the circulating concentration of sevoflurane. Such a method of product reduction, by inhibiting sevoflurane breakdown, will lessen a potentially significant route of sevoflurane loss from partially closed circuits.[7,8]

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