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Only Carbon Dioxide Absorbents Free of Both NaOH and KOH Do Not Generate Compound A during In Vitro *Closed-system Sevoflurane*

Evaluation of Five Absorbents

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Background: **Insufficient data exist on the production of compound A during closed-system sevoflurane administration with newer carbon dioxide absorbents.**

Methods: **A modified PhysioFlex apparatus (Dräger, Lübeck, Germany) was connected to an artificial test lung (inflow at the top of the bellow ≅ 160 ml/min CO_2; outflow at the Y piece of the lung model ≅ 200 ml/min, simulating oxygen consumption). Ventilation was set to obtain an end-tidal carbon dioxide partial pressure of approximately 40 mmHg. Various fresh carbon dioxide absorbents were used: Sodasorb (n = 6), Sofnolime (n = 6), and potassium hydroxide (KOH)–free Sodasorb (n = 7), Amsorb (n = 7), and lithium hydroxide (n = 7). After baseline analysis, liquid sevoflurane was injected into the circuit by syringe pump to obtain 2.1% end-tidal concentration for 240 min. At baseline and at regular intervals thereafter, end-tidal carbon dioxide partial pressure, end-tidal sevoflurane concentration, and canister inflow ($T°_{in}$) and canister outflow ($T°_{out}$) temperatures were measured. To measure compound A_{insp} concentration in the inspired gas of the breathing circuit, 2-ml gas samples were taken and analyzed by capillary gas chromatography plus mass spectrometry.**

Results: **The median (minimum–maximum) highest compound A_{insp} concentrations over the entire period were, in decreasing order: 38.3 (28.4–44.2)* (Sofnolime), 30.1 (23.9–43.7) (KOH-free Sodasorb), 23.3 (20.0–29.2) (Sodasorb), 1.6 (1.3–2.1)* (lithium hydroxide), and 1.3 (1.1–1.8)* (Amsorb) parts per million (*$P < 0.01$ *vs.* Sodasorb). After reaching their peak concentration, a decrease for Sofnolime, KOH-free Sodasorb, and Sodasorb until 240 min was found. The median (minimum–maximum) highest values for $T°_{out}$ were 39 (38–40), 40 (39–42), 41 (40–42), 46 (44–48)*, and 39 (38–41) °C (*$P < 0.01$ *vs.* Sodasorb), respectively.**

Conclusions: **With KOH-free (but sodium hydroxide [NaOH]–containing) soda limes even higher compound A concentrations are recorded than with standard Sodasorb. Only by eliminating KOH as well as NaOH from the absorbent (Amsorb and lithium hydroxide) is no compound A produced.**

DURING sevoflurane anesthesia, particularly in low-flow and closed-system procedures, compound A can be formed. Whether compound A has an effect clinically on renal function has been debated, but some authors question the use of sevoflurane in low-flow conditions.[1] However, different carbon dioxide absorbents vary enormously in their capacity to produce compound A.[2–4] In the soda limes of the various manufacturing companies, sodium hydroxide (NaOH) and potassium hydroxide (KOH) are mostly used as initiators in the carbon dioxide chemical binding process. However, they are highly reactive compounds, which cause the breakdown of sevoflurane in the canister in the breathing circuit. In experimental conditions the formation of compound A was reportedly less with KOH-free soda limes,[3] which were then produced by various companies, and alternate NaOH-free and KOH-free carbon dioxide absorbents became available.

The aim of this study was to measure the formation of compound A during *in vitro* closed-system sevoflurane administration, using five different carbon dioxide absorbents whereby results were obtained during a previous study performed in the department in almost identical circumstances[6]: (1) KOH-free soda limes (Sofnolime and KOH-free Sodasorb; Molecular Products, Thaxted, UK, and Grace, Epernon, France, respectively); (2) NaOH-free and KOH-free absorbents (Amsorb[5]; and lithium hydroxide; Armstrong, Coleraine, Northern Ireland and Chemetall, Frankfurt, Germany, respectively); and (3) classic sodalime Sodasorb (Grace).

Materials and Methods

A special artificial test lung was used. Provided that 100% O_2 was used in the setup, patient oxygen consumption was simulated. To approach as closely as possible the actual clinical conditions, a continuous flow of carbon dioxide was introduced through a needle situated in the bellow of a test lung (Dräger, Lübeck, Germany). A flow rate of approximately 160 ml/min was used. To simulate the oxygen consumption of a patient, a continuous flow of the gas mixture containing oxygen and carbon dioxide was taken out at a flow rate of

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Table 1. Chemical Composition of the Carbon Dioxide Absorbents Examined

CO_2 absorbent	$Ca(OH)_2$ (%)	KOH (%)	NaOH (%)	LiOH (%)	$CaCl_2$ (%)	H_2O (%)	Company
Sodasorb	89	3	2.68			12–19	Grace, Epernon, France
Sofnolime	> 75	—	3	—	—	12–19	Molecular Products, Thaxted, UK
KOH-free Sodasorb	91.5	0.005	3.75	—	—	12–19	Grace, Epernon, France
Amsorb*	> 75	—	—	—	0.7	14.5	Armstrong, Coleraine, Northern Ireland
Lithium hydroxide	—	—	—	99.1	—	—	Chemetall, Frankfurt, Germany

* Amsorb also contains polyvinylpyrrolidine.

approximately 200 ml/min at the T-piece fixed at the outlet of the test lung. This gas was brought to a stand-alone Ultima gas analyzer (Datex, Helsinki, Finland) for measuring all respiratory gases. The outlet gases of the gas analyzer were scavenged.

The Y piece of a modified PhysioFlex (Dräger) computer-controlled, closed-system anesthetic machine was connected to the artificial lung. The built-in fan (for circulating the breathing gases) of the original PhysioFlex machine was switched off, and two classic unidirectional valves (Dräger) were incorporated into the breathing circuit. It has been shown that by this modification, in contrast to the original PhysioFlex machine, compound A is generated in larger quantities.[7] A respiratory frequency of 10 breaths/min was used, and a tidal volume of 490 ml, aiming at an end-tidal carbon dioxide partial pressure of 40 mmHg, measured at the Ultima gas analyzer. By computer control the "consumed" oxygen or volume loss is replaced by an identical (volume/volume [vol/vol]) inflow of oxygen, visualized on the PhysioFlex machine as oxygen consumption. The experimental setup was cleaned before each use and checked carefully for complete air-tightness. After initial preparation and equilibration, liquid sevoflurane was injected with a syringe pump (Model 3500; Graseby, Watford, United Kingdom) into a small copper reservoir included in the breathing circuit. The aim was an end-tidal sevoflurane concentration of 2.1%, a target used in a previous study.[7]

Two thermistors (Arbo, Yellow Springs, OH) were introduced into the absorbent lime canister, which has a capacity of 800 ml CO_2 absorbent, to measure the temperature. One was sited in the lower inflow, measuring inflow temperature ($T°_{in}$), and one in the upper outflow, measuring outflow temperature ($T°_{out}$). Gas samples of 2 ml were taken by means of airtight syringes for the determination of compound A. The syringes were connected to the breathing circuit using three-way valves and Luer-lock connections, one in the inspiratory limb (for compound A_{insp} measurement) and one in the expiratory limb (for compound A_{exp} measurement) of the breathing circuit. The gas samples were transferred immediately to glass headspace vials and stored briefly at room temperature.

Compound A was assayed by capillary gas chromatography combined with mass spectrometric detection (Model HP 6890-5973MSD; Hewlett-Packard, Palo Alto, CA).[8] Injection was fully automated in a technique based on headspace sampling (1 ml). To enter enough analyte mass into the analytic system and thus reach the intended sensitivity, cryofocusing on Tenax® (Alltech Associates, Deerfield, IL) sorbent (liquid nitrogen coolant, −80°C), placed in the injector liner, followed by flash desorption (250°C), was applied, and the compounds transferred onto the capillary column. In the ensuing chromatographic separation stage the use of a thick-film capillary column (CP-select 624, a 6% cyanopropylphenyl-dimethylsilicone stationary phase (Chrompack, Middelburg, The Netherlands) allowed adequate retention and isothermal separation at 38°C. The mass spectrometric detector was operated in the full-scan mode. The mass spectrum (electron impact ionization mode) of compound A is characterized by prominent peaks at m/z values of 69, 128, 161 and 180. The ion at m/z 128 was selected as the target ion for quantitative purposes. Before each analysis a standard curve consisting of eight points, including a zero-calibrator, was prepared and injected. Standards of compound A in the gas phase were prepared starting from liquid volumetric dilutions of stock solutions of compound A and sevoflurane in ethyl acetate. 1-Iodo-2,2,2-trifluoroethane was chosen as an internal standard. Before analysis, 0.5 μl of a liquid solution containing the internal standard in ethyl acetate was added to each vial. Calibration curves were linear over a range of 0.3–75 parts per million (ppm; vol/vol). An average correlation coefficient of 0.996 (n = 10) was obtained for the relation between the peak area ratio (ratio of compound A to internal standard) and the calibration concentrations. Within-day reproducibility (n = 6) and total reproducibility (n = 10) were tested at three different concentration levels (0.5, 10, and 75 ppm). The coefficients of variation varied from 4.1 to 10.0%. The limit of detection, using the signal-to-noise criterion 3, was 0.1 ppm, and the limit of quantification was 0.3 ppm, using signal-to-noise criterion 10 and taking reproducibility criteria into consideration.

A total of 33 independent runs were made. Classic soda lime (Sodasorb) was previously used in six runs; KOH-free soda lime (Sofnolime) and KOH-free Sodasorb were used in six and seven runs, respectively; alternate carbon dioxide absorbents Amsorb and lithium hydroxide were used in seven runs each. Their chemical com-

position, according to the available information, is shown in table 1.

During the preparation of the test-lung setup new carbon dioxide absorbent (800 ml) was always used. For the first Sodasorb runs, a minimal amount of 0.2% sevoflurane had to be dialed on the PhysioFlex machine to electronically close the special canister filled with active charcoal; after a technical change this dialing was no longer necessary for all the runs with the four other absorbents, which were made in random order. At the end of the preparation of the experimental setup and 5, 15, 30, 60, 90, 120, 150, 180, 210, and 240 min after the start of sevoflurane administration, data on end-tidal carbon dioxide partial pressure, end-tidal sevoflurane concentration, $T°_{in}$, $T°_{out}$, compound A_{insp}, and compound A_{exp} were recorded. Because of the presence of asymmetry in the data distribution and the relatively low number of runs per group (n = 6 or 7), it was preferable to summarize the data by median (range), as well as to apply nonparametric statistical methodology. To summarize repeated measures over time for all variables, areas under the curve (AUCs) were calculated for individual runs. For compound A_{insp}, canister $T°_{in}$, and canister $T°_{out}$, the maximal value over time for each individual run was identified, and these were submitted for further analysis.

For overall comparisons of the AUCs between the five groups, the Kruskal-Wallis test was applied, followed by Wilcoxon rank sum tests for multiple pairwise comparisons. To compare the difference between compound A_{insp} and compound A_{exp}, within-group Wilcoxon signed rank tests were applied on the AUCs of the individual runs. The same test was applied to compare within group adjacent time points. Spearman correlation coefficients were calculated between canister $T°_{in}$, canister $T°_{out}$, and compound A_{insp}.

For the overall Kruskal-Wallis tests, for the correlation coefficients, and for the within-group Wilcoxon signed rank tests, significance was set at $P < 0.05$. To correct for multiple pairwise comparisons between the five groups, the statistical significance for the Wilcoxon rank sum test was set at $P < 0.01$.

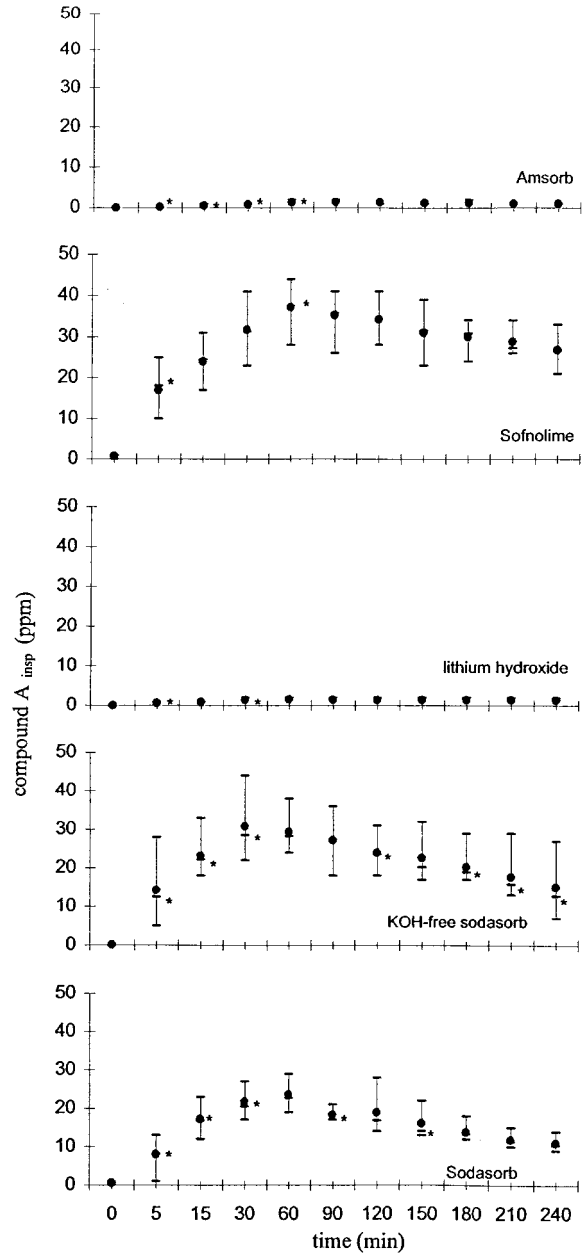

Fig. 1. Median (−), mean (●), and minimum and maximum values (parts per million [ppm]) of compound A_{insp} concentrations in the inspiratory gas flow in the different groups (*P < 0.05 *vs.* the previous value in time).

Results

The median values for end-tidal carbon dioxide partial pressure (40–42 mmHg) and for end-tidal sevoflurane concentration (2.0–2.2%) were similar in all runs and without statistically significant differences over the entire measurement period. The total median (with range) amounts (in millimeters) of liquid sevoflurane injected into the circuit during the 240-min examination period were 7.3 (6.9–7.9) (Sodasorb), 7.4 (6.6–9.4) (Sofnolime), 7.3 (6.7–8.7) (KOH-free Sodasorb), 6.2* (4.1–7.0) (Amsorb) and 7.4 (6.9–7.0) (lithium hydroxide) (*P < 0.01 *vs.* the other four groups).

The results for compound A_{insp} with the different carbon dioxide absorbents are shown in figure 1. Because differences between compound A_{insp} and compound A_{exp} were almost nonexistent, the last results are not reported. The values for compound A_{insp} with Sofnolime were higher ($P < 0.01$) than with all the other groups, and those with KOH-free Sodasorb higher ($P < 0.01$) than with the remaining groups, whereas the Sodasorb results were higher ($P < 0.01$) than those for Amsorb and lithium hydroxide. The results for canister $T°_{in}$ and $T°_{out}$ are shown in figure 2. The $T°_{in}$ values were higher ($P < 0.01$) for lithium hydroxide than for the other four

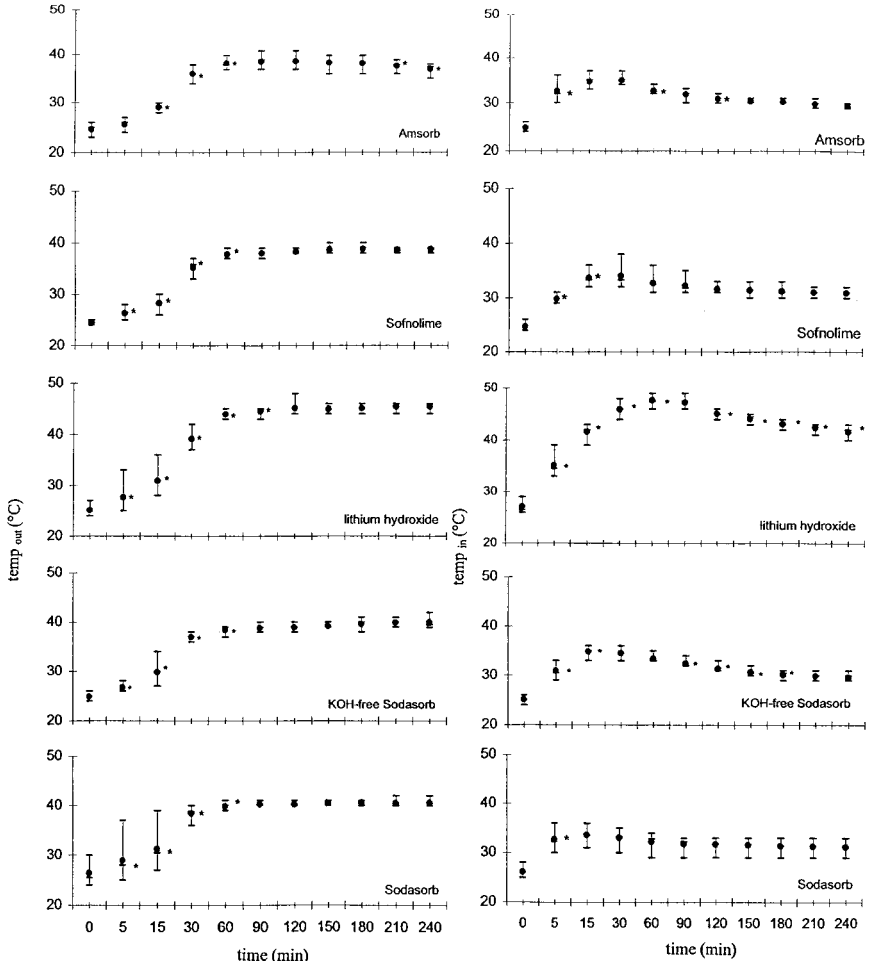

Fig. 2. Median (−), mean (●), and minimum and maximum values of canister inflow and canister outflow ($T°_{in}$ and $T°_{out}$ [°C]) in the different groups (*$P < 0.05$ *vs.* the previous value in time).

groups (difference between those four groups was not significant). The $T°_{out}$ values were higher ($P < 0.01$) for lithium hydroxide than for the other four groups, whereas the Sodasorb values were higher ($P < 0.01$) than in the remaining three groups.

Correlation analyses were performed only in the compound A–producing groups. A significant correlation ($P < 0.05$) was found between the compound A_{insp} values and canister $T°_{in}$ in the Sofnolime ($r = 0.35$), KOH-free Sodasorb ($r = 0.50$), and Sodasorb ($r = 0.32$) groups. A significant correlation ($P < 0.05$) was found between compound A_{insp} values and canister $T°_{out}$ in the Sofnolime ($r = 0.49$) group only.

Discussion

Today, numerous carbon dioxide absorbents have become available commercially for routine clinical application or for experimental use. The search for methods to prevent carbon monoxide generation during desflurane administration with dry limes and compound A generation with sevoflurane has pushed industrial companies to produce alternate absorbents. In a recent study, it was reported that carbon dioxide absorbents differ enormously in their capacity to produce compound A and carbon monoxide.[4] There is increasing evidence that the presence of strong bases, such as NaOH and KOH, as initiators in the carbon dioxide binding process may be the important factor in the dehalogenation of sevoflurane to compound A. Stabernack *et al.*[4] reported that KOH *versus* NaOH *versus* $Ca(OH)_2$ (calcium hydroxide) have inconsistent effects on compound A production. In contrast, Cunningham *et al.*[3] found that the correlation with compound A generation was stronger for KOH (expressed as percentage base) than for NaOH. In a detailed study on carbon monoxide formation from volatile anesthetics, it was also reported that KOH was more reactive than NaOH.[9] These findings were a strong argument for our group to study in detail KOH-free absorbents.

Our most striking results are that two carbon dioxide absorbents, Amsorb and lithium hydroxide, are devoid of compound A production, whereas the three other absorbents produce compound A in varying concentrations. In the Amsorb-containing or lithium hydroxide–containing systems, compound A_{insp} was present in concentrations almost equal (maximum median value for Amsorb was 1.3 ppm and for lithium hydroxide was 1.6 ppm) to

those contained intrinsically in commercial sevoflurane (1.06 ± 0.28 ppm).[10] With the three other absorbents (Sodasorb, Sofnolime, and KOH-free Sodasorb), compound A concentrations increased with time up to 30–60 min, then decreased slightly. A possible explanation is that the absorbents not only degrade sevoflurane to compound A, but also degrade the compound A formed.[11] However, the compound A concentrations were significantly higher (intergroup difference, $P < 0.05$) in the KOH-free Sofnolime group compared with all other groups. A less pronounced increase, but with a similar time curve, was also seen with the KOH-free Sodasorb (group difference, $P < 0.05$ with all remaining other groups), when compared with the NaOH-containing as well as KOH-containing Sodasorb. Compared with Sofnolime, KOH-free Sodasorb contains a somewhat higher concentration of NaOH and also a small amount of KOH; both of these might be an element in the intermediate position of this absorbent for compound A generation.

Our results with the KOH-free but NaOH-containing limes are in conflict with those of a recent report,[12] in which less compound A was generated with the KOH-free (0.003% KOH) sodalimes Drägersorb 800 plus and Medisorb (Datex-Ohmeda, Bromma, Sweden), than with the classic Drägersorb 800.[12] However, Medisorb contained only 1% NaOH, and Drägersorb 800 plus, 2% NaOH (such as was contained in Drägersorb 800 also), whereas in the KOH-free Sodasorb we studied, there was 3.75% NaOH. Our KOH-free absorbent results are also in contrast to the results of another study,[13] in which with KOH-free Medisorb (Datex-Ohmeda, Louisville, CO) lower compound A concentrations were found than with conventional soda lime (Wakolime, Wako, Tokyo, Japan). The higher concentration of NaOH in the Sofnolime and KOH-free Sodasorb that we used can partly explain the difference with their results. These facts suggest the importance not only of the presence or absence of KOH or NaOH, or both, in the carbon dioxide absorbent, but also, the exact concentration.

The small concentration of compound A (4 or 5 ppm) that was present initially in the first Sodasorb group to be examined was generated by the minimal quantity of 0.2% sevoflurane which we had to introduce into the circuit to close electronically the charcoal canister present in the PhysioFlex machine. By making a further technical change, this was no longer necessary during the preparation period in the other four groups.

In general, our compound A concentrations were close to those found in the *in vitro* experiment by Stabernack *et al.*[4] However, in that study, 30-ml syringes immersed in water at a constant temperature of 45°C were used, whereas in our setup we have an artificial lung with carbon dioxide production, which comes close to clinical conditions and in which the canister temperature was a function of the actual carbon dioxide binding process. In the study of Stabernack *et al.*,[4] dramatically lower compound A concentrations were also found with Amsorb and lithium hydroxide.

The canister temperatures were almost the same for all absorbents examined, with $T°_{out}$ higher than $T°_{in}$; the only exception was with lithium hydroxide, which generated much higher temperatures ($P < 0.05$), with $T°_{in}$ during the first 120 min higher than $T°_{out}$. The reason for this difference is not clear, but such a reaction has also been observed by other authors.[14] The presence of a correlation between compound A concentrations and the temperature of the absorbent is generally accepted.[10] A significant correlation ($P < 0.05$) was found between compound A_{insp} concentrations and canister $T°_{in}$ for the compound A–producing Sodasorb, Sofnolime, and KOH-free Sodasorb. Despite the higher canis-

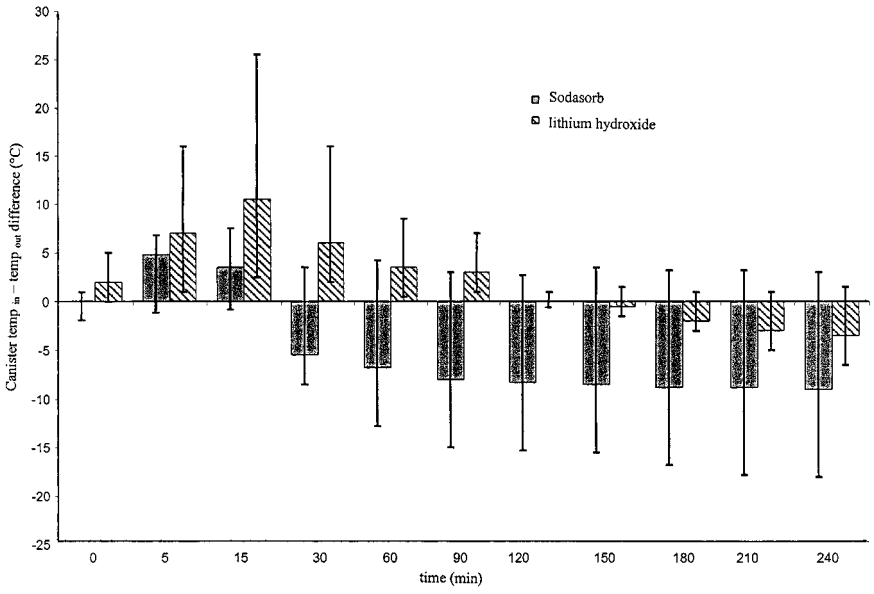

Fig. 3. Canister inflow–canister outflow ($T°_{in}$–$T°_{out}$) difference (°C). The median (range, minimum and maximum) values for lithium hydroxide and Sodasorb are shown. (If $T°_{in}$ was greater than $T°_{out}$, the difference was positive; if $T°_{out}$ was greater than $T°_{in}$, the difference was negative).

ter temperature with lithium hydroxide, no noticeable amount of compound A was formed in our study, as was also found in the study of Förster *et al.*[14]

The *peak* median (and extreme) concentrations of compound A_{insp} and canister $T°_{in}$ and $T°_{out}$ temperatures were measured over the entire examination period. The peak values were found at different times: compound A_{insp} values peaked at 60 min for Sodasorb and Sofnolime, whereas for KOH-free Sodasorb the maximum value was at 30 min. The peak value for canister $T°_{in}$ was between 15 and 60 min, whereas that for $T°_{out}$ was later, as shown in figure 2. The time frame for the peak concentrations of compound A is seemingly different from that of the maximum temperature of the absorbents.

At an identical carbon dioxide charge, a particular aspect is shown with lithium hydroxide with its continuous increase of temperature, which is significantly higher ($P < 0.05$) than with the other carbon dioxide absorbents, but with $T°_{in}$ moderately higher than $T°_{out}$, suggesting not only an intense, but also a fast, binding of carbon dioxide. This suggestion is evidenced in figure 3, in which the canister $T°_{in}$–$T°_{out}$ difference is shown: In the first time period, the temperature difference was larger for lithium hydroxide than for all the other absorbents (for simplicity, only Sodasorb is depicted in figure 3). Although for all the other absorbents the temperature gradient was reversed and became pronounced in the second time period, it took much longer for the gradient with lithium hydroxide to reverse to somewhat lower values. This lends support to the notion of intense and rapid carbon dioxide binding early in the inlet part of the canister.

An interesting finding is also that the amount of liquid sevoflurane injected in the system to generate a stable end-tidal concentration of sevoflurane was significantly less ($P < 0.05$) in the presence of Amsorb than with all the other absorbents. A plausible hypothesis that less sevoflurane was broken down by the non–compound A–producing Amsorb, has to be rejected because with the other non–compound A–producing lithium hydroxide this did not occur. A difference in absorption of sevoflurane in the used absorbents (standard hydrated, not dry in our setup) might be another possibility because Stabernack *et al.*[4] reported that absorbents differently eliminated sevoflurane from the outflow in their setup. Technically, we could not measure the sevoflurane concentrations at the inlet and outlet of the absorbent canister, so, for the time being, we can only speculate on the exact reasons.

In conclusion, our results show strongly that a working hypothesis of only eliminating KOH from soda lime to reduce the production of compound A with sevoflurane administration is not supportable because two different brands of KOH-free soda lime not only produced compound A, but also produced compound A in even higher quantities than the classic Sodasorb. Seemingly, factors other than KOH alone, such as, particularly, the concentration of NaOH, are even more important in the generation of compound A. Only by eliminating both KOH and NaOH from the absorbent is no compound A produced; thus, we can comply with the message about "putting the brakes on anesthetic breakdown" of a recent editorial on that subject.[15] Our *in vitro* assessment clearly shows that Amsorb is devoid of significant compound A generation and is the answer for the clinical practice, as has already been reported.[12,13] The other agent devoid of compound A generation was lithium hydroxide, but the intense airway-irritating effect of this drug in the presentation examined makes it unsuitable for use in clinical practice, unless a better formulation can be found.

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