Compound A production from sevoflurane is not less when KOH-free absorbent is used in a closed-circuit lung model system

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In an *in vitro* study, less compound A was formed when a KOH-free carbon dioxide absorbent was used. To confirm this observation we used a lung model in which carbon dioxide was fed in at 160 ml min^{-1} and sampling gas was taken out for analysis at 200 ml min^{-1}; ventilation aimed for a PE'_{CO_2} of 5.4 kPa. The soda lime canister temperatures in the inflow and outflow ports (T_{in} and T_{out}) were recorded. In six runs of 240 min each, a standard soda lime, Sodasorb (Grace, Epernon, France) was used and in eight runs KOH-free Sofnolime (Molecular Products, Thaxted, UK) was used. Liquid sevoflurane was injected using a syringe pump to obtain 2.1% E′. Compound A was measured by capillary gas chromatography combined with mass spectrometry. Median (range) compound A_{insp} increased to a maximum of 22.7 (7.9) ppm for Sodasorb and 33.1 (20) for Sofnolime at 60 min and decreased thereafter; the difference between groups was significant ($P<0.05$) at each time of analysis up to 240 min. The canister temperatures were similar in both groups and increased to ~40°C at 240 min. Contrary to expectation, compound A concentrations were greater with the KOH-free absorbent despite similar canister temperatures with both absorbents.

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During sevoflurane anaesthesia, particularly during low flow and closed-circuit procedures, compound A can be formed. This is the main breakdown product of the reaction of sevoflurane with the carbon dioxide absorbent used in the circuit. Compound A concentrations are greater when Baralyme is used as carbon dioxide absorbent than when soda lime is used.[1 2] However, soda lime varies according to the manufacturer. NaOH and KOH are mostly used as initiators in the carbon dioxide binding process. These highly reactive products could provoke the breakdown of sevoflurane in the canister in the breathing circuit. In experimental conditions less compound A was formed with a KOH-free soda lime.[3] We studied the *in vitro* behaviour of a KOH-free commercial soda lime (Sofnolime; Molecular Products, Thaxted, UK) using closed circuit conditions, to maximize the eventual production of compound A.

Experimental set-up

A test lung was used to obtain stable, identical concentrations of sevoflurane and carbon dioxide. To simulate clinical conditions, a continuous flow of 160 ml min^{-1} carbon dioxide was delivered through a needle in the bellows of the test lung. To simulate oxygen consumption, a continuous flow of 200 ml min^{-1} was taken out of the test lung at a T-piece at the outlet. This gas flow was fed to a gas analyser (Ultima; Datex, Helsinki, Finland) for assessing all respiratory gases and was scavenged, rather than being returned to the circuit. If 100% oxygen was used, oxygen consumption was simulated satisfactorily.

The Y-piece of a circle system was connected to the artificial lung. A modified PhysioFlex (Dräger, Lübeck, Germany) closed-circuit anaesthetic machine was used (Figure 1). The built-in fan (for circulating the breathing gases) was switched off and two classical unidirectional valves were placed in the breathing circuit. A respiratory frequency of 10 bpm and a tidal volume of 490 ml were used to obtain a PE'_{CO_2} of 5.4 kPa. In this system the 'consumed' oxygen or volume loss is replaced by an equal (vol/vol) inflow of oxygen, and displayed on the screen of the machine as oxygen consumption. The apparatus was cleaned carefully before each use to eliminate any contam-

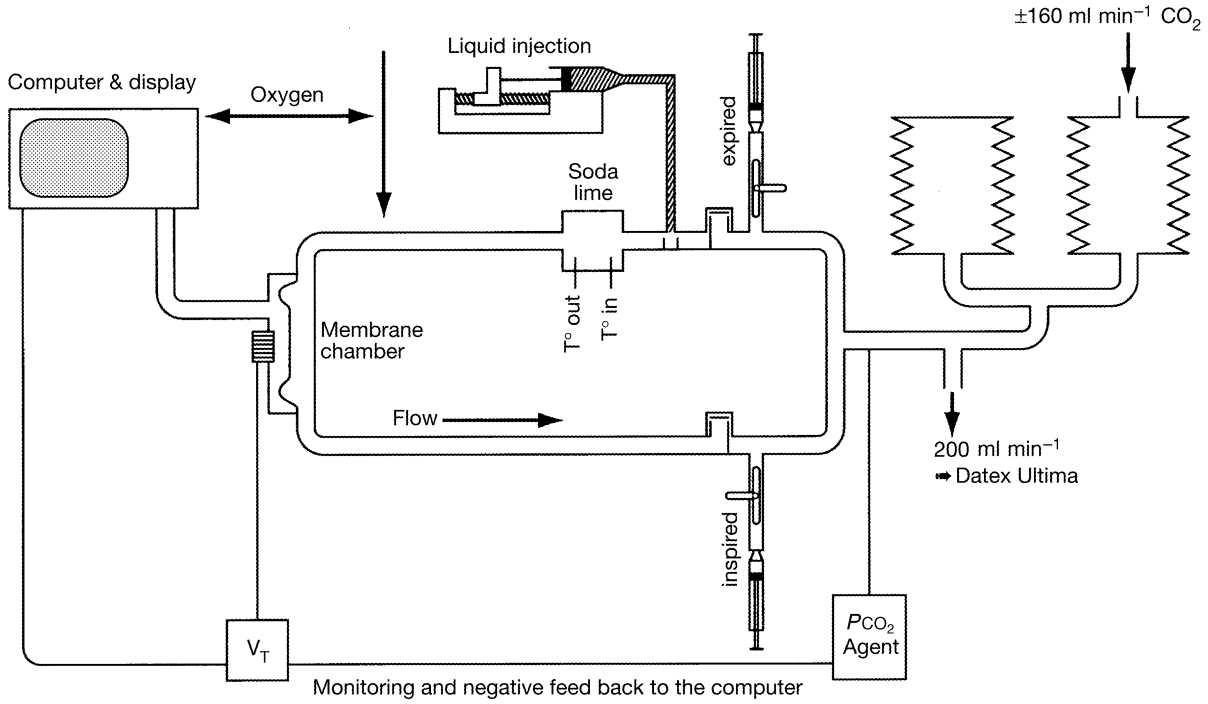

Fig 1 Schematic design of the modified PhysioFlex machine connected to the 'model lung'.

ination from a previous study and checked for complete airtightness. At the start of the study the lowest possible setting of 0.2% sevoflurane had to be set to close the active charcoal canister, which would otherwise have absorbed compound A. After initial equilibration, liquid sevoflurane was given using a syringe pump (Graseby 3500; Watford, UK), injected in a small copper reservoir fitted to the breathing circuit. The aim was an end-tidal sevoflurane concentration of 2.1 vol%.

Two thermistors were placed in the 800 ml soda lime canister to measure the temperature. One was in the inflow port, measuring the inflow temperature (T_{in}) and the other in the outflow port (T_{out}). From the outflow the gases passed through an inner cylindrical pipe within the canister to the breathing circuit. Another thermistor was placed in the Y-piece of the breathing circuit to measure the temperature there (T_Y).

Eight runs with fresh Sofnolime and six runs with standard Sodasorb soda lime (Grace, Epernon, France) were carried out in random order. Fresh commercially available soda limes, stored under normal conditions, were used for each run. According to the available information, the Sofnolime contained 3% NaOH, >75% $Ca(OH)_2$ and 12–19% H_2O and the Sodasorb contained 2.68% NaOH, 3% KOH, 89% $Ca(OH)_2$ and 12–19% H_2O. Gas samples of 2 ml were taken in airtight syringes for the determination of compound A. The syringes were connected to the breathing circuit by three-way valves and Luer-lock connections, one situated in the inspiratory limb (for compound A_{insp}) and one in the expiratory limb (for compound A_{exp}). The gas samples were immediately transferred to sealed glass head-space vials.

Compound A was assayed by capillary gas chromatography combined with mass-spectrometric detection (HP 6890-5973 MSD). Injection was fully automated by a technique based on head-space sampling (1 ml). In order to place enough analyte mass on to the capillary columm, cryofocusing on Tenax sorbent (liquid nitrogen, –80°C) placed in the injector liner was used. A thick-film capillary column (CP-select 624, a 6% cyanopropylphenyl-dimethylsilicone stationary phase) allowed adequate retention and excellent isothermal separation (38°C). Helium was used as carrier gas at a flow rate of 1 ml min^{-1}. The mass-spectrometer detector was operated in the full-scan mode. The mass spectrum (electron ionization mode) of compound A is characterized by prominent peaks at *m/z* 69, 128, 161 and 180, the last representing the molecular ion (M^+). The ion at *m/z* 128 was selected as the target ion for quantitative purposes. Before each analysis, a standard curve of eight points was prepared and injected. Standards of compound A in the gas phase were prepared, using 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. Good linearity over a range of 0.5–75 ppm (v/v) was obtained (average correlation coefficient 0.996 (N=10)). Within-day (N=6) and total (N=10) reproducibility were tested at three different concentrations (0.5, 10 and 75 ppm). The coefficients of variation ranged from 4.1 to 10.0%. The limit of detection (LOD), using a signal-to-noise ratio of 3, was 0.1 ppm, whilst the limit of

quantification (LOQ) was 0.3 ppm, using a signal-to-noise criterion of 10 and still assayed with adequate reproducibility (CV%<15%).

At the end of the preparation of the apparatus, and 5, 15, 30, 60, 90, 120, 150, 180, 210 and 240 min after the start of sevoflurane administration, we recorded $P\mathrm{E}'_{\mathrm{CO}_2}$, sevoflurane E', T_{in}, T_{out}, compound $\mathrm{A}_{\mathrm{insp}}$ and compound $\mathrm{A}_{\mathrm{exp}}$. The data were analysed using repeated measures Anova and/or Mann–Witney U-tests. A P value of <0.05 was considered statistically significant.

Results

The means for $P\mathrm{E}'_{\mathrm{CO}_2}$ (5.4–5.7 kPa) and for sevoflurane E' (2.1–2.2%) in both groups of carbon dioxides were similar and not significantly different over the entire measurement period. The inflow of oxygen (indicated on the PhysioFlex screen) was around 200 ml/min in both groups. The total amount (mean (SD)) of liquid sevoflurane injected into the circuit was also identical (Sodasorb group, 7.32 (0.35) ml; Sofnolime group, 7.26 (1.0) ml). The median and range of T_{in} and T_{out} are shown in Figures 2 and 3. No statistically significant difference was found between the Sodasorb and Sofnolime canister temperatures recorded at any time. The increase in T_{out} was significant (P<0.05) up to 30 min, but not significant after 30 min, in both the Sodasorb and Sofnolime groups. No difference was found for T_{Y}, which remained between 24 and 25.5°C throughout the study. The median and range of compound $\mathrm{A}_{\mathrm{insp}}$ and compound $\mathrm{A}_{\mathrm{exp}}$ are shown in Figures 4 and 5. Compound $\mathrm{A}_{\mathrm{insp}}$ increased up to 60 min (median (range) 22.7 (7.9) ppm in Sodasorb and 33.1 (20.0) ppm in Sofnolime), after which it declined. A statistically significant difference (P<0.05) between Sodasorb and Sofnolime was found at each time for compound $\mathrm{A}_{\mathrm{insp}}$ and compound $\mathrm{A}_{\mathrm{exp}}$, the values for Sofnolime always being greater.

Discussion

The presence of strong bases such as NaOH and KOH may be a factor in the dehalogenation of sevoflurane to compound A. Cunningham and co-workers[3] found that the correlation with compound A generation was stronger for KOH (expressed as percentage base) than for NaOH. They found the lowest concentration of compound A with 5% NaOH, and KOH-free Sofnolime was also associated with the lowest concentration of compound A, but these findings are controversial. Dry absorbent containing only $\mathrm{Ca(OH)_2}$ produces less carbon monoxide with desflurane than any other lime, with KOH having a greater capacity to generate carbon monoxide than NaOH (4).

In the present study the inspired and expired concentrations of compound A increased sooner with the KOH-free Sofnolime than with the classical Sodasorb; the difference was always significant. However, the curves of these concentrations were similar with time. The peak was seen

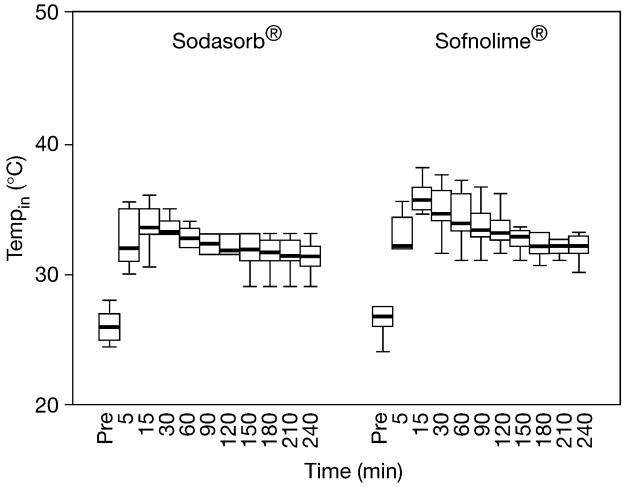

Fig 2 Median, interquartile values and range of canister T_{in} in Sodasorb and Sofnolime groups.

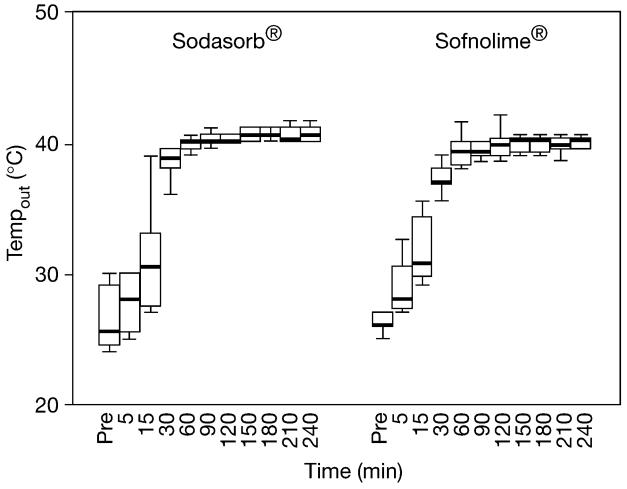

Fig 3 Median, interquartile values and range of canister T_{out} in Sodasorb and Sofnolime groups.

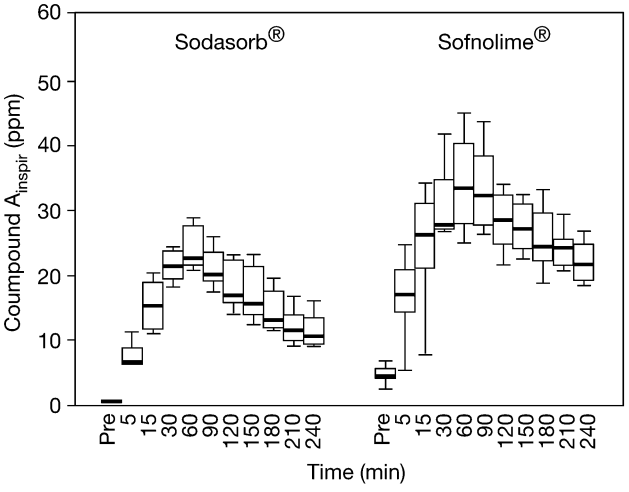

Fig 4 Median, interquartile values and range of compound $\mathrm{A}_{\mathrm{insp}}$ in Sodasorb and Sofnolime groups: statistical significance at P<0.05 between the two groups at all assessment times.

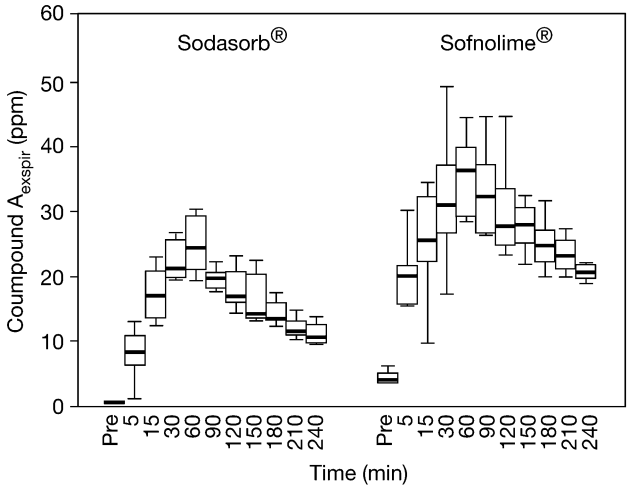

Fig 5 Median, interquartile values and range of compound A_{exp} in Sodasorb and Sofnolime groups: statistical significance at $P<0.05$ between the two groups at all assessment times.

at 60 min, with a mean compound A difference of 14 ppm between the two carbon dioxide absorbents; the one for Sofnolime was greater. Compound A values decreased slowly up to 240 min, as has also been reported in clinical studies.[5] In the early preparation of the circuit, when a very low sevoflurane concentration of 0.2% E′ had to be set, to close the activated charcoal canister, a much greater inspired concentration of compound A was found with Sofnolime than with Sodasorb (mean 4.5 and 0.6 ppm, respectively; $P<0.05$), suggesting that compound A is generated very rapidly with Sofnolime. The canister temperature T_{in} was initially greater than T_{out}, but from 30 min onwards T_{out} was greater than T_{in} and attained 40°C with both soda limes. No temperature difference was found at any time between either soda lime, showing that the higher compound A concentrations with Sofnolime could not have been generated by a greater canister temperature. This might have been assumed, knowing that a positive correlation has been found between soda lime temperature and compound A generation,[6 7] but other, as yet unknown factors must also be involved in the production of compound A. In experimental conditions with *dry* soda lime, less compound A was generated with Sofnolime than with normal soda lime.[8]

Our results contrast with those reported in recent clinical low-flow studies.[9 10] Higuchi and coworkers[10] found that less compound A was generated with KOH-free soda limes Drägersorb 800 Plus and Medisorb, which contain only 0.003% KOH, than with classical Drägersorb 800. The Sofnolime used in our study contained 3% NaOH, whereas Medisorb contained only 1% NaOH and Drägersorb 800 Plus 2% NaOH. The Sodasorb used in our study contained 2.68% NaOH, more than the 2% present in Drägersorb 800. These facts may explain the differences in their results and suggest the importance of the KOH and/or NaOH concentration in the carbon dioxide absorbent. The same considerations apply to the results of Yamakage and colleagues,[9] who compared Medisorb with the classical soda lime Wakolime, which contains 2.6% KOH and 1.3% NaOH. These authors report that Drägersorb 800 Plus has a KOH concentration of 3.0%, whereas Higuchi and colleagues[10] quote a concentration of 0.003%, making scientific comparison difficult.

We could not support the hypothesis that simply eliminating KOH from soda lime would reduce the formation of compound A. Indeed, we found even higher concentrations than with classical soda lime Sodasorb. Factors other than KOH, such as the concentration of NaOH, are even more important in the generation of compound A. Although our study is entirely experimental, it does simulate carbon dioxide production and oxygen consumption. Our results need to be confirmed in future clinical studies.

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