Compound A does not accumulate during closed circuit sevoflurane anaesthesia with the Physioflex

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We have investigated inspiratory and end-tidal gas composition during sevoflurane anaesthesia in a closed circle system with continuous gas flow (70 litre min$^{-1}$, Physioflex) to determine possible accumulation of sevoflurane degradation products. During five abdominal operations in adults lasting more than 2 h, anaesthesia was maintained with an end-tidal concentration of 2% sevoflurane in 40% oxygen–air. The circle included an absorbing canister filled with 1 litre of fresh soda lime. Samples were obtained at the end of an expiration from the tracheal tube and from the inspiratory limb before, and at selected times after, addition of sevoflurane. The temperature of soda lime was 24.7$\pm$0.7°C at the beginning and reached a maximum of 31.2$\pm$1.0°C after 20–30 min, followed by a plateau. Inspiratory compound A (CH$_2$F–O–C(5CF$_2$)(CF$_3$)) 3–8 ppm was detected after 10 min, but did not accumulate in the circle over 2 h without flushing. Expired concentrations were consistently lower with 1.5–3 ppm signalling absorption by patients. Calculated total amounts absorbed over 2 h varied between 2.0 and 7.2 ppm h. Other degradation products such as compound B or methanol were not detected. In summary, we did not detect sevoflurane metabolites with soda lime in significant amounts during closed circle anaesthesia with the Physioflex. The observed concentrations of compound A were below the threshold of nephrotoxicity in rats by a factor of more than 20.

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During the introduction of sevoflurane (Sevorane) into routine anaesthesia, the potential toxicity of a reaction product with soda lime, compound A, was a concern. Generation of the vinyl-ether compound A (CH$_2$F–O–C(=CF$_2$)(CF$_3$)) is dependent on temperature, humidity and the chemical composition of the absorbent. A high fresh gas flow, usually chosen for example in Japan, flushes the degradation products out of the anaesthesia circle. In 1995, the US Food and Drug Administration required that the manufacturer recommend the use of a minimum fresh gas flow of 2 litre min$^{-1}$ with sevoflurane to avoid accumulation in rebreathing systems. Minimizing fresh gas flow offers considerable savings by reducing wastage of volatile agent. Optimal conditions would be attained using a closed circuit where only the amount of volatile agent needed is taken up by the patient.

Because of its low blood-gas partition coefficient, only a few millilitres of sevoflurane are required in such a system to induce and maintain deep inhalation anaesthesia. There are only minimal data on generation and accumulation of compound A in closed anaesthesia circles. Bito and Ikeda used a conventional circle system with very low fresh gas flows (>200 ml min$^{-1}$, values not shown) and a bag-in-bottle ventilator. The closed circle anaesthesia machine, Physioflex, which is the most widely used closed system in Europe, incorporates a fan in the circle system. The fan produces a permanent flow of 70 litre min$^{-1}$ in the circle and the absorbent canister, generating specific environmental conditions for carbon dioxide absorption and sevoflurane degradation by soda lime. To clarify differences with other machines and to further elucidate possible exposure and uptake of compound A during closed circuit anaesthesia, we have investigated inspiratory and end-tidal gas composition using the Physioflex closed system anaesthesia apparatus.

Materials and methods

The Physioflex apparatus (Draeger, Luebeck, Germany) uses a valveless high flow (70 litre min$^{-1}$) closed circle system (Fig. 1). The patient’s lungs are ventilated by displacement of part of the circle volume into the lungs by means of up to four parallel moving membranes, which are
powered by a secondary pressure. Exhalation is caused by pressure release in the secondary circle. The volume in the circle is regulated, depending on membrane position, before and after each ventilation cycle by a computer using PID (proportional integrating and differentiating) algorithms. Regulation of $P_{O_2}$ is based on oxygen loss and has the highest priority. The computer maintains $P_{O_2}$ and volume with 5-ml pulses of oxygen or the selected carrier gas, respectively. To avoid accumulation of foreign gases, the computer requests fresh gas flushing if the fraction of gases not identified by the infrared detector exceeds 5%, or after 1 h. For the purpose of our study, these flushes were postponed until the end of the second hour.

After obtaining approval from our Institutional Review Board, we studied seven adult patients (Table 1) with no pre-existing renal or hepatic disease (ASA I and II) undergoing open abdominal surgery of at least 2 h duration. Anaesthesia was induced with fentanyl, propofol and rocuronium. After tracheal intubation, ventilation was performed with the Physioflex using 40% oxygen in air with a tidal volume of 10 ml kg$^{-1}$. Frequency was set to yield an end-tidal $P_{CO_2}$ of 4.3–4.8 kPa. After 5 min of equilibration, an end-tidal concentration of 2% sevoflurane or 1.1% isoflurane (controls) was selected. The Physioflex injects pre-calculated amounts of liquid volatile anaesthetic into the circle and requires 30–60 s to attain the selected concentration.

Before studying each patient, newly processed reusable silicone hoses with water traps were fitted to the machine. The absorbent canister contained 1 litre of fresh soda lime with 2.9% potassium hydroxide (KOH) (Draegersorb 800, Draeger, Luebeck, Germany) or without KOH (<0.01%, Sofnolime, Molecular Products, Essex, GB). Gas leakage in the circuit was measured during the self-test of the apparatus and was considered acceptable only if less than 100 ml min$^{-1}$ at a pressure of 40 mm Hg. Actual leakage during anaesthesia was approximated as described previously$^{10}$ by flow of fresh air and was 0–70 ml min$^{-1}$. The total volume of the circle system was 2.8–3.7 litre. The temperature of the soda lime at the top and bottom of the canister and relative humidity of the gas at the outlet of the canister (SMD-Module, Hygrotec, Titisee-Neustadt, Germany) were recorded. Gas flow through the soda lime was from top to bottom. Gas samples of 10 ml were obtained before introduction of the volatile agent and at selected times thereafter. We used non-interchangeable glass syringes (Popper and Sons, New York, NY, USA) with ethanol as internal standard. An inspiratory sample was obtained at the outlet of the canister. To obtain true end-expiratory gas, another sample was obtained shortly before the end of a manual respiratory cycle at the proximal end of the tracheal tube (Fig. 1).

Gas chromatography combined with a mass spectrometer (Hewlett Packard 5890 with MSD 5971A) was used for identification of gas components and purity check of compound A (CH$_2$F–O–C(=CF$_2$)(CF$_3$)). Compound A was synthesized by one of the investigators (MG$^{11}$) and characterized by $^1$H-NMR, $^{13}$C-NMR and CH analysis, and IR spectroscopy. Measurement of CH$_3$OH and compound A was achieved by GC-FID detection using a Fisons 8000 equipped with a 50-µl heated (70°C) injection loop, a 2 m × 0.53 mm id deactivated fused silica transfer line (Alltech, Munich, Germany), a Supel-Q Plot 30 m × 0.53 mm id capillary column (Supelco, Bellafonte, FL, USA) and a carrier pressure of 100 kPa (helium). Oven temperature was maintained isothermically at 100°C. Linearity of detection was given over the whole range of concentrations. A standard sample was prepared before each analysis for calibration of the GC-MS. Interassay consistency was assessed by the amount of ethanol found in the standard sample. The lower limit of detection was 0.02 nmol ml$^{-1}$ (0.5 ppm) for compound A and 0.8 nmol ml$^{-1}$ for methanol. Recovery rate was 97±13% for compound A (2.5 nmol ml$^{-1}$) and 99±5% for methanol (80 nmol ml$^{-1}$).

**Statistical analysis**

Descriptive statistics and testing were performed using SPSS software. Because of the small sample size, data were not normally distributed. Hence Wilcoxon’s signed rank sum test for matched pairs was applied to inspired and expired compound A concentrations.

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**Table 1 Patient data and diagnoses of those that received sevoflurane (Sevo.) and those that received isoflurane (Iso.)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Body weight (kg)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevo. 1</td>
<td>46</td>
<td>M</td>
<td>86</td>
<td>Neoplasm stomach</td>
</tr>
<tr>
<td>Sevo. 2</td>
<td>62</td>
<td>M</td>
<td>50</td>
<td>Neoplasm colon</td>
</tr>
<tr>
<td>Sevo. 3</td>
<td>61</td>
<td>M</td>
<td>78</td>
<td>Neoplasm colon</td>
</tr>
<tr>
<td>Sevo. 4</td>
<td>49</td>
<td>M</td>
<td>73</td>
<td>Neoplasm pancreas</td>
</tr>
<tr>
<td>Sevo. 5</td>
<td>67</td>
<td>F</td>
<td>75</td>
<td>Diverticulitis</td>
</tr>
<tr>
<td>Iso. 1</td>
<td>55</td>
<td>F</td>
<td>82</td>
<td>Neoplasm colon</td>
</tr>
<tr>
<td>Iso. 2</td>
<td>62</td>
<td>M</td>
<td>72</td>
<td>Neoplasm stomach</td>
</tr>
</tbody>
</table>

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**Fig 1** Schematic diagram of the valveless high flow closed system device (Physioflex) used in the study. The membranes form an airtight barrier between driving pressurized air and the closed system. The arrows indicate the direction of flow in the circuit. The measuring devices for temperature and humidity and the inspiratory sampling port were added for this experimental series.
The concentration of compound A did not exceed 7.6 ppm. There was no apparent accumulation of compound A. Without sevoflurane, compound A or methanol was not detected in the circuit. During two control studies, with administration of 1.1% isoflurane for 2 h, compound A or methanol was not detected. Ten minutes after introduction of 2% sevoflurane, compound A was found in the inspiratory and end-tidal gas. The concentration–time profile is given in Figure 2. The concentration of compound A did not exceed 7.6 ppm.

There was no apparent accumulation of compound A. Flushing of the system, performed by the computer program (5 litre min\(^{-1}\) fresh gas for 2 min), reduced inspiratory and end-tidal concentrations by 50%. As end-tidal concentrations were consistently lower (Table 2), we assume that patients absorbed a portion of the compound. To calculate patient uptake, we used the difference in the areas under the concentration curves (AUC). This procedure gave a mean uptake of 4.4 (SD 2.1) ppm h. In only two of the five studies was methanol detected in trace quantities (less than 200 nmol ml\(^{-1}\) gas; mean 5 nmol ml\(^{-1}\)).

### Discussion

The nephrotoxic potential of sevoflurane has been attributed to compound A, a degradation product of sevoflurane with soda lime, resulting in biochemical and historical evidence of glomerular and tubular injury in rats at doses of >150 ppm h.\(^{12}\) However, toxicity in humans is hypothetical. Persistent renal or other organ injury to humans anaesthetized with sevoflurane has not been reported, despite more than 30 million applications. In clinical practice, sevoflurane is administered with high fresh gas flow rates of 3–6 litre min\(^{-1}\) in Japan and with flows of more than 2 litre min\(^{-1}\) in the USA. With lower fresh gas flows, the concentration of compound A in anaesthesia circles increases,\(^{13}\) possibly because of the reduction in washout by waste gas. However, even long-term low flow (1 litre min\(^{-1}\)) anaesthesia with sevoflurane does not alter sensitive markers of renal function.\(^{14–16}\)

During closed circuit anaesthesia, only the amount of gas taken up by the patient is replaced, resulting in a fresh gas flow of 200–300 ml min\(^{-1}\) in adults. To our knowledge, concentrations of compound A in a closed anaesthesia circle system have only been reported by Bito and Ikeda.\(^{8}\) These investigators found a maximum circuit concentration of compound A of 19.5±5.4 ppm. Our values were lower by a factor of more than 3. Other investigators, using low and minimal flow systems, consistently found higher concentrations (Table 3).

These differences may be explained by the special features of the Physioflex machine, which is prone to reduce the amount of compound A in the circuit.

1. Absorbent temperature is a major determinant of sevoflurane degradation.\(^{3}\) In our investigation, the temperature of the soda lime never exceeded 32.5°C. This may be explained by the high flow through the soda lime which cools by evaporation of water generated during carbon dioxide absorption. Our lime temperatures were similar to those of Wissing, Kuhn and Kessler,\(^{17}\) obtained during laboratory investigations with the Physioflex using no volatile anaesthetic. As sevoflurane degradation by alkali–metal hydroxides is a strongly exothermic reaction,\(^{5}\) one might suppose that degradation is minimal within this circle system, despite the high amount of sevoflurane vapour passing the lime canister per unit time.

2. Equally important for sevoflurane degradation is the water content of the absorbent.\(^{2,5}\) The measured increase in relative humidity at the outflow of the canister signals increased water content of the soda lime. Moriwaki, Bito and Ikeda\(^{18}\) decreased maximum concentrations of compound A during low-flow sevoflurane anaesthesia from 16±5 to 1.4±1.0 ppm by adding

![Fig 2 Time-concentration profile of compound A. Values are mean (SD).](Image 74x597 to 288x738)

Table 2 Mean and maximum concentrations of compound A (ppm) during 120 min of closed circle anaesthesia with sevoflurane (end-tidal (ET) concentration 2%). Draegersorb is a pellet-shaped soda lime brand with 2.8% KOH, while Sofnolime has irregular granules and contains no KOH.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Absorbent</th>
<th>Inspiratory maximum</th>
<th>Inspiratory mean</th>
<th>End-tidal mean</th>
<th>ET/Inspir.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Draegersorb 800</td>
<td>7.4</td>
<td>4.7</td>
<td>2.9</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>Sofnolime</td>
<td>7.6</td>
<td>3.5</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>Sofnolime</td>
<td>5.1</td>
<td>2.6</td>
<td>0.9</td>
<td>2.8</td>
</tr>
<tr>
<td>4</td>
<td>Draegersorb 800</td>
<td>5.4</td>
<td>6.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>5</td>
<td>Sofnolime</td>
<td>6.0</td>
<td>5.0</td>
<td>2.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>5.9</td>
<td>4.4</td>
<td>2.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

### Results

The temperature of soda lime increased from 24.7±0.7°C to a maximum of 31.2±1.0°C and it was always higher at the top of the canister (inflow). The highest value recorded was 32.5°C. Ambient temperature was 20–22°C. Relative humidity behind the canister (inspiratory limb of the circle system) was 67–69% at the beginning, increasing slowly to approximately 90% after 1 h and then decreasing during the second hour to 78–82%. For temperature and humidity, we found no differences compared with the two control patients. Without sevoflurane, compound A or methanol was not detected in the circle. During two control studies, with administration of 1.1% isoflurane for 2 h, compound A or methanol was not detected. Ten minutes after introduction of 2% sevoflurane, compound A was found in the inspiratory and end-tidal gas. The concentration–time profile is given in Figure 2. The concentration of compound A did not exceed 7.6 ppm.
stereile water to fresh soda lime (10% v/v). Our experi-
mental set-up incorporated two sources of water: the
patient’s lungs and carbon dioxide absorption. Further-
more, the Physioflex uses only minor amounts of dry
fresh gas thus preserving moisture in the circle.

(3) Partially exhausted soda lime containing absorbed
carbon dioxide also inhibits formation of compound
A. In a closed circuit such as the Physioflex, all of
the carbon dioxide produced by the patient has to be
absorbed. Hence, partial exhaustion of soda lime is
attained earlier.

(4) Compound A itself is degraded by soda lime, mostly
to compound B. This compound is not volatile at
temperatures of approximately 30°C as its boiling point
is 131°C. Thus soda lime may act as a trap for
compound A, especially if one considers the repeated
contact by the high flow of 70 litre min−1 in the system.

The negligible amounts of methanol detected by our
analysis indicated only minor degradation of sevoflurane
in this circle system. Methanol is formed from sevoflurane by
a degradation path differed from that of compound A and
reacts with it to form other compounds. In previous work, we
used a model circuit with sevoflurane and either fresh or
dry soda lime and found high amounts of methanol only
with intentionally dried lime.

One point of concern may be continuous uptake of
compound A by the patient. Determined as the difference in
the areas under the inspiratory and expiratory concentration
curves, patients absorbed a mean dose of compound A 4.4
(SD 2.1) ppm h. Kharash and colleagues reported mean
uptake of 26±16 ppm h. At this dose, they found no
difference in renal or hepatic function compared with low-
uptake of 26 ppm h.

Table 3 Survey of publications on compound A (CA) concentrations during anaesthesia with low and minimal fresh gas flow. FGF=Steady-state fresh gas flow;
CA insp/ET=mean peak concentration of compound A; CA max= highest value of compound A observed; Sevo ET=mean end-tidal sevoflurane concentration;
time=duration of sevoflurane administration; temp.=maximum temperature of absorbent

<table>
<thead>
<tr>
<th>Reference</th>
<th>FGF (litre min−1)</th>
<th>CA insp (ppm)</th>
<th>CA ET (ppm)</th>
<th>CA max (ppm)</th>
<th>Sevo ET (%)</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frink24</td>
<td>0.77</td>
<td>8.2 (2.7)</td>
<td>3.6 (1.5)</td>
<td>14.2</td>
<td>–0.9</td>
<td>4</td>
<td>37.8</td>
<td>Closed circuit</td>
</tr>
<tr>
<td>Bito25</td>
<td>–0.25</td>
<td>19.5 (5.4)</td>
<td>30</td>
<td>2.2</td>
<td>3–6</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bito25</td>
<td>1</td>
<td>23.6 (2.9)</td>
<td>37.4</td>
<td>–1.6</td>
<td>12–16</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frink22</td>
<td>2</td>
<td>5.4 (4.4)</td>
<td>3.7 (2.7)</td>
<td>15</td>
<td>2.8</td>
<td>4</td>
<td>41</td>
<td>Children</td>
</tr>
<tr>
<td>Munday26</td>
<td>0.5</td>
<td>19 (6)</td>
<td>32</td>
<td>1.2–2.4</td>
<td>3</td>
<td>38–46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kharash15</td>
<td>1</td>
<td>27 (13)</td>
<td>18</td>
<td>67</td>
<td>–1.9</td>
<td>3.8</td>
<td>Baralyme</td>
<td></td>
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<tr>
<td>Moriwaki18</td>
<td>1</td>
<td>16 (5)</td>
<td></td>
<td></td>
<td>1.9</td>
<td>3.4</td>
<td>Fresh lime</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4 (1.8)</td>
<td>1.7</td>
<td>3</td>
<td>37</td>
<td>Exhaust lime</td>
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<tr>
<td>1</td>
<td>1.4 (1.0)</td>
<td>1.8</td>
<td>3</td>
<td>40.8</td>
<td>Lime + H2O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebert14</td>
<td>1</td>
<td>39 (6)</td>
<td></td>
<td></td>
<td>3</td>
<td>4</td>
<td>Baralyme</td>
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<tr>
<td>Present study</td>
<td>0.2–0.35</td>
<td>5.9</td>
<td>3.1</td>
<td>7.6</td>
<td>2</td>
<td>2</td>
<td>31.2</td>
<td>Closed circuit</td>
</tr>
</tbody>
</table>

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