Wash-in kinetics for sevoflurane using a disposable delivery system (AnaConDa®) in cardiac surgery patients

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Background. The use of volatile anaesthetics has increased in situations where conventional anaesthetic machines are inadequate or unavailable, for example, cardiac surgery and intensive care. The disposable anaesthetic conserving device, AnaConDa®, allows vaporization of liquid volatile anaesthetics from a syringe pump and rebreathing of exhaled anaesthetic. Clinical use requires understanding of device-specific anaesthetic agent kinetics, which are not fully known. We compared the wash-in kinetics for sevoflurane administered by a conventional vaporizer in a non-rebreathing system and the AnaConDa® and evaluated if a standard anaesthesia gas monitor gave accurate readings while using the AnaConDa®.

Methods. Cardiac surgery patients were randomized to maintenance of anaesthesia with sevoflurane either via a vaporizer or via the AnaConDa® (n=8 in each group). Sevoflurane in arterial blood and airway gas was measured with gas chromatography and standard gas monitoring.

Results. The initial increase in arterial sevoflurane tension was greater with the vaporizer than with the AnaConDa®, but the time to reach 80% of maximum sevoflurane tension was close to 8 min in both groups. End-tidal sevoflurane tension mirrored arterial tension in both groups, whereas measured inspired tension was lower than expired and arterial tensions with the use of the AnaConDa®.

Conclusions. The wash-in kinetics for sevoflurane delivered by the AnaConDa® are similar to a vaporizer. End-tidal sevoflurane tension accurately reflects arterial tension whereas inspired tension may be underestimated using an AnaConDa®.


Keywords: anaesthetics volatile; pharmacokinetics, model

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The concept of pharmacological preconditioning of the myocardium for tolerance to ischaemia has renewed the interest in the use of volatile anaesthetics in cardiac anaesthesia.1,2 Severe lung dysfunction is not uncommon in a population of patients presenting for cardiothoracic surgery, in particular after postoperative complications or with end-stage disease. Furthermore, volatile anaesthetics can be used for sedation in intensive care.3 In both these settings, anaesthetic machines may be inadequate or unavailable. On the other hand, advanced ventilators with open non-rebreathing circuits cannot be used for cost-effective and environmentally acceptable administration of volatile anaesthetics in these situations. The disposable anaesthetic agent delivery system, AnaConDa®, is a modified heat–moisture exchanger (HME) containing a carbon filter. Liquid volatile anaesthetic agent delivered by a standard syringe pump is evaporated on the patient side of the filter, and partial rebreathing of exhaled gas is accomplished by adsorbing–desorbing to the filter,4,5 a principle originally described by Thomasson and colleagues.6 The AnaConDa® makes possible the administration of volatile anaesthetics without anaesthetic machines, and advanced ventilators may be used. Knowledge of the kinetics of a volatile anaesthetic is an important guide to appropriate clinical use. The wash-in kinetics of sevoflurane using the AnaConDa® are, however, not known.

Previous studies have demonstrated a well-defined relationship between alveolar volatile anaesthetic partial pressure and anaesthetic effect.7,8 A disadvantage of measuring volatile agents in airway gas is that neither...
inspired nor end-tidal concentrations are equal to the vaporizer setting. Most anaesthetic agent analyser monitors display agent values as inspiratory and end-tidal concentration. Since these values are determined from the plateaus of the concentration, they may be inaccurate when the shape of the trace differs from that which is found when a volatile anaesthetic is administered conventionally.

The present study was undertaken to compare a vaporizer in a non-rebreathing circuit with the AnaConDa® with regard to time to reach desired blood concentration of sevoflurane in cardiac surgery patients. We also analysed if the end-tidal value given by a standard gas monitor accurately reflected sevoflurane arterial blood tension when using the AnaConDa®.

Methods

Patients

The study was approved by the local research ethics committee. Sixteen patients (14 men and two women) presenting for elective coronary arterial bypass grafting (CABG) or aortic valve replacement (AVR) were recruited. Fourteen patients underwent CABG, one patient an AVR, and one a combined CABG and AVR procedure. All patients had normal echocardiographic left ventricular ejection fraction before the operation. Patients with restrictive lung disease or obstructive disease with more than one inhalation prescription drug (steroid or beta-stimulator) were excluded. After giving informed and written consent, patients were randomly allocated to receive sevoflurane by the use of either a vaporizer (n=8) or an AnaConDa® (Sedana Medical AB, Uppsala, Sweden; n=8).

One additional patient, undergoing CABG, was recruited by the same criteria for the purpose of detailed measurement of airway gas concentrations during use of the AnaConDa®.

Experimental procedures

All patients were managed before and during the operation by one and the same anaesthetist. After insertion of a radial artery cannula, anaesthesia was induced i.v. with a bolus dose of fentanyl (2–3 μg kg⁻¹) and the infusion of propofol. Oro-tracheal intubation was facilitated with succinylcholine. Patients received volume cycled intermittent positive pressure ventilation with a Servo 900C ventilator (Siemens-Elema, Solna, Sweden) through a non-rebreathing tubing arrangement. The inspired oxygen concentration was set to 50%, inspiratory time and post-inspiratory pause were 25% and 10% of the ventilatory cycle, respectively, and a PEEP of 4 cm H₂O was applied. In the vaporizer group, an HME (HCH 5708, Vital Signs Inc., Totowa, NJ, USA), placed between the Y-piece of the ventilator tubing and the tracheal tube, was used which added 50 ml of apparatus dead space. The corresponding volume of the identically placed AnaConDa® is 100 ml. Tidal volume was set to 5.0 ml kg⁻¹ body weight with an additional 50 ml in the AnaConDa® group to compensate for the extra apparatus dead space. The ventilatory frequency was 16 bpm throughout in all cases and the tidal volume was maintained unchanged until measurements were completed. Anaesthesia was maintained by the propofol infusion and additional boluses of fentanyl were given at the discretion of the anaesthetist during insertion of central venous lines, after which the administration of sevoflurane was started and propofol was discontinued. Haemodynamic stability as judged by heart rate (HR) and arterial pressure was strived for, and infusions of norepinephrine and dopamine were used to balance the haemodynamic effects of variations in anaesthetic depth on transition from i.v. to inhalation anaesthesia.

In the vaporizer group, a Sigma Elite vaporizer (Penlon Ltd, Oxon, UK) set to 1.2% was used. The vaporizer was placed in the fresh gas supply line connected to the low-pressure inlet of the ventilator. With the AnaConDa®, the infusion rates for liquid sevoflurane were derived from the desired end-tidal anaesthetic concentration, patient body weight, and ventilator settings using a nomogram provided by the manufacturer. The nomogram is a table built on the model of Belda and colleagues, yielding one infusion rate for the first 10 min, and one for the following hour for strata of body weight and ventilatory volume. The infusion rate was determined by interpolation between the strata of the nomogram, and the syringe pump (Alaris CC, Alaris Medical UK Ltd, Basingstoke, UK) was adjusted accordingly. Vaporizer and AnaConDa® settings aimed at an end-tidal concentration of 1.0% during steady state. Inspired and end-tidal gas concentrations were monitored continuously using infrared spectrometry by an anaesthesia monitor (IntelliVue MP90 with an M1026A Airway Gases unit, Philips Medizin Systeme, Böblingen, Germany). The M1026A samples airway gases side stream with a flow of 150 ml min⁻¹ which causes a sample delay time of 3 s. Rise times for the carbon dioxide and sevoflurane signals are 410 and 570 ms, respectively. In order to reflect usual clinical practice, airway gas sampling in both groups was performed at manufacturer designated ports of the respective devices. Thus, in the vaporizer group, sampling was from the port on the ventilator side of the HME, and in the AnaConDa® group from the designated port on the patient side of the device.

A control sample for the determination of arterial blood tensions of carbon dioxide (Paco₂) and oxygen (Pao₂) and the absence of sevoflurane was collected in each patient before administering the inhalation anaesthetic. These data are presented as baseline values. The tubing from syringe to AnaConDa® was empty at the start of infusion to ensure complete absence of sevoflurane until otherwise intended. The infusion was set to nomogram first 10 min
rate, and was not purged to fill the empty tubing. After detection by the anaesthesia gas monitor of sevoflurane in the breathing circuit, blood samples were collected after 60 s and every 60 s up to and including 300 s. Further samples were collected every 5th minute until and including 30 min. At 10, 20, and 30 min, additional samples were collected for determination of $P_{a CO_2}$ and $P_{a O_2}$. Infusion rate for sevoflurane in the AnaConDa® group of patients was reduced immediately after sampling at the 10 min time point. No patient was sternotomized before the 10 min sample, and all samples were collected before the pleura were opened.

Simultaneously, with the sampling of blood, the following variables were recorded from the anaesthesia monitor: end-tidal CO$_2$ concentration, inspired and end-tidal sevoflurane concentration, HR, and mean arterial pressure (MAP).Expired tidal volume, as measured by the ventilator, was recorded. All blood gas measurements were performed in the operating theatre (ABL 700, Radiometer, Copenhagen, Denmark) and were completed within 10 min of collecting the 30 min sample. All technical equipment was maintained and calibrated according to the hospital policies.

In one additional patient, airway gas concentrations with the use of an AnaConDa® were measured in greater detail. In addition to gas sampled from the gas monitor port of the AnaConDa®, gas was also analysed from a port on the connector to the tracheal tube situated 5 cm downstream from the AnaConDa® port. A different infrared spectrometry gas analyzer (Vamos, Dräger Medical AG, Lübeck, Germany), response time $<$350 and $<$500 ms for CO$_2$ and sevoflurane, respectively, was used. It has an RS232 serial interface through which data were collected at a sampling rate of $\sim$10 Hz by a personal computer running LabVIEW v. 7.0 (National Instruments, Austin, TX, USA) under MS Windows 2000 Professional. The output of the software is a table of concentrations of CO$_2$ and inhaled anaesthetic agent, and each sample is given a time stamp. Sampling was made during two 30 s periods, 1 min apart during the 9th and 10th minute of wash-in, and sampling was performed in succession with gas from the AnaConDa® port first. Means of traces from five breaths were calculated. Curves were plotted so that the lowest values for CO$_2$ were denoted time point zero. Sevoflurane curves were plotted to match the time points of the corresponding CO$_2$ curve.

**Gas chromatography**

Sevoflurane partial pressure in arterial blood was determined with a gas chromatography headspace technique described by Smith and colleagues,$^{12}$ which yields blood sevoflurane tension as a fraction of dry gas. In brief, four 0.6 litre cylinders with different known tensions of sevoflurane in nitrogen were prepared and the gas mixtures were used as standards before analysis of the blood samples. Each 1.5 ml blood sample, drawn from the arterial line into a heparinized syringe, was transferred to a gas tight 4.75 ml vial immediately after collection of the 30 min sample. The blood concentration of sevoflurane was measured after equilibration for 30 min at 37°C by injecting 50 μl of the headspace gas into a Perkin-Elmer 3920 gas–liquid chromatograph with flame ionization detection.$^3$ Two headspace readings were obtained from every blood sample and the mean was used in the subsequent calculations. For three randomly assigned blood samples of each patient, 1 ml of the equilibrated blood was transferred into a new 4.75 ml gas tight vial. After another 30 min equilibration at 37°C, the headspace was analysed. This double headspace technique enables the calculation of the blood–gas partition coefficient.$^{12}$ The mean blood/gas partition coefficient for sevoflurane was found to be 0.76 (sd 0.029, n=16). This value was used in the subsequent calculations of sevoflurane tension in arterial blood. The gas chromatographer was blinded to the delivery system used (vaporizer or AnaConDa®) throughout the study.

**Analysis of data**

Sevoflurane tensions in airway gas and blood are given as dry gas tensions and O$_2$ and CO$_2$ tensions are given as body temperature and pressure, saturated with water vapour. Results are expressed as mean (sd). The number of determinations used for statistical calculations equals the number of patients and is given as n. Data were statistically analysed using SigmaStat for Windows 3.0.1 (SPSS Inc.). Values expressing changes over time were analysed using two-way repeated measures ANOVA for the two factors time and parameter. The parameters were tension in arterial blood, inspired gas, and end-tidal gas. ANOVA was followed by the Holm–Sidak post hoc test when appropriate. Durations were compared using Student’s t-test. P-values of $<0.05$ were considered to indicate statistical significance.

**Results**

**Patient characteristics**

The two groups of patients were similar with respect to age, body weight, length, and BMI (Table 1).

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Vaporizer</th>
<th>AnaConDa®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Male (n)</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Age (yr) [median (range)]</td>
<td>65 (46–82)</td>
<td>69 (46–74)</td>
</tr>
<tr>
<td>Weight (kg) [median (range)]</td>
<td>80 (54–92)</td>
<td>81 (69–99)</td>
</tr>
<tr>
<td>Height (m) [median (range)]</td>
<td>1.73 (1.57–1.83)</td>
<td>1.76 (1.66–1.86)</td>
</tr>
<tr>
<td>Body mass index (kg m$^{-2}$) [median (range)]</td>
<td>25.5 (21.9–30.4)</td>
<td>25.6 (24.2–28.6)</td>
</tr>
</tbody>
</table>
Haemodynamics
Neither HR nor MAP changed significantly from baseline. All mean HR and mean MAP values were within 85–100% and 83–106% of baseline, respectively.

Respiratory gas exchange
Expired minute volume did not change between measurements. Mean \( P_{a\text{CO}_2} \) was significantly higher at all time points measured in the AnaConDa® group. Mean (SD) \( P_{a\text{CO}_2} \) values within the groups did not change significantly: 6.9 (0.9) and 5.5 (0.7) kPa at baseline for the AnaConDa® and vaporizer groups, respectively. Equivalent values at 30 min were 6.5 (0.7) and 5.4 (0.9) kPa, respectively. Mean end-tidal \( P_{a\text{CO}_2} \) values at baseline were 5.6 (0.8) and 4.4 (0.5) kPa for the AnaConDa® and vaporizer groups, respectively. After 30 min, the mean end-tidal \( P_{a\text{CO}_2} \) values were 5.0 (0.5) and 4.2 (0.7) kPa, respectively. Mean arterial to end-tidal \( P_{a\text{CO}_2} \) difference for the AnaConDa® group was 1.3 (0.6) at baseline and 1.5 (0.4) at 30 min. Corresponding values for the vaporizer group were 1.1 (0.3) and 1.2 (0.4) kPa. Neither between- nor within-group differences were statistically significant.

At baseline, mean \( P_{a\text{O}_2} \) did not differ between the groups. Mean \( P_{a\text{O}_2} \) remained unchanged in the AnaConDa® group. In the vaporizer group, however, mean \( P_{a\text{O}_2} \) increased from 25 (7.1) to 28 (7.8) at 10 min, and mean \( P_{a\text{O}_2} \) then remained significantly higher than at the vaporizer and AnaConDa® groups, respectively. To facilitate graphical comparison of wash-in kinetics of sevoflurane in the presence of this group difference, sevoflurane tensions of each patient were normalized to the value at 30 min, which can be regarded as close to steady state (Fig. 1). After the detection of sevoflurane by the gas monitor, sevoflurane tension in arterial blood increased steadily and levelled off after 20 and 10 min for sevoflurane administered via a vaporizer and AnaConDa®, respectively. The arterial tension in patients receiving sevoflurane via the AnaConDa® was lower than for patients receiving sevoflurane via a vaporizer during the first 5 min (Fig. 1). This relationship was reversed after 10 min and from 15 min onwards arterial sevoflurane tension was similar in the two groups (Fig. 1). The time required to reach 80% of the arterial partial pressure of sevoflurane measured at 30 min was similar in the two groups, 8.1 (1.7) and 7.5 (0.34) min after the detection of sevoflurane by the gas monitor for the vaporizer and AnaConDa® groups, respectively.

Airway gas monitoring
Conventional vaporizer
Mean end-tidal sevoflurane tension at 30 min was 0.99 (0.10) kPa. Sevoflurane tension in inspired gas as measured by the gas monitor was significantly lower than the arterial tension at all time points (Fig. 2). End-tidal sevoflurane tension measured by the gas monitor was slightly, but statistically significantly higher than the arterial partial pressure for the first 10 min (Fig. 2).

AnaConDa®
Mean end-tidal sevoflurane tension at 30 min was 1.04 (0.10) kPa. Sevoflurane tension in inspired gas measured by the gas monitor was significantly lower than the arterial tension at all time points (Fig. 3). End-tidal sevoflurane tension measured by the gas monitor did not differ significantly from the arterial partial pressure (Fig. 3).

Airway gas variation within the respiratory cycle with an AnaConDa®
The averaged breaths from AnaConDa® and tube port were both 3.9 s long (Fig. 4). Lowest inspiratory \( CO_2 \) tension was 0.34 and 0.31 kPa at the AnaConDa® and tube port, respectively, and end-tidal values were 5.2 kPa in both cases. Minimum sevoflurane tensions were 0.51 and 0.71 kPa at the AnaConDa® and tube ports, respectively. Sevoflurane tensions at the end of the expired plateau were 0.93 and 1.0 kPa at the AnaConDa® and tube...
ports, respectively. Higher concentrations were not seen later in the cycle at the AnaConDa® port, although the expiratory plateau for sevoflurane lasted 0.59 s longer than for carbon dioxide. At the tube port, however, sevoflurane concentrations increased to a peak 0.50 s beyond the expiratory CO₂ plateau, well into the inspiratory phase of the CO₂ trace. The difference in plateau lengths between the two gases is not likely explained by different response times of the monitor alone, since this was in the order of 0.15 s.

Discussion

Our results show that the wash-in kinetics for sevoflurane administration aiming at a steady-state arterial tension of 1 kPa are similar when using an AnaConDa® or a vaporizer in a non-rebreathing circuit. The target sevoflurane tension was reached within the time of the study (30 min) for both the vaporizer and the AnaConDa® group of patients. This demonstrates that with the nomogram used, a pre-selected arterial tension can be generated with the AnaConDa® in adult cardiac surgery patients. It should be noted that both women in the study were randomly allocated to the vaporizer group. It is unclear whether this had any impact on the results.

The choice of target concentration for sevoflurane was limited by the nomogram provided by the manufacturer of the AnaConDa®, in which the maximum value allowed for is 1%. Although 1% sevoflurane does not provide surgical anaesthesia as a sole drug, it is of interest in a cardiac surgery setting. Symons and Myles reviewed several studies using sevoflurane for the purpose of myocardial protection. Seven of those studies used the agent in a fashion similar to our protocol, and indicated successful regimens using 0.5–4% sevoflurane. It therefore seems reasonable that the concentration used in the present study is clinically relevant.
airway gas was considerably longer with the use of an AnaConDa® than with a vaporizer. The volume of the tubing from syringe to evaporator of the AnaConDa® is 1.2 ml. The evaporator contains another 0.2 ml but does not need to be saturated before anaesthetic gas vapour can be detected (personal communication, Sedana Medical). The observed delay of 5–9 min is thus what is to be expected with the first 10 min flow of sevoflurane used to fill the tubing in this study. In clinical practice, this time could be reduced to a minimum with an appropriate pre-filling routine.

The value for inspired sevoflurane given by the anaesthesia gas monitor increased rapidly in the vaporizer group and levelled out within 15 min at a value close to the vaporizer setting and well above the arterial blood tension. That is what is to be expected when delivering a volatile anaesthetic via a high-flow non-rebreathing system. The inspired sevoflurane tension given by the gas monitor in the AnaConDa® group was, however, constantly lower than the arterial blood tension. The observation is not compatible with a wash-in phase when there must be a sevoflurane gradient from inspired gas to arterial blood, and indicates that the value reported here for inspired sevoflurane in the AnaConDa® group is not representative of inspired gas. One reason for this is illustrated by the detailed averaged breaths sampled at two different ports downstream of the device. Whereas at the AnaConDa® port proper, no increase in sevoflurane above end-tidal concentration was seen during inspiration, an inspiratory peak could be observed further downstream, as previously suggested. Assuming a homogenous gas mixture, the area under the time–tension curve should be identical at the two sampling sites. This was not the case, probably due to incomplete mixing of gas at the level of the sampling port of the AnaConDa®, explaining why monitoring of inspired sevoflurane concentration at that port may not yield clinically useful numbers. In practice, inspired concentration is, however, of minor importance compared with end-tidal.

End-tidal sevoflurane tension, as measured with the anaesthesia gas monitor, mirrored arterial blood tension in both the vaporizer and the AnaConDa® groups. With an AnaConDa®, airway gas concentration of the inhaled anaesthetic is the only variable readily available for assessing concentrations of the drug. We have demonstrated that also with an AnaConDa®, end-tidal gas monitoring may be useful to assess blood sevoflurane tensions and thereby indirectly brain tensions and anaesthetic depth. Caution is required, however, since we have observed that in one other anaesthesia gas monitor, connected to the sampling port of the AnaConDa®, inspired and end-tidal sevoflurane concentrations were presented in lieu of each other. This could be due to differences in response times, how different monitors assign different parts of the gas trace to be the inspired or end-tidal value, or both. Furthermore, uneven gas mixing may contribute, suggesting that different monitor types must be individually assessed for applicability before use with an AnaConDa®.

The $P_{a\text{CO}_2}$ values were higher in the AnaConDa® than in the vaporizer group throughout the 30 min observation time. The study protocol aimed at compensating for the larger apparatus dead space of the AnaConDa® compared with the conventional HME, by using a greater tidal volume with the former device. This study was designed to use commercially available equipment with as little modification of routine as possible. When ventilating with different apparatus dead space, the adjustment of tidal ventilation by a volume equal to the difference in internal volume of the components used should result in equal alveolar ventilation since this is defined as the difference between tidal and dead space ventilation. It is obvious that the measure was not enough to provide similar CO₂ elimination in the groups of this study, but the amount of gas delivered to the alveoli should have been similar. It is thus not entirely clear whether the observed higher $P_{a\text{CO}_2}$ values in the AnaConDa® group actually represent lowered alveolar ventilation. In fact the group with the higher $P_{a\text{CO}_2}$ received larger tidal volumes at an identical rate, that is, had larger mass movement of gas through the airways. Differences in alveolar ventilation influence anaesthetic gas uptake, but the effect of varying $P_{a\text{CO}_2}$, as brought about in this study, has to our knowledge not been explored. The reason for the observed relative hypercapnia in the AnaConDa® group is not clear. We suggest that adsorption in the AnaConDa® of exhaled CO₂ could have contributed to the relative hypercapnia by way of rebreathing. The assumption is supported by the observation in the detailed averaged breaths that the CO₂ tension was never below 0.3 kPa. Thus, the AnaConDa® should be used only with careful monitoring and higher ventilatory volumes in patients where the $P_{a\text{CO}_2}$ value needs to be under tight control, for example, during neurosurgery. This calls for further studies.

Accurate assessment of blood tension of a volatile anaesthetic by chromatographic measurement using the head-space technique is dependent on an accurate value for the blood/gas partition coefficient. We used the two-stage head-space analysis method described by Smith and colleagues, which allows for the simultaneous calculation of the blood/gas partition coefficient independent of the sevoflurane tension in the sample. The value found, 0.76, was higher than that reported by Strum and Eger, (0.69). Another recent investigation arrived at the same value as that obtained in the present study, and it cannot be excluded that the earlier value represents an underestimation. It should be noted that the blood/gas partition coefficient only affects the calculation of the absolute value of the tension of dissolved sevoflurane and that comparisons of relative levels are possible also when the blood/gas partition coefficient is slightly offset.

In conclusion, wash-in kinetics for sevoflurane are similar when delivered by an AnaConDa® and by a vaporizer in a
non-rebreathing circuit. Under the conditions of this study, the desired steady-state arterial tension is obtained within 30 min using the nomogram to determine the infusion rate to the AnaConDa® supplied by the manufacturer. End-tidal sevoflurane tension measured at the gas monitoring port of the AnaConDa® by an anaesthetic gas analyser accurately reflected arterial tension, but inspired tension was underestimated while using the AnaConDa®.

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References