ELSEVIER

Journal of Chromatography B, 668 (1995) 41–52

JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL APPLICATIONS

Analysis of sevoflurane degradation products in vapor phase samples

David D. Cunningham*, Jack Webster, Don Nelson, Brad Williamson

Solutions Development, D-971, AP4, Hospital Products Division, Abbott Laboratories, Abbott Park, IL 60064, USA

First received 5 October 1994; revised manuscript received 1 February 1995; accepted 1 February 1995

Abstract

Sevoflurane degradation products were measured by GC–flame ionization detection in vapor phase samples using manual and automated injection methods. Sample handling techniques allowed the transfer and storage of samples for up to 72 h. Compound A, fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether, was the major vapor phase degradation product formed in simulated clinical conditions. Recoveries of 4–32 ppm (v/v) compound A concentrations using the manual method were in the range of 88–117% ($n = 12$, mean = 102%, R.S.D. = 9%).

1. Introduction

Sevoflurane is a fluorinated derivative of methyl isopropyl ether which is under development for use as an inhalation anesthetic. Sevoflurane is a pleasant-smelling liquid, boils at 58.5°C and has a vapor pressure of 27 kPa (200 torr) at 25°C, with a low distribution coefficient into blood [1]. It provides rapid, pleasant, irritation-free inhalational induction and rapid emergence from anesthesia.

The degradation scheme for sevoflurane shown in Fig. 1 was proposed after identification of compounds A–E in liquid samples degraded with sodalime [2]. In anesthesia circuits, the major degradation product was compound A (fluoromethyl 2,2-difluoro-1-(trifluoromethyl)-vinyl ether) [2–6]. The level of compound A in an anesthesia circuit may increase when the vapor is repeatedly recirculated over a carbon dioxide scrubber containing strong base. Somewhat surprisingly, sevoflurane was found to degrade to methanol and the methanol can add across the double bond of compound A to form compound B. Trace levels of compound B (2 ppm) have been reported in anesthesia circuits [2,5–6]. The disappearance of sevoflurane from closed systems and conventional anesthetic circuits has been reported [7–10].

Measurement of the absolute amount of sevoflurane degraded in an anesthesia circuit is difficult. Sevoflurane may be absorbed. Hydrofluoric acid may react with sodalime to form insoluble calcium fluoride. Methanol may remain in the moist sodalime or dissolve in the water traps in the carbon dioxide scrubber and anesthesia circuit. However, sevoflurane degradation is only of potential concern when the degradation products are volatile compounds delivered to the patient through the anesthesia circuit in clinical practice.

This work describes a method for the analysis

* Corresponding author.

0378-4347/95/$09.50
SSDI 0378-4347(95)00069-0

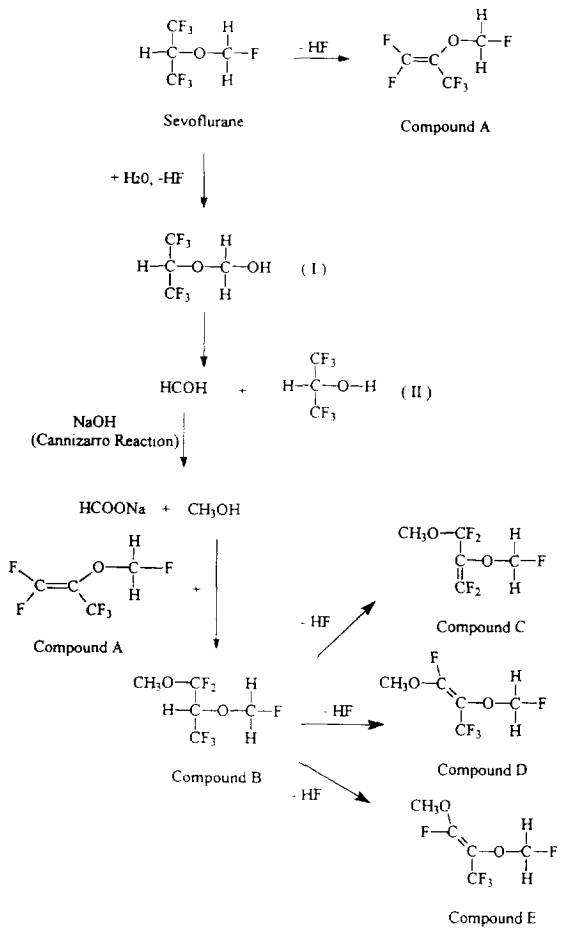

Fig. 1. Sevoflurane degradation scheme.

of trace levels of compound A in vapor phase samples in greater detail than in previous publications. Dilute gaseous preparations were made using calibrated gas-sampling bulbs and gas-tight syringes. The response factor of compound A relative to sevoflurane was determined so that sevoflurane could be used as a surrogate standard. Special sample handling procedures were developed to avoid contamination or changes in concentration of the sample over a 72-h period. Standard addition/recovery experiments in the range of 4–32 ppm were found to give an overall recovery of 102% ($n = 12$, range 88–117%, R.S.D. 9%). Normal instrument-to-instrument and day-to-day variations were observed. The method was automated in conjunction with an anesthesia machine. Levels of compound A and other gaseous degradation products in the anesthesia circuit were determined under worst case conditions. The method permitted the study of compound A levels in inhalation gas delivered to patients during normal clinical practice, and the study of compound A formation under simulated clinical conditions.

2. Experimental

2.1. Chemicals

Sevoflurane, fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether was supplied by Abbott Laboratories (Abbott Park, IL, USA). Compressed gas cylinders of standard sevoflurane (10–20 ppm in air) were supplied by Matheson Gas Products (Joliet, IL, USA). Compound A, fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether, was supplied by Central Glass (Tokyo, Japan). The *n*-butyl chloride used as an internal standard (I.S.) was HPLC grade. Chemetron Medical (St. Louis, MO, USA) supplied Baralyme brand barium hydroxide lime, USP.

2.2. Materials

Gas-sampling bulbs (Alltech Cat. Nos. 7012, 7011, 7043, 6950, 6954, 6940, 6944), 10-μl syringes (Hamilton, Cat. No 803662) and 2- or 5-ml gas-tight syringes (Dynatech Precision Sampling, Series A-2, Cat. No. 050034 and 050035) were supplied by Alltech (Deerfield, IL, USA). Round sample bottles of untreated Type 1 flint glass (Wheaton Tubing Products, Millville, NJ, USA) were sealed with 20-mm stoppers (West 888 gray, West Co., Phoenixville, PA, USA) using aluminum crimp caps and a West C-205F crimper.

2.3. Equipment

The gas chromatographic systems (Hewlett-Packard Models 5790, 5890, and 5890 series II) included a flame ionization detector and an

electronic data-handling system (Hewlett-Packard or Spectra Physics). The method was automated using the valve controls of an HP 5890 series II GC. A diagram of the stainless-steel tubing and electric/pneumatic solenoids is shown in Fig. 2. The injector loop in valve 1 (Valco AC6UW valve, A90 actuator, SL2506UW sample loop, and Humphrey 41E1-120V solenoid) was 250 μl. The six-position selector valve 2 (Valco CSD6UW valve, A6 actuator, Humphrey 41E1-120V solenoid), low dead-volume on-off selector valve 4 (Valco AC4UW valve, A90 solenoid, Humphrey 41E1-120V solenoid) and electronic 3-way valve 3 (Humphrey 41E1-120V solenoid) were supplied by Humphrey Products (Kalamazoo, MI, USA) and Valco Valves (Houston, TX, USA). The sequence of steps for the automated system is shown in Table 1.

The column was a 1.8 m × 2 mm I.D. glass column with a liquid phase of 1% Alltech AT-1000 on 60/80 mesh Graphpac GB (Alltech Cat. No. 8517). The injector, detector, and oven temperatures were 135°C, 225°C, and 110°C, respectively. The gas flow-rates were 20 ml/min helium carrier gas, 35 ml/min hydrogen, and 350 ml/min air.

2.4. Sample and standard preparation

A stock internal standard was prepared by adding 4 μl of *n*-butyl chloride into a 1000-ml gas-sampling bulb. A working internal standard (WIS gas bulb) was prepared by adding precisely 1 ml of stock internal standard into a 500-ml gas-sampling bulb. A stock standard was prepared by adding precisely 10 μl of sevoflurane into a 1000-ml gas-sampling bulb (SS gas bulb). A working standard was prepared by adding

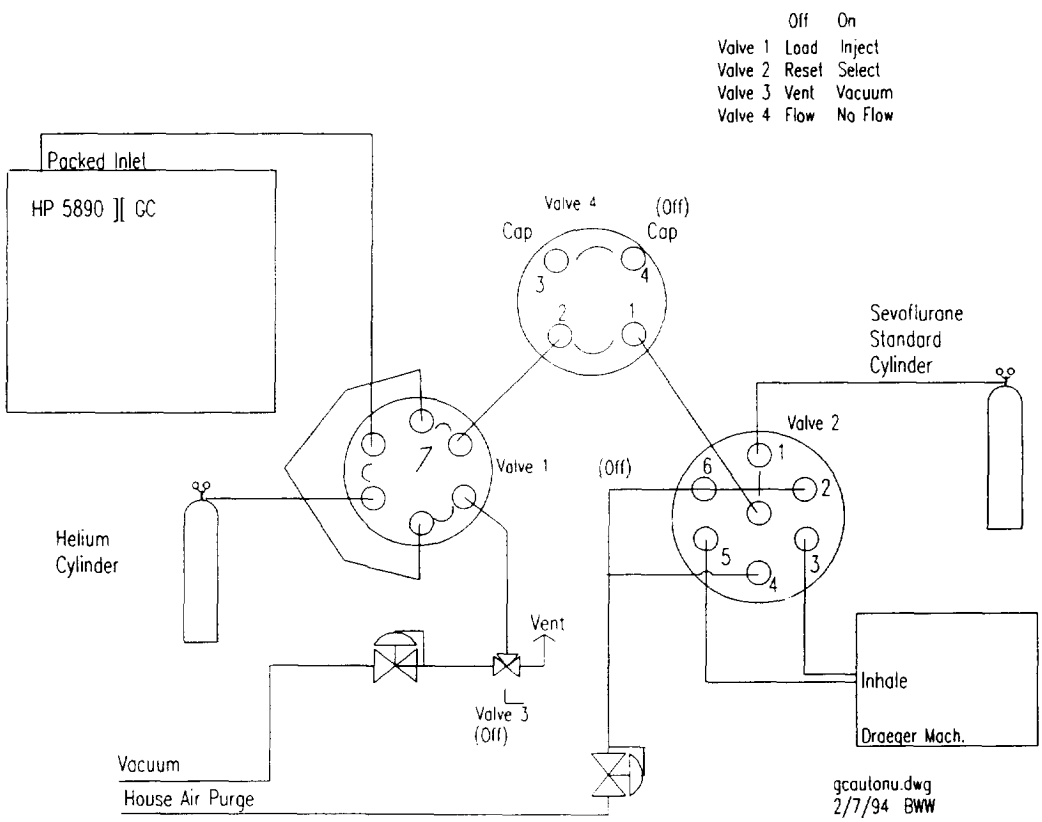

Fig. 2. Automated injector system.

Table 1
Sequence of steps for automated method

Step	Time (min)	dT[a] (s)	Off/on Load/ inject Valve 1	Off/on Reset/ turn Valve 2	Position	Off/on Vent/ vacuum Valve 3	Off/on Flow/no flow Valve 4	Status
1	0.00		Off	Off	Air	Off	Off	Start
2	0.01	0.60		On	Spl/Std[b]			Select sample
3	0.05	2.40				On		Start vacuum pull
4	0.25	12.00		Off	Reset	Off		Reset selector, vent
5	0.50	15.00					On	Block system
6	0.52	1.20	On					Inject
7	0.54	1.20		On	Air	On	Off	Select air unblock system vacuum
8	0.57	1.80				Off	On	Vent block system
9	0.61	2.40	Off	Off	Reset		Off	Stop inject, reset selector unblock system
10	0.85	14.40	Off	Off		Off	Off	Stand by: purge

[a] dT = time allowed for each step.
[b] Spl/Std = select standard or sample.

precisely 0.5 ml of stock standard and 0.5 ml of stock internal standard into a 500-ml gas-sampling bulb (WS gas bulb). The peak area ratio, R_{std}, for the working standard was determined using 1-ml injections. A separate "low concentration" syringe was used for injection of the working standard since the PTFE portion of the syringe may become contaminated with traces of sevoflurane during preparation of the standards and injection of samples.

Samples (4 ml) were withdrawn from the anesthesia circuit and added to sealed sample bottles (25.4 ml) using a 5-ml gas-tight syringe. In the analytical laboratory, a 2-ml gas-tight locking syringe was inserted into the sample bottle, the plunger withdrawn to about 2 ml, and the syringe closed. The plunger was adjusted to precisely 1.5 ml and the syringe was opened to the environment (overdrawing the syringe and adjusting the sample to room pressure each time permitted repeated sampling from a bottle). Next, the syringe was closed and the plunger withdrawn to precisely 2 ml. The needle was inserted into the 500-ml gas-sampling bulb containing the working internal standard and the syringe was opened for about 1–2 s. The sample and I.S. mixture was compressed to about 1 ml prior to injection into the chromatograph. For convenience, concentrations are given in ppm (v/v).

2.5. Anesthesia system

The anesthesia machine was a Narkomed Standard from North American Drager (Telford, PA, USA) with a sevoflurane vaporizer. The system was operated under low-flow conditions of 1.5% sevoflurane, 250 ml/min oxygen, and 250 ml/min nitrous oxide circulated at 7 l/min (14 × 500 ml) using a ventilator. A rubber bag surrounded by an elastic band functioned as a model lung, which was connected to the anesthesia machine at the patient Y-site. A Marquest Medical Products (Englewood, CO, USA) SCT 3000 humidifying chamber and heated-wire breathing circuit was used to introduce moisture into the circuit. Carbon dioxide (340 ml/min) was introduced at the Y-site of the circuit and samples were withdrawn through a rubber reseal. Gas levels in the breathing circuit were monitored with a Capnomac Ultima Monitor supplied by Datex (Helsinki, Finland). The

carbon dioxide absorbent canister was filled with 1.0 kg of W.R. Grace (Lexington, MA, USA) Sodasorb brand sodalime.

3. Results and discussion

3.1. Method development

The carbon-based column packing material with a large surface area (100–110 m^2/g) retained many volatile compounds and allowed the use of fairly high and thus better-controlled column temperatures. Use of a packed column rather than a capillary column allowed the use of much higher carrier-gas flow-rates and the direct on-column injection of the gas samples. Gas-tight syringes were available in a variety of sizes. The sample injection volume of 2 ml was convenient to handle and was large enough to give the method good low-level sensitivity. The 2-ml injection was swept onto the column in about 6 s, so the band-broadening due to the injection volume was acceptable. Injection of a mock low-level sample on the day of analysis was used to assure that the system was sensitive enough to detect low levels of compound A (ca. 1 ppm). The width of the I.S. peak was typically 0.7 min and remained fairly constant over a number of months. The carrier gas flow-rate was fairly low to reduce the back pressure on the septum. Peak areas of the surrogate standard and I.S. were reasonably consistent when the hydrogen (25–35 ml/min) and air flow-rates (300–350 ml/min) were varied.

A dilute gaseous preparation of sevoflurane was used as a surrogate standard since it is commonly available in very high purity. Note, however, that sealing sevoflurane or compound A in glass ampuls can lead to significant degradation and formation of hydrofluoric acid. As an I.S., *n*-butyl chloride was chosen for its availability, volatility, and retention characteristics. It is well separated from the main sevoflurane peak and gives a fairly short run time. Flame-ionization detection was chosen since it is generally viewed as a rugged and sensitive means of detection.

The gasses are brought to atmospheric pressure in the syringe throughout the method so that accurate amounts of the gas can be taken from vessels originally under positive or negative pressures. When vessels may be under negative pressure, the syringe is filled with more than the desired volume and the volume of the specimen is compressed in the syringe prior to opening the syringe to atmospheric pressure. In this way, a specimen originally under a slight vacuum is not diluted with air when the syringe is opened to the atmosphere.

The sample is originally diluted by adding a known amount of sample to a sealed bottle. The sample mixes fairly quickly with the air in the sample bottle and the dilution can be calculated. If a small amount of the diluted sample leaks from the bottle prior to testing, the concentration of the sample is still accurately determined.

During method development, several procedures were used to remove traces of sevoflurane from the gas syringes. No fast, convenient, reliable method was found using solvents, heat, or vacuum. Thus, one syringe was used for injection of samples with high concentrations of sevoflurane and another syringe was used for injections of the low concentration standard.

3.2. Chromatography and specificity

Compound A is well separated from a manufacturing impurity [$(CF_3)_2CHOCH_2F$, compound M], sevoflurane, and *n*-butyl chloride (I.S.). Injection of the sample resulted in an immediate pressure-induced peak. Unretained oxygen (and nitrous oxide, when present) gave a positive peak at the time corresponding to the void volume of the column. Since an anesthesia machine may be used to deliver agents other than sevoflurane, the retention times of other agents were determined to assure that the other agents do not co-elute with compound A or the I.S. Typical retention times of the compounds of interest are shown in Table 2. None of the compounds co-eluted with compound A or the I.S.

Sevoflurane was used as a surrogate standard

Table 2
Typical retention times of anesthetic gasses and compounds of interest

Compound	Retention time (min)
Methanol	0.50
Desflurane	2.00
Compound A	3.80
Compound M	4.62
Enflurane	4.90
Halothane	5.48
Isoflurane	5.60
Sevoflurane	5.68
n-Butylchloride	8.94
Compound C[a]	27.8
Compound D[a]	34.9
Compound E[a]	37.2
Compound B[a]	38.0

[a] Tentative identification based on peak area ratios of degraded sevoflurane and capillary GC–MS work.

with the I.S. *n*-butyl chloride. A typical chromatogram of the working standard is shown in Fig. 3. Sevoflurane normally contains a trace amount of compound A. A preparation of about 0.3% sevoflurane, which corresponds to an undiluted sample concentration of about 2%, was injected into the chromatograph as a system suitability preparation. A typical chromatogram is shown in Fig. 4. The compound A peak is clearly visible above the baseline noise. A mock low-level sample preparation was made with a small amount of compound A (equivalent to a circulating concentration of about 0.9 ppm compound A) and sevoflurane (equivalent to a circulating concentration of about 1.4%). A chromatogram of the mock low-level sample after 72-h storage in the laboratory is shown in Fig. 5. The compound A and I.S. peaks are well resolved from the main sevoflurane peak. The sevoflurane contains a small amount of compound M which appears to elute at 4.8 min. Additional, unidentified small peaks were observed at 3.1 and 4.2 min, as well as on the trailing edge of the main sevoflurane peak (broad unintegrated peak). The unidentified peak at 4.2 min is a volatile component from the stopper that slowly increases with time. This

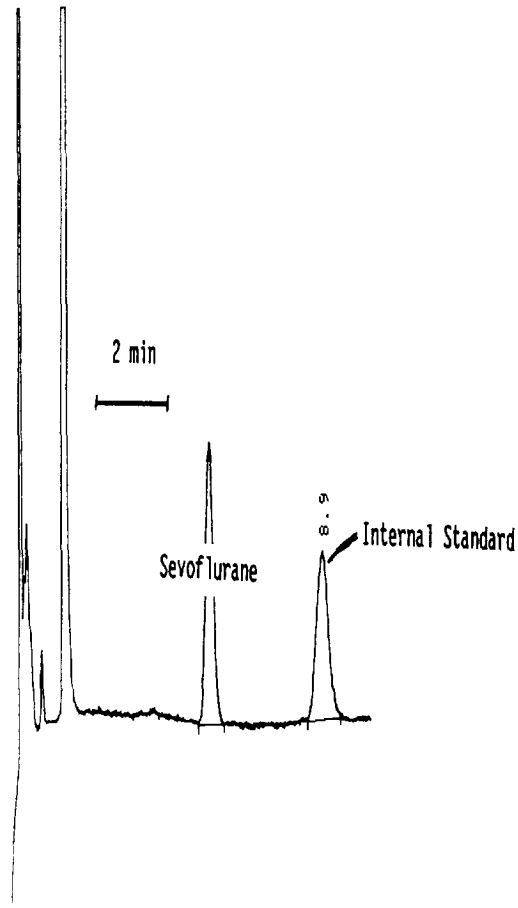

Fig. 3. Chromatogram of working standard, 1-ml injection.

peak did not grow-in significantly when stoppered bottles were heated at 40°C for up to 1 h. Thus, the peak at 4.2 min can be ignored since it grows to a level of less than 1 ppm in 72 h, and is partially separated from the compound A peak.

4. Calculations

Calculation of concentrations assume a density of 1.525 for sevoflurane and 1.48 for compound A. A molar volume of 24470 ml/mol was used throughout the work since the gas mixtures were dilute and the ambient temperature was always near 25°C. The gas volume may change about 0.3%/°C, but the laboratory temperature is

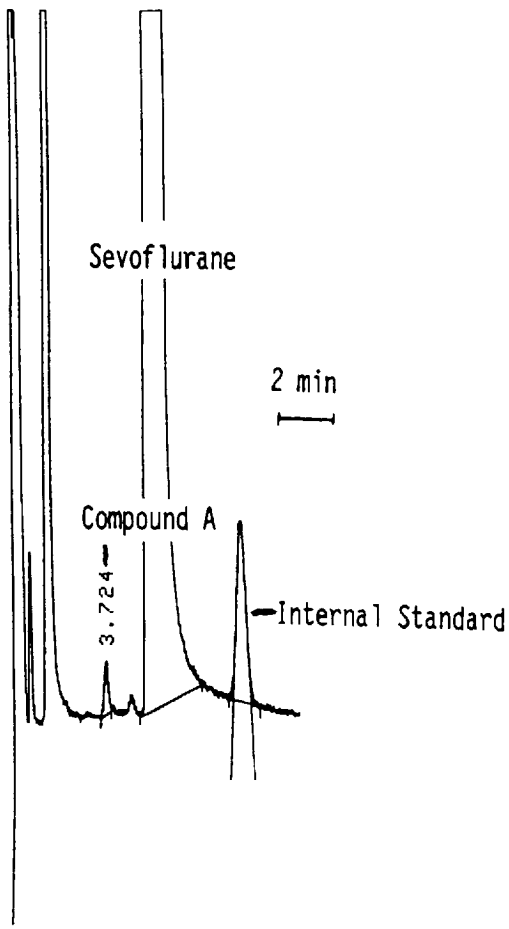

Fig. 4. Chromatogram of system suitability preparation, 2-ml injection. $N = (8.8/0.66)^2 = 2844$.

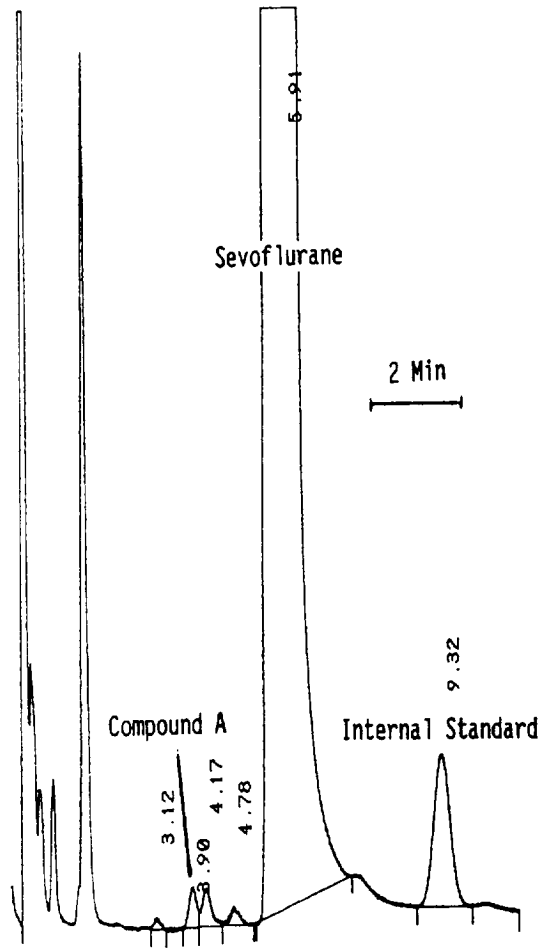

Fig. 5. Chromatogram of a mock low-level sample containing 0.9 ppm compound A after storage at room temperature for 72 h, 2-ml injection.

normally maintained close enough to 25°C that a temperature correction was unnecessary.

Volumes of the gas-sampling bulbs varied from their nominal values. Individual 0.5- and 1-l bulbs were found to contain 105–113% of their nominal volumes and 125-ml gas-sampling bulbs were found to contain 133–146 ml. Therefore, volume corrections were incorporated into the calculations. The sample bottles had an average volume of 25.4 ml and each individual bottle measured was within 1.5% of the average volume.

The relative response factor of compound A to sevoflurane was determined by adding known volumes of the liquids to gas bulbs and preparing dilute mixtures. Multiple injections of the mixtures by two analysts using two instruments gave an average relative response factor of compound A to sevoflurane of 0.864 on a v/v basis. The responses of compound A and sevoflurane are expected to be nearly equal on an equal-mass basis. On a volume basis, there is 10% less weight of compound A since its molecular mass is lower. Thus, the v/v response factor of 0.864 corresponds to a nearly equal response on a weight basis, as expected. The concentration of compound A was calculated as follows:

$$\frac{R_u}{R_{std}} \cdot \frac{1.865\text{ ml Sevo}}{1.865\text{ ml} + \text{SS bulb vol}} \cdot \frac{0.5\text{ ml}}{1\text{ ml} + \text{WS bulb vol}} \cdot \frac{10^6}{0.864} \cdot \frac{29.4\text{ ml}}{4\text{ ml}} \cdot \frac{1 + \text{WS bulb vol}}{1 + \text{WIS bulb vol}} \cdot \frac{1\text{ ml STD}}{1.5\text{ ml sample}} = \text{ppm compound A}$$

Refer to section 2.4. for a description of the symbols.

4.1. Linearity and standard addition/recovery

Plots of the peak-area ratios of compound A to I.S. versus the concentration of compound A were linear in the range studied, 0.2–9 ppm, corresponding to 1.5–65 ppm in undiluted samples (analyst 1, ratio = 1.13 (ppm) + 0.10, R^2 = 1.0000; analyst 2, ratio = 1.07 (ppm) + 0.14, R^2 = 0.9998). Mock samples were prepared with about 4, 9, or 32 ppm compound A and assayed by two analysts. The results are shown in Table 3. At two other laboratories, standard addition/recovery experiments were performed by adding low levels of sevoflurane to the sample bottles and measuring the sevoflurane concentrations. The average recoveries from the two labs were 97% (n = 3, R.S.D. = 6%) and 105% (n = 3, R.S.D. = 5%). The variation in the standard addition/recovery results includes any variation in the preparation of the samples, as well as the normal variation in the assay.

4.2. Sample stability

Sample stability was measured by preparing several bottles with mock samples containing 1.4% sevoflurane with either 0.92 or 9.08 ppm compound A, and measuring the samples over a period of several days. The results are shown in Table 4. The results show that the samples are stable over a period of several days. Again, the variation in the results includes variation in the preparation of the individual samples and the normal variation in the assay. The average recoveries for the 0.92 ppm and 9.08 ppm levels were 75% and 96%, respectively.

4.3. Interfering substances

Several types of containers were initially considered for storage of the samples. Evacuated Vacutainer brand blood collection tubes have been used to prepare sevoflurane vapor phase standards [11]. In our study, Vacutainer tubes containing either glycerol- or silicon-based stopper sealants were found to contain a number of volatile compounds from either the stopper or sealant which interfered with the determination. The level of compound A in Hewlett-Packard Head-Space sample vials was found to decrease about 30% per day, presumably due to adsorption into the PTFE coating of the cap. Six stoppers were screened for possible use. The West 888 gray stopper was found to have the cleanest blank chromatogram and a high compound A recovery.

The patient's expired breath will comprise a

Table 3
Standard addition/recovery of compound A

Analyst	Recovery (%)		
	4 ppm	9 ppm	32 ppm
A	90.5	98.7	96.6
A	97.7	98.4	98.6
B	106.1	117.3	116.0
B	88.0	109.7	106.6
Mean	95.6	106.0	104.4
R.S.D.	± 8.5	± 8.7	± 8.5
Overall mean	102.0		
Overall R.S.D. (%)	± 9.1		

Table 4
Stability of mock samples

Time (h)	Analyst	Instrument	Compound A (ppm)	
			0.92	9.08
0	A	1	0.77	9.0
2.5	A	1	0.79	8.6
3.5	B	2	0.76	9.4
23	A	1	0.59	7.4
25	A	1	0.62	9.1
25.5	B	2	0.89	9.7
43.5	A	1	0.55	8.5
47	A	2	0.79	9.0
48	A	1	0.47	8.1
49.5	A	1	0.41	8.3
49.5	A	2	0.76	8.3
72.5	B	2	0.86	8.7
Mean			0.69	8.7
S.D.			± 0.16	± 0.6
R.S.D. (%)			± 23	± 7.2

portion of the sample and patients may expire a variety of volatile compounds. In order to assure that expired volatile compounds would not interfere with the method, three individuals expired a breath into a 1-l bag and re-breathed the expired air one time. An undiluted portion of the expired/re-breathed air was injected into the chromatograph. The only significant peak in the retention time window from 2–11 min was at the sevoflurane retention time; however, the peak was not sevoflurane since the unidentified compound eluted on the trailing edge of the sevoflurane peak in a mixed sample. No peaks were found to elute at the compound A or I.S. retention times, indicating that interfering volatile compounds are not normally present in expired breath.

4.4. Automation

The sampling and analysis of the anesthesia machine breathing circuit was automated in order to handle the large number of samples generated. The gas chromatograph was equipped with gas-sampling valves as shown in Fig. 2. A gas standard was custom-prepared and standardized using the manual injection technique ($n = 44$, mean = 13 ppm, R.S.D. = 6%). The I.S. was not necessary since a fixed-loop injector was used. Several high levels of compound A were generated in the breathing circuit using low-flow conditions with several varieties of carbon dioxide scrubbers and large flow-rates of carbon dioxide. In all cases, the compound A levels determined using the two methods were comparable.

The peak area response of the sevoflurane gas standard using the automated method had an R.S.D. of 1% ($n = 63$) over a 3-week period. Using the manual injection method and ten separate preparations of the gas bulbs, the R.S.D. values of the sevoflurane peak area, the I.S. peak area, and the peak area ratio were 9%, 6%, and 5%, respectively. These manual injection results indicate that the I.S. increased the precision of the method, since the R.S.D. of the ratio was smaller than the R.S.D. of the peak area. However, the automated method was more precise than the manual method. The automated injection method could be used for laboratory studies; however, the manual method was re-

quired for clinical studies where samples had to be transferred from the operating room to the laboratory.

4.5. Capillary inlet injector systems

The method was modified for use on a Hewlett-Packard 5890 Series II chromatographic mainframe fitted with a capillary inlet system and a packed column. A packed column can be connected to a capillary inlet system since the diameter of the packed column and the diameter of a split/splitless insert are the same [12]. The capillary inlet injection system contains additional tubing for split/splitless injections and septum purging so small amounts of the injection can enter the additional tubing. Injections were made over a period of 10–15 s without prior compression so that the main sevoflurane peak did not tail into the I.S. peak. The I.S. was allowed to mix with the sample for 5–10 min to assure that any loss was homogeneous with respect to sample and I.S. Carry-over of traces of sevoflurane was eliminated by injections of air prior to injection of the working standard. Obviously, a packed column injector should be used, if available.

4.6. Formation of additional degradation products

During the degradation of sevoflurane by sodalime, compound A may combine with methanol to produce trace amounts of four other degradation products as shown in Fig. 1. Compounds A–E were prepared by refluxing sevoflurane in the presence of base. The degradation products were measured by injection of the degraded liquid on a Quadrex 007-624 (bonded methyl phenyl cyanopropyl silicone) 30 m × 0.32 mm, 3.0 mm film thickness column using a previously validated method [13]. The ratio of degradation products is shown in Table 5. A gas phase sample was prepared from each degraded liquid, and the retention times for compounds B–E shown in Table 2 were measured. In breathing circuit samples containing high levels of compound A, the compound B–E peaks at 27–38 min were very broad and difficult to measure. Thus, the column temperature was raised to 160°C for quantitation of compounds B–E in vapor phase samples. Under these conditions, compound A eluted at 1.4 min, sevoflurane eluted at 1.9 min, and the other degradation compounds eluted in a single peak at 6.9 min.

The concentrations of compound A and the other volatile impurities were measured in the breathing circuit. Since the moisture content of the carbon dioxide scrubber was previously shown to affect the disappearance of sevoflurane in the breathing circuit [9–10], the sodalime was dried to obtain various moisture contents. The results determined after 105 min of low-flow conditions using 1 kg of sodalime are shown in Table 6. Surprisingly, the amount and ratio of

Table 5
Ratio of volatile degradation products produced by refluxing with base

Compound	Type of base		
	Sodalime	Baralyme	KOH
A	1[a]	1[a]	1[b]
B	8.4	6.2	0.02
C	1.2	0.8	0.03
D	1.8	0.7	0.03
E	6.4	1.9	0.10

[a] By definition.
[b] Level of compound A much larger (100 ×) than with sodalime or Baralyme.

Table 6
Effect of sodalime moisture content on levels of compound A and other volatile degradation products

Moisture (%)	Compound A (ppm)	Other Compounds[a] (ppm)
16	28	4
14	31	1
11	28	6
6	20	74
2	4	22

[a] Calculated as compound A.

the degradation products were found to change significantly when the moisture content of the sodalime was well below the monograph limits (12.0–19.0%) [14]. Note that sodalime is not normally supplied with a low moisture content since the carbon dioxide scrubbing efficiency is much lower at low moisture contents [15,16]. At very low moisture levels (i.e., 2%), most of the sevoflurane disappeared from the circuit as indicated by the low sevoflurane levels measured by the Datex monitor (i.e., ca. 0.3% sevoflurane measured vs. 1.5% expected at 75 min) and the lower than expected areas of the sevoflurane peak. At 11–16% moisture, the sevoflurane levels reached the expected values and the degradation product profiles appeared fairly consistent. These results suggest that the route of the degradation reaction is substantially different on a wet and a dry sodalime surface.

The concentrations of compound A and the other volatile impurities were measured under extreme conditions in a breathing circuit containing sodalime with a moisture content of 11%. The results are shown in Fig. 6. The levels of compound A were nearly constant after 45 min. The combined concentration of the other degradation compounds increased to about 12 ppm (calculated as compound A) in 3.5 h. These results demonstrate that the main volatile degradation product in the breathing circuit was compound A. Note that with the normal compound A assay conditions the other degradation compounds elute at much longer retention times (27–38 min), resulting in very broad peaks which do not interfere with the detection and integration of the peaks of interest.

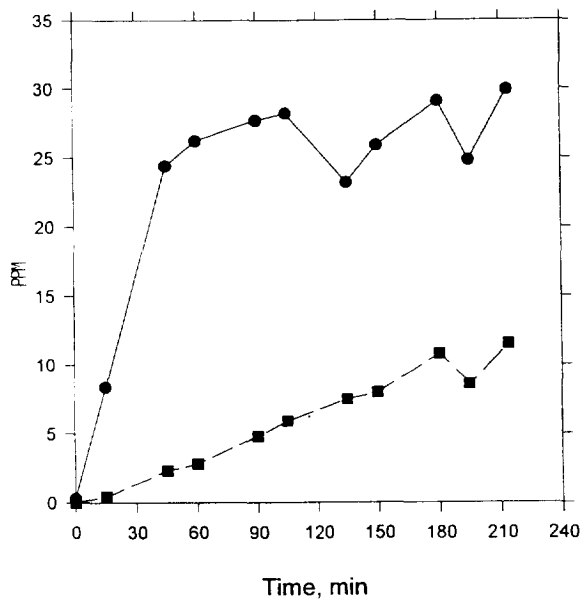

Fig. 6. Concentration of compound A (●) and other degradation products (■) formed in a low-flow anesthesia circuit with dried sodalime (11% moisture), oxygen (250 ml/min), nitrous oxide (250 ml/min), carbon dioxide (340 ml/min), and sevoflurane (1.5%).

5. Conclusion

Under simulated clinical conditions sevoflurane was found to degrade to compound A and minor amounts of other volatile degradation compounds, in agreement with previous studies. Well-established analytical tools and special sample handling procedures were used to develop accurate manual and automated methods for the analysis of trace levels of compound A in vapor phase samples. Application of the method in clinical studies will be reported elsewhere.

Acknowledgments

The authors thank John Oberdier, Shuyen Huang, Dennis Stephens, Frank van Pelt, Nigel

Foden and Mark Malcomson for technical advise and assistance.

References

[1] R. Wallin, B. Regan, M. Napoli and I. Stern, Anesth. Analg., 54 (1975) 758.
[2] C. Hanaki, K. Fujii, M. Morio and T. Tashima, Hiroshima J. Med. Sci., 36 (1987) 61.
[3] C. Huang, V. Venturella, A. Cholli, F. Venutolo, A. Silbermann and G. Vernice, J. Fluorine Chem., 45 (1989) 239.
[4] E. Frink, Jr., T. Malan, S. Morgan, E. Brown, M. Malcomson and B. Brown, Jr., Anesthesiology, 77 (1992) 1064.
[5] H. Bitoh and K. Ikeda, Anesthesiology, 75 (1991) A343.
[6] M. Morio, K. Fujii, N. Satoh, M. Imai, U. Kawakami, T. Mizuno, Y. Kawai, Y. Ogasawara, T. Tamura, A. Negishi, Y. Kumagai and T. Kawai, Anesthesiology, 77 (1992) 1155.
[7] D. Strum, B. Johnson and E. Eger II, Anesthesiology, 67 (1987) 779.
[8] J. Liu, M. Laster, E. Eger II, S. Taheri, Anesth. Analg., 72 (1991) 785.
[9] D. Wong and J. Lerman, Can. J. Anaesth., 39 (1992) 366.
[10] D. Strum and E. Eger II, Anesth. Analg., 78 (1994) 340.
[11] M. Watts, M. Escarzaga and C. Williams, J. Chromatogr., 577 (1992) 289.
[12] Hewlett Packard 5890 Series II Operating Manual.
[13] S. Huang, private communication.
[14] National Formulary XVII, United States Pharmacopeial Convention, Rockville, MD, 1990, p. 1978.
[15] V. Collins, Principles of Anesthesiology, Lea and Febiger, Philadephia, 1993, ch. 18.
[16] E. Brown, V. Bakamjian and A. Seniff, Anesthesiology, 20 (1959) 613.