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Clinical Characteristics and Biotransformation of Sevoflurane in Healthy Human Volunteers

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Sevoflurane was submitted to phase-1 studies in man following extensive testing in animal species without evidence of toxicity. Sevoflurane, 2–3 per cent inspired during maintenance, was administered with oxygen to produce one hour of anesthesia in six healthy adult male volunteers. Respiratory and cardiovascular functions, the electroencephalogram, arterial blood gases, blood sevoflurane, inorganic fluoride and total, nonvolatile fluorine concentrations, and inspired and mixed expired sevoflurane concentrations were measured during exposure. Concentrations of expired sevoflurane, blood and urinary fluoride, and total nonvolatile fluorine metabolites were also measured after anesthesia. During exposure spontaneous respiratory frequency increased 28 per cent, respiratory minute volume changed insignificantly, and Pa_{CO_2}s averaged 50 torr. Pa_{O_2}s remained near 400 torr. Arterial systolic blood pressure declined an average of 17 per cent. Pulse rate changed insignificantly. After an hour of exposure arterial blood serum inorganic fluoride concentrations averaged 22 μM and plasma nonvolatile organic fluorine concentrations averaged 9.1 mg/l, or 61.3 μM. Uptakes of sevoflurane averaged 94 (±63 SD) mmol. Following exposure 37 (±12) mmol of unaltered sevoflurane were estimated to be excreted in exhaled air and 0.90 mmol of inorganic fluoride and 163 mg, or 1.43 (±0.26) mmol of organic fluorine were excreted in the urine. Recoveries in exhaled air and urine averaged 51.5 (±22.4) per cent of uptake. There was no significant drug-exposure-related change in the chest radiogram, electrocardiogram, electroencephalogram, urinalysis results, complete blood count, prothrombin time, serum electrolytes, transaminases, or hepatic and renal functions during four weeks following exposure compared with preexposure values. Sevoflurane produced anesthesia of excellent quality; it appears to undergo limited biotransformation and to have little or no systemic toxicity. (Key words: Anesthetics, volatile: sevoflurane. Biotransformation: fluorometabolites. Pharmacokinetics: excretion; uptake. Toxicity: metabolites.)

SEVOFLURANE (fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether; fig. 1), a promising new, nonflammable inhalational anesthetic agent, has undergone extensive testing in experimental animals without evidence of tissue toxicity. It has a blood–gas partition coefficient of 0.60[1] and an oil–gas partition coefficient of 55.[2] It has vapor pressures of 160 and 200 torr at 20° C and 25° C, respectively. It has a MAC in the rat of 2.5 per cent,[2] and a predicted MAC in man[3] of 2.6 per cent based on its oil–gas partition coefficient. The present phase-1 studies were undertaken to determine its clinical safety and extent of biotransformation in normal man.

Methods

Following approval by the institutional committee on human subjects in research, six fully informed, young adult male volunteers were selected for exposure to sevoflurane for one hour. The subjects' average age was 22.5 (±4.0 SD) years; their average height was 181 (±4.2) cm, and their average weight was 79.5 (±7.7) kg. Their body fat was 7.6 (±3.5) per cent of body weight, calculated from the empirical relationship[4]:

> Per cent fat = 100 (4.201/specific gravity) − 3.813, in which specific gravity = antilog 0.848 (0.242 log height [cm] − 0.1 log weight [g] − 0.0172)

All were free of systemic disease and had normal hepatic function and normal renal function as determined by medical history, physical examination, radiographic examination of the chest, electrocardiogram (ECG), electroencephalogram (EEG), complete blood count, prothrombin time, urinalysis, and clinical laboratory tests that included serum glucose, cholesterol, blood urea nitrogen, creatinine, uric acid, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), creatinine phosphokinase, calcium, phosphate, total protein, albumin, sodium, potassium, chloride, serum hemoglobin, CO_2, ferritin and insulin. In addition, 24-hour urine collections were analyzed for creatinine, sodium, potassium, fluoride ion, and organic fluorine contents. Prior to exposure, the complete blood count, urinalysis, clinical laboratory tests, and 24-hour urine collection analyses were repeated twice.

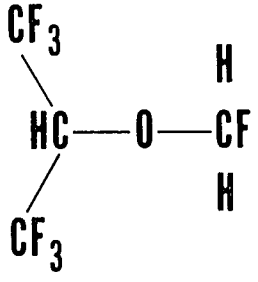

FIG. 1. Sevoflurane.

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The subjects were hospitalized overnight to obtain basal measurements of blood pressure, pulse and respiratory rates, and to insure fasting from 6:00 P.M. the night before exposure. Immediately prior to exposure an intravenous infusion of 5 per cent dextrose in lactated Ringer's solution was started. In three subjects, following demonstration of a negative Allen's test, an arterial cannula was inserted in a radial artery for continuous recording of the arterial blood pressure on a Hewlett Packard Model 7786A polygraph and to facilitate sampling for arterial blood gases. During exposure the lead II electrocardiogram and left parieto-frontal electroencephalogram were recorded continuously on the polygraph. In the three remaining subjects, arterial blood pressure was determined by the Riva-Rocci method, and arterial blood samples were obtained by needle punctures. Respiratory minute volume, measured with a Wright respirometer, and respiratory frequency were obtained at 3–10-min intervals. Samples of inspired and mixed expired air were obtained at 2–5-min intervals for analysis of sevoflurane concentration. Arterial blood samples were obtained at 15, 30, 45, and 60 min during exposure for determination of blood-gas tensions, sevoflurane concentration, and inorganic and organic nonvolatile fluorine metabolites. Axillary temperature was monitored by use of a thermistor.

Sevoflurane was administered by mask in oxygen from a Vernitrol® vaporizer via a partial rebreathing circuit using fresh gas flows of 5 l/min during induction and 3 l/min during the maintenance phase of anesthesia. The CO_2-absorbing canister was charged with fresh Baralym® moistened with 10 ml of water per 1,000-g disposable canister. The circle-system breathing circuit consisted of polyethylene breathing tubes and duplicate nonrebreathing valves in tandem at the machine and in the Y piece. A mixing chamber having a capacity of 3.80 l was interposed in the exhalation tubing.[5]

Induction of anesthesia was achieved by progressively increasing the concentration of sevoflurane in the fresh gas to 1, 3, 5, 7, and 10 per cent over 1–3 min. The concentration was maintained at 10 per cent until the pupils were centered and small, and eye movements had ceased. The concentration was then gradually reduced over the next 5–10 min to 3 per cent, at which point the total flow was reduced to 3 l/min. Beccause cumulative uptake and depth of anesthesia appeared excessive, the maintenance concentration was adjusted to 2 per cent during the exposure of the last two subjects. An oral and/or nasopharyngeal airway was inserted as necessary to maintain unobstructed spontaneous ventilation. Exposure was maintained for exactly 60 min, at the end of which the breathing circuit was disconnected from the anesthesia machine and the subject was permitted to breathe room air through the mask and breathing valves. Samples of mixed expired air were obtained from the exhalation tube mixing chamber at 2–5-min intervals for the first 30 min following exposure. Commencing at 30 min, or when the volunteer was able to walk, samples of mixed expired air were obtained at 5-min intervals for the next 90 min. The method of obtaining mixed exhaled air was to have the subject breathe in through his nose and exhale through his mouth through a Wright respirometer into an all-glass vessel having a volume of approximately 2.5 l.[6] Samples of mixed expired air were drawn from the out port of the vessel with a gas-tight syringe, analyzed immediately by gas chromatography, and repeated until the concentrations in three or four samples were constant. Minute ventilation and respiratory frequency were measured during this sampling. Mixed expired air was analyzed at 20-min intervals from two to four hours following exposure, and hourly thereafter through the seventh hour. Further samples were obtained for the next four days in the morning, at noon, and in the late afternoon.

Urine was sampled in 12-hour collections commencing the morning of exposure and continuing to the fourth postexposure day. The volumes, *p*H values and specific gravities of the urine samples were recorded and samples of each urine collection were analyzed for inorganic fluoride and total fluorine content. Consecutive 12-hour samples were combined and analyzed as 24-hour samples for creatinine, sodium, and potassium contents. Venous blood for repeat clinical chemistry tests was drawn each morning on postexposure days 1 through 4 and days 7, 14, 21, and 28. Spot urine samples were also obtained for routine urinalysis on days 1–4, 7, 14, 21, and 28.

Analytical Methods

Sevoflurane vapor concentrations were determined by gas chromatography against known gas standards. A 1.3 m × 2 mm ID glass column packed with diisodecylphthalate on Chromasorb P® was maintained at 60° C in a Hewlett-Packard Gas Chromatograph Model 7610A. The injection port was maintained at 100° C and the flame ionization detector was at 150° C. Blood sevoflurane concentrations were determined by the method of Fink and Morikawa.[7] Inorganic fluoride and total nonvolatile fluorine concentrations in urine and total fluorine in plasma were measured with a fluoride ion-specific electrode as previously described.[8] One-milliliter volumes of urine

TABLE 1. Respiratory and Circulatory Variables during Anesthesia (Mean ± SD) (n = 6)

	Before Sevoflurane Exposure*	After Sevoflurane Exposure			
		15 Min	30 Min	45 Min	60 Min
Respiration					
Frequency (min^{-1})	15 ± 2.5	20 ± 6.3	18 ± 20	19 ± 36	18 ± 3.6
Minute volume (l/min)	7.2 ± 1.1	6.5 ± 2.1	7.0 ± 1.7	7.3 ± 1.4	7.4 ± 6.3
*p*Ha		7.32 ± .02	7.33 ± .03	7.34 ± .01	7.33 ± .03
Pa_{CO_2} (torr)		53.1 ± 5.3	50.0 ± 5.0	50.4 ± 3.8	47.2 ± 7.0
Pa_{O_2} (torr)		392 ± 58	427 ± 82	398 ± 94	401 ± 102
Circulation					
Systolic BP (torr)	116 ± 7.1	95 ± 12	95 ± 9	97 ± 9	94 ± 12
Diastolic BP (torr)	70 ± 12.5	50 ± 10	51 ± 9	53 ± 9	52 ± 10
Pulse rate (min^{-1})	64 ± 11	63 ± 16	62 ± 15	65 ± 12	64 ± 16

* Preexposure blood pressures (BP) and pulse rates are based on three measured values obtained from each subject prior to the day of exposure.

samples collected during the preexposure period and the first 72 hours after exposure were incubated with bovine glucuronidase for one hour and extracted with ether. The ether extracts were analyzed by gas chromatography. Cyclohexanol was added to samples prior to incubation as an internal standard. Chromatograms were compared with a standard ether solution of hexafluoroisopropanol and cyclohexanol. Serum inorganic fluoride in excess of control serum fluoride was measured by the method of Yoshimura *et al.*[9] Arterial blood gases were measured on an Instrumentation Laboratory Model 113 analyzer.

The uptake rate of sevoflurane was calculated according to the following equation:

$$\dot{V} = (C_I - C_E)(\dot{V}_E + 0.6\ \dot{V}_f)$$

where $\dot{V}$ is uptake, C_I is the inspired concentration, C_E is the concentration in the exhalation tubing beyond the mixing chamber, $\dot{V}_E$ is minute ventilation, and $\dot{V}_f$ is fresh gas flow into the breathing circuit. The factor 0.6 was used as the fraction of the respiratory cycle occupied by exhalation to correct for fresh gas inflow during inhalation. Cumulative uptake was calculated as the product of uptake and time interpolated midway between measurements.

Pulmonary excretion of sevoflurane was calculated as the sum of integrals of three exponential curves obtained by successive subtraction of those functions with longer time constants from those with shorter time constants. These reflect the clearance rates from three assumed compartments, nominally a vessel-rich group (VRG), a muscle group (MG), and a fat group (FG), as defined in the model of Eger.[10]

Organic fluorine in urine and plasma was calculated as the difference between total nonvolatile fluorine and inorganic fluoride. Excess total organic fluorine and excess inorganic fluoride excretion were estimated from the extrapolated urinary excretion curves less preexposure excretion rates.

Results

Induction was rapid and smooth. Several subjects volunteered that their first awareness of the odor of the anesthetic was followed by loss of consciousness before the fifth breath. All subjects appeared relaxed during exposure. Following induction pupils remained small and centered. Tests for response to pain (pressure on periosteum of clavicle, pinch of trapezius muscle,[11] pressure on supraorbital nerve) during maintenance of anesthesia revealed analgesia in all subjects tested.

Respiration

Respiratory function was depressed moderately during induction and maintenance of anesthesia. During induction respiratory frequency increased slightly, and tidal volume decreased. Insertion of an oral or nasopharyngeal airway was tolerated, and increased minute ventilation toward preexposure levels (table 1). Arterial blood carbon dioxide tension (Pa_{CO_2}) was elevated moderately throughout exposure, and arterial blood *p*H was correspondingly reduced. Averaged Pa_{O_2}s ranged from 392 to 427 torr, and calculated values for base excess remained in a normal range.

Circulation

Systolic blood pressure fell 24 (±8 SD) per cent during induction of anesthesia, but returned to within 11 (±16) per cent of the resting preexposure blood pressure during maintenance. The pulse rate decreased an average of 4.6 (±6.8) per cent, but returned to preinduction levels during maintenance (table 1). The electrocardiogram showed normal sinus rhythm in all subjects during exposure.

Electroencephalogram

The electroencephalographic record (EEG) was displayed and recorded continuously. Examination of

each record revealed no period of electrical silence. The most prevalent pattern was 10 Hz with higher frequencies superimposed, consistent with light anesthesia.

Emergence

Two subjects showed transient excitement in response to stimulation during emergence from anesthesia. Emergence was otherwise uneventful. There was no shivering, excessive salivation, vomiting, or retching; there was no aberrant muscle activity, laryngospasm, or hiccough. Blood pressure rapidly returned to preinduction levels.

Post-exposure Laboratory Survey

One subject had elevations within the normal range of SGOT, SGPT, and lactate dehydrogenase (LDH) on day 14 after exposure, and had values that exceeded the normal ranges by 180 per cent, 29 per cent, and 2 per cent, respectively, on day 21, but these values reverted to preexposure levels by day 24 or 28. Interrogation revealed that the subject had exercised and drunk alcoholic beverages during the weekends preceding the day 14 and day 21 samplings. Aside from these abnormalities, no clinically significant alteration in the hematologic, renal, hepatic, or metabolic values occurred in any of the six subjects.

Blood Levels of Sevoflurane

During exposure arterial blood concentrations of sevoflurane varied between 45 and 115 mg/l; the average was 71 (±15 SD) mg/l (n = 23; table 2). Based on a blood–gas partition coefficient of 0.6, these concentrations reflect alveolar concentrations of 0.9–2.4 per cent and an average of 1.5 per cent. The concentrations in two samples of arterial blood obtained 10 and 15 min, respectively, following exposure were 25 per cent and 10 per cent of the mean during exposure.

Table 2. Arterial Blood Concentrations of Sevoflurane and Its Metabolites (Mean ± SD) (n = 6)

	Sevoflurane (μM)	Fluoride (μM)	Organic Fluorine* (μM)
During exposure			
15 min	419 ± 91.5	10.5 ± 2.8	55.0 ± 44.8
30 min	334 ± 65	17.0 ± 5.0	57.3 ± 26.5
45 min	325 ± 49	19.5 ± 6.6	60.0 ± 22.3
60 min	341 ± 61	22.1 ± 6.1	61.3 ± 41.4
After exposure			
10 min	{17.3}†		{36.6}
15 min	{7.4}	{17.3}	
Day 1		4.4 ± 1.3	21.6 ± 18.0
Day 2		3.3 ± 2.6	6.1 ± 5.3

* Measured as fluoride and assuming six atoms of fluorine per molecule.

† Bracketed values represent values obtained by single measurements.

Table 3. Uptake and Elimination of Sevoflurane (Mean ± SD) (n = 6)

	Sevoflurane (mmol)	Half-time (Hours)
Uptake	93.5 ± 62.7	
Pulmonary elimination		
Vessel-rich group	17 ± 3.0	0.18 ± 0.03
Muscle group	14 ± 7.5	1.8 ± 0.2
Fat group	6 ± 3.5	20.0 ± 6.0
Total	37 ± 11.5	
Urinary metabolites		
Fluoride ion	0.9 ± 0.18	16.3 ± 1.9
Organic fluorine (RF_6)	1.43 ± 0.26	13.8 ± 4.6
Ratio ($RF/2F^-$)	4.96 ± 0.77	
Recovery*	38 ± 11.4	

* Recovery represents the sum of pulmonary elimination and urinary organic fluorine.

Uptake and Pulmonary Excretion of Sevoflurane

Our estimates of drug absorbed during the 60-min exposure by each subject decreased progressively from 37.6 g to 7.9 g. The average was 18.7 g or 93.5 (±62.7 SD) mmol. Our recoveries of unaltered drug in exhaled air varied much less, and ranged from 56 to 27.5 mmol. The average was 37 (±11.5 SD) mmol (table 3). The pulmonary excretion curves lent themselves to analysis as the sum of three exponential processes (fig. 2). Interpreting them as release from three more or less distinct compartments, a vessel-rich group of visceral organs (VRG), a muscle group (MG), and a fat group (FG), we observed that the fraction of pulmonary excretion released from fat depots tended to vary directly with the fraction of body weight calculated to be fat.[4] On the average, 49 (±11 SD) per cent of the amount exhaled was released from the VRG, 35 (±9.2) per cent from the MG, and 15 (±5.6) per cent from the FG. The half-times for release from the three compartments were 10.8 (±2.1) min, 1.8 (±0.2) hours, and 20 (±6) hours, respectively (table 3).

Metabolites in Blood and Urine

During exposure, blood levels of nonvolatile organic fluorine increased dramatically; inorganic fluoride increased less. Excess serum fluoride concentrations averaged 0.42 (±.12) mg/l, or 22.1 (±6.1) μM, at the end of one hour of exposure (table 2). The maximum elevation over preexposure levels observed during exposure was 31.1 μM. Fifteen minutes after exposure, excess serum fluoride decreased to 95 per cent of one subject's maximum, and, on the average, to 4.4 (±1.3)

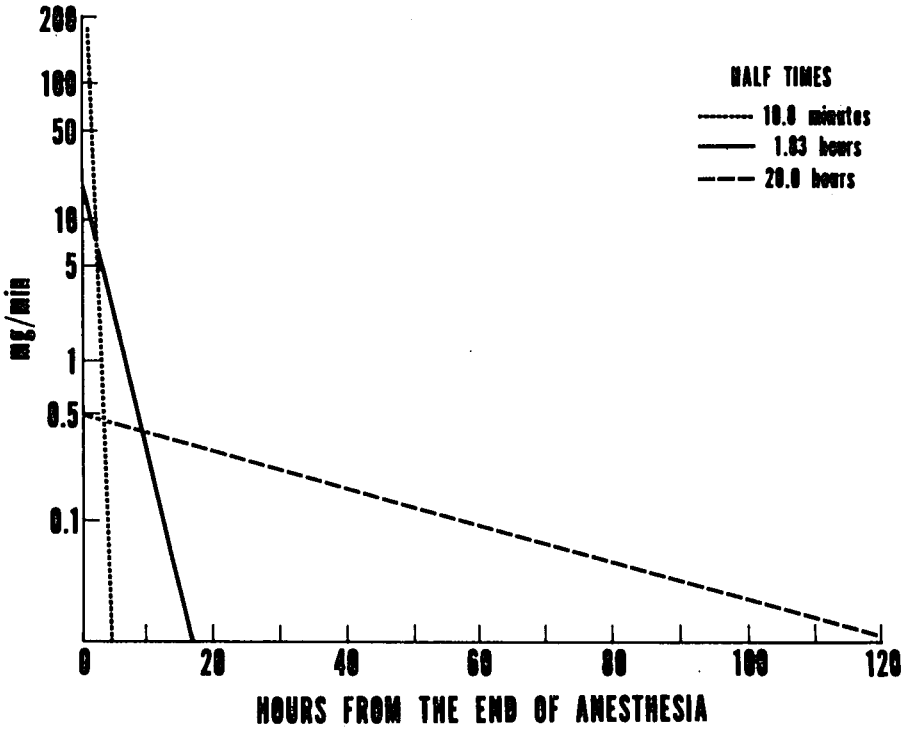

FIG. 2. Pulmonary excretion data of all six subjects were combined to obtain representative pulmonary excretion rates from three compartments. Refer to the text for the method of calculation. The equations for each function are:

$Y_1 = 191\ e^{-3.40\ t}$

(77 measurements, r = 0.85)

$Y_2 = 17.2\ e^{-0.41\ t}$

(76 measurements, r = 0.81)

$Y_3 = 0.51\ e^{-0.03\ t}$

(66 measurements, r = 0.83)

μM on day 1 following exposure. At end of exposure concentrations of nonvolatile organic fluorine in arterial plasma averaged 61.3 (±41.4) μM, assuming six fluorine atoms per molecule. One subject showed a reduction of arterial organic fluorine from 113.4 μM at the end of exposure to 36.6 μM 10 min later. Plasma organic fluorine was 21.6 (±18) μM on day 1 and 6.1 (±5.3) μM on day 2.

Examination of daily urinary creatinine, sodium and potassium excretions gave assurance that 24-hour urine collections were complete. Nonvolatile, fluorine-containing urinary metabolites included fluoride ion and an organic fluorine compound. Volatile urinary metabolites were not detectable in frozen urine samples collected during the first 72 hours following exposure. After incubation with glucuronidase, a strong peak coinciding with that of hexafluoroisopropanol (HFIP) was detected by gas chromatography. Simultaneous analyses for HFIP and organic fluorine in preexposure and six consecutive postexposure 12-hour samples indicated that HFIP accounted for 82 per cent of the organic fluorine; the average correlation coefficient between HFIP and organic fluorine for the six subjects was 0.98 (±0.02). The quantities of fluoride and organic fluorine excreted were 0.90 (±0.18) mmol of fluoride and 163 (±29) mg of organic fluorine measured as fluoride, or, assuming a molecule containing six fluorine atoms, 1.43 (±0.26) mmol. The half times for excretion of the inorganic fluoride and organic fluorine were 16.3 (±1.9) and 13.8 (±4.6) hours, respectively (table 3; fig. 3).

Discussion

The attributes of an inhalational anesthetic that determine clinical usefulness include nonflammability, rapid induction and emergence, lack of effects on vital functions during administration, and absence of organ system toxicity. The quality of anesthesia produced by sevoflurane appeared similar to that produced by other fluorinated volatile anesthetics (halothane, enflurane, isoflurane, methoxyflurane). All depress respiration and blood pressure during induction of anesthesia in spontaneously breathing subjects, but with surgical stimulation, respiration and blood pressure tend to return toward normal during maintenance anesthesia.[12] Sevoflurane appeared to differ from the other fluorinated drugs in the rapidity of induction and recovery, and the high degree of subject acceptance of an inhalational induction.

Extensive studies of the biochemical interactions of the volatile anesthetics with the microsomal enzyme systems of the body have supported the view that potential for toxicity is linked with biotransformation.[13] Accordingly, the search for safer inhalational anesthetics now stipulates resistance to biotransformation and conversion to harmless metabolites. Our present attempt to account for measured uptake by the sum of

exhaled, unaltered drug plus urinary metabolites[14] was undertaken to determine the extent of biotransformation.

The average of the individual recoveries of absorbed sevoflurane as expired sevoflurane and urinary metabolites was 50 (±22.6 SD) per cent. The greatest recovery was 88 per cent, obtained in the last subject studied. This is contrary to the results obtained in a previous quantitative metabolic balance study of isoflurane in patients,[15] in which 95 per cent of the absorbed drug was accounted for. Factors that can contribute to a discrepancy between uptake and recovery include experimental error and long-term retention of metabolites as a result of irreversible binding to fixed cellular components.[14] The large standard error of our average recovery precludes an evaluation of the role of the latter factor; however, in this study of sevoflurane two uncontrollable factors were present that were not present in the study of isoflurane: 1) The previous study was done on intubated patients who underwent surgical operations and remained hospitalized during the measurements of pulmonary excretion. The present study was of necessity performed on healthy volunteers, who went about their normal activities (work or study) during the time when measurements of pulmonary excretion were made. Increases in cardiac output and blood flows to muscle and fat resulting from workaday pursuits and exercise may have accelerated excretion of the drug considerably above the rates that were present while measurements were made during periods of sitting at rest. 2) Leaks around the mask would tend to exaggerate the quantity absorbed. Hence, our estimates of uptake probably are too high and those of excretion too low. They are included, nevertheless, in this report, because they bracket the true values and can be used to estimate the maximum amount of drug that underwent biotransformation.[14] The proportional amounts of inorganic fluoride and organic fluorine can be used similarly to determine the principal pathway of biotransformation.

It has been shown that approximately half of ingested or injected soluble fluoride salts is deposited in bone[16] and the rest is excreted in the urine with a half-time of four to five hours. The estimated quantity of fluoride ion released, therefore, would be twice that measured. The ratio of organic fluorine to inorganic fluoride formed thus approximated 5.0 (±0.8 SD). This suggests that the sevoflurane molecule lost one fluorine atom. We believe this probably resulted from hydrolysis of the ether linkage, the metabolites being fluoride ion, carbon dioxide, and hexafluoroisopropanol, which then was conjugated.

The quantity of sevoflurane metabolized should be represented by two times the urinary fluoride, or 1.80 mmol, or one sixth of the organic fluorine, or 1.43 mmol. These quantities represent 1.64 and 1.30 per cent, respectively, of estimated uptake, and 4.65 and 3.73 per cent, respectively, of our estimate of the total amount of drug excreted. Accordingly, sevoflurane is similar to enflurane with respect to biotransformation in man, or slightly more subject to biotransformation.

Two characteristics of a volatile anesthetic molecule determine the extent of its biotransformation: tissue solubility and chemical stability.[17] The low blood–gas and oil–gas partition coefficients of sevoflurane favor its rapid excretion. This can account for the rapid awakening time observed and the rapid reductions of arterial blood concentrations of sevoflurane and its

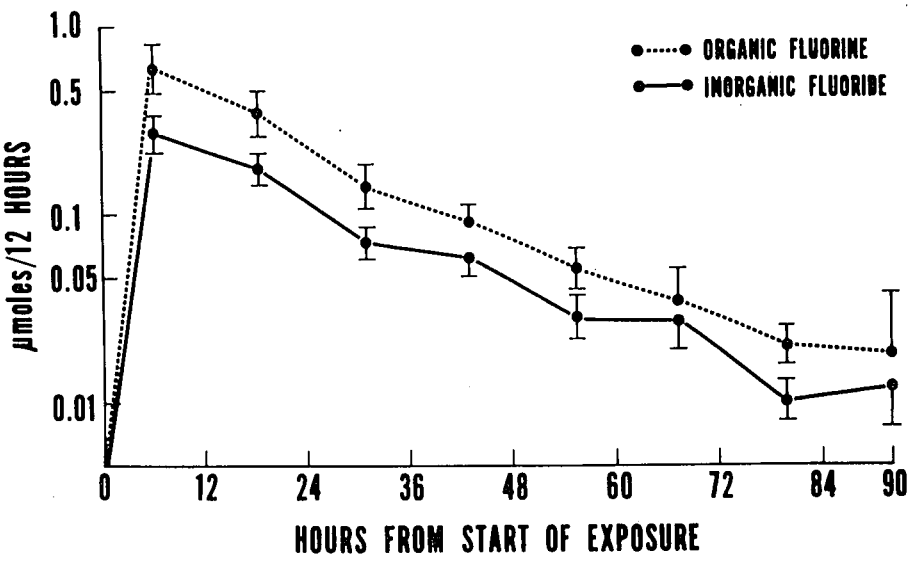

FIG. 3. Mean urinary excretion rates of fluoride ion and organic fluorine metabolites following sevoflurane anesthesia. Vertical lines are the standard errors of mean 12-hour excretions.

fluorine metabolites found in a few instances (table 2). Low tissue solubility also would cause most of the biotransformation to occur during exposure,[17] and would account for the finding that the fraction of sevoflurane metabolized was similar to or slightly greater than that of enflurane. The average half-times for urinary excretion of the fluoride and organic fluorine were 16 and 14 hours, respectively, further insuring that blood levels of these metabolites were insignificant 24–48 hours after exposure.

Before sevoflurane can be made available for general use it must undergo additional limited, phase-2 trials in surgical patients to determine the safe dosage range and other pharmacologic actions, then broad, phase-3 clinical trials to establish its safety in the presence of various diseases and conditions. This preliminary survey of its effects in normal man, however, suggests that sevoflurane may prove suitable for use in clinical practice.

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