Anesthesiology
82:1369–1378, 1995
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Clinical Sevoflurane Metabolism and Disposition

I. Sevoflurane and Metabolite Pharmacokinetics

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Background: **Sevoflurane has low blood and tissue solubility and is metabolized to free fluoride and hexafluoroisopropanol (HFIP). Although sevoflurane uptake and distribution and fluoride formation have been described, the pharmacokinetics of HFIP formation and elimination are incompletely understood. This investigation comprehensively characterized the simultaneous disposition of sevoflurane, fluoride, and HFIP.**

Methods: **Ten patients within 30% of ideal body weight who provided institutional review board-approved informed consent received sevoflurane (2.7% end-tidal, 1.3 MAC) in oxygen for 3 h after propofol induction, after which anesthesia was maintained with propofol, fentanyl, and nitrous oxide. Sevoflurane and unconjugated and total HFIP concentrations in blood were determined during anesthesia and for 8 h thereafter. Plasma and urine fluoride and total HFIP concentrations were measured during and through 96 h after anesthetic administration. Fluoride and HFIP were quantitated using an ion-selective electrode and by gas chromatography, respectively.**

Results: **The total sevoflurane dose, calculated from the pulmonary uptake rate, was 88.8 ± 9.1 mmol. Sevoflurane was rapidly metabolized to the primary metabolites fluoride and HFIP, which were eliminated in urine. HFIP circulated in blood primarily as a glucuronide conjugate, with unconjugated HFIP ≤ 15% of total HFIP concentrations. In blood, peak unconjugated HFIP concentrations were less than 1% of peak sevoflurane concentrations. Apparent renal fluoride and HFIP clearances (mean ± SE) were 51.8 ± 4.5 and 52.6 ± 6.1 ml/min, and apparent elimination half-lives were 21.4 ± 2.8 and 20.1 ± 2.6 h, respectively. Renal HFIP and net fluoride excretion were 4,300 ± 540 and 3,300 ± 540 μmol. Compared with the estimated sevoflurane uptake, 4.9 ± 0.5% of the dose taken up was eliminated in the urine as HFIP. For fluoride, 3.7 ± 0.4% of the sevoflurane dose taken up was eliminated in the urine, which, because a portion of fluoride is sequestered in bone, corresponded to approximately 5.6% of the sevoflurane dose metabolized to fluoride.**

Conclusions: **Sevoflurane was rapidly metabolized to fluoride and HFIP, which was rapidly glucuronidated and eliminated in the urine. The overall extent of sevoflurane metabolism was approximately 5%. (Key words: Anesthetics, volatile: sevoflurane. Ions: fluoride. Kidney: urine. Liver: metabolism. Metabolism. Metabolites: fluoride; hexafluoroisopropanol. Pharmacokinetics.)**

SEVOFLURANE is a new volatile anesthetic with a blood:gas solubility coefficient of 0.6–0.69.[1–3] Sevoflurane undergoes biotransformation to the primary metabolites fluoride and hexafluoroisopropanol (HFIP).[2] Several investigators have characterized the uptake and distribution of sevoflurane in humans.[2,4–6] Fluoride formation and excretion during and after sevoflurane anesthesia have been well described.[2,4,7–12] In contrast, blood sevoflurane concentrations have not been well described. Only a few investigators have reported sevoflurane blood concentrations, and no rigorous mathematical analysis was provided.[2,8,13,14] Furthermore, the systemic disposition of HFIP has not been described, and HFIP pharmacokinetics are incompletely understood. The purpose of this investigation was to characterize the disposition of sevoflurane and its metabolites by simultaneous measurement of sevoflurane in blood and fluoride and HFIP in blood, plasma, and urine.

Materials and Methods

Patient Selection and Clinical Protocol

Ten nonsmoking ASA physical status 1 or 2 patients undergoing anesthesia for elective surgery with antic-

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Received from the Departments of Anesthesiology and Medicinal Chemistry, University of Washington, Seattle, Washington; Abbott Laboratories, Abbott Park, Illinois; and the Department of Pharmaceutics, University of Minnesota, Minneapolis, Minnesota. Submitted for publication November 3, 1994. Accepted for publication March 6, 1995. Supported by grants from the National Institutes of Health (RO1 GM48712) and Abbott Laboratories and by a Pharmaceutical Research and Manufacturers of America Foundation Faculty Development Award (to Dr. Kharasch). Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 15–19, 1994.

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ipated duration of 3–5 h were studied. Eligible patients were 18–70 yr of age, within 30% of ideal body weight, and had normal indexes of liver and renal function. Patients were excluded if there was a history of hepatic or renal insufficiency, current use of medications known to alter hepatic drug metabolism, or prior exposure to sevoflurane or if they had undergone general anesthesia within 8 weeks of the study. No patient consumed more than a 1–2 U of ethanol (1 U equals one-half pint of beer, one glass of wine, or one mixed drink) per day. The investigational protocol was approved by the Institutional Human Subjects Committee, and all patients provided written informed consent. Patients abstained from alcohol-containing beverages or medications beginning the day before surgery, and lasting through 4 days after surgery. Patients also abstained from caffeine beginning 24 h before receiving sevoflurane. Patients were (mean ± SD) 44 ± 4 yr of age (range 23–68), weighed 73 ± 5 kg (55–102), and had a body mass index of 26 ± 2 (22–35). Three men and seven women were studied.

After midazolam (1 mg, intravenous), anesthesia was induced with propofol (1–2.5 mg/kg) and fentanyl (50–100 μg), and succinylcholine was administered to facilitate tracheal intubation. Immediately after the trachea was intubated, anesthesia was maintained with sevoflurane (2.7% end-tidal concentration) in oxygen (2–5 l/min). Inspired and end-tidal sevoflurane concentrations were monitored continuously (Capnomac, Datex Medical Instrumentation, Tewksbury, MA) *via* a sampling port located at the Y piece of the anesthesia circuit. The inspired sevoflurane percentage was carefully titrated to maintain the desired end-tidal sevoflurane concentration of 2.7% (1.3 MAC). Sevoflurane MAC (2.05 end-tidal percent[15]) was not adjusted for age. Use of muscle relaxants was avoided when possible; otherwise, patients received atracurium. No neuraxial local anesthetics or opioids were used intraoperatively. Sevoflurane (2.7%) end-tidal concentration was maintained for 3 h, unless the surgical procedure ended before that time. For operations lasting longer than 3 h, the sevoflurane was discontinued after 3 h, total gas flows were increased to 6 l/min, and anesthesia was maintained with propofol, nitrous oxide, and fentanyl. Nitrous oxide was not started until the end-tidal sevoflurane concentration had decreased to less than 0.2%. The nitrous oxide flow rate was not specified. Inspired and end-tidal sevoflurane concentrations were recorded at 15-min intervals while patients were intubated.

Venous blood samples for determination of blood sevoflurane and HFIP (unconjugated and total) concentrations were obtained before induction, 5 min after the start of sevoflurane, at hourly intervals during sevoflurane administration, when sevoflurane was discontinued, and 1, 2, 3, 4, 6, and 8 h after the end of sevoflurane administration. Blood was drawn into a plastic syringe (Sarstedt, Princeton, NJ), and the syringe was capped and stored on ice until frozen at −20°C for later analysis. Venous blood samples for determination of plasma fluoride and HFIP concentration were obtained before induction, hourly during sevoflurane administration, when sevoflurane was discontinued, and 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 84, and 96 h after the end of sevoflurane administration (or until the time of hospital discharge). Samples were collected into plastic tubes containing EDTA and centrifuged, and the plasma was frozen at −20°C until analysis. Urine for determination of fluoride concentration was obtained before induction and for the following consecutive intervals beginning at the start of sevoflurane anesthesia: 0–12, 12–24, 24–36, 36–48, 48–72, and 72–96 h (or until the time of hospital discharge). Urine was thoroughly mixed, the volume was measured, and an aliquot was frozen at −20°C for later analysis. Analytical methods for determination of blood sevoflurane, plasma and urine fluoride, and plasma, blood, and urine HFIP are provided in the Appendix.‖

Data Analysis

Anesthetic dose was calculated as the product of end-tidal (alveolar) sevoflurane concentration (F_A, expressed as MAC, uncorrected for age, where MAC = 2.05%) and time, determined in 2-min intervals until 10 min after incision and every 15 min thereafter. Total sevoflurane exposure is expressed in MAC-hours.

Sevoflurane uptake was approximated and used as a second measure of delivered dose, as described previously.[2,5] Uptake rate was calculated as

$$\dot{V}_U = \dot{V}_E \cdot (F_I - F_M), \qquad (1)$$

where $\dot{V}_U$ was the total pulmonary uptake rate (ml anesthetic vapor/min), $\dot{V}_E$ was the minute ventilation (ml/min), and F_I and F_M were the inspired and mixed expired sevoflurane concentrations, respectively, de-

‖ Details regarding analytical methods will be published separately (Lanni C, Guliad A).

termined in 15-min intervals. F_M was calculated according to

$$F_M = (f_A \cdot F_A) + (f_D \cdot F_I), \quad (2)$$

where f_A and f_D represent the fraction of ventilation coming from the alveoli and dead space, respectively. Values for f_A and f_D during mechanical ventilation were taken as 0.5 each, as described previously.[16] Values for total pulmonary sevoflurane uptake (l/min) were converted to moles/min by application of the general gas equation PV = nRT, where P is pressure in kilopascals (kPa), V is volume in liters, n is the number of moles of gas, R is the universal gas constant (8.31 kPa $\cdot$ l $\cdot$ $K^{-1} \cdot mol^{-1}$), and T is temperature in degrees Kelvin. Computations assumed atmospheric pressure (101.325 kPa) and a temperature equal to body temperature for the inhaled and exhaled vapors (37°C, 310.16°K). The sum of the products of pulmonary sevoflurane uptake rate and exposure time for each interval gave the total dose in moles.

Sevoflurane C_{max}, T_{max}, $t_{1/2}$, AUC, AUMC, MRT, CL, and V_{ss} were computed for each subject. Sevoflurane half-life ($t_{1/2}$) was determined by log-linear regression of the terminal portion of the blood concentration-time curve. Area under the blood concentration-time curve (AUC_{0-t}) from the start of anesthesia to the last measured concentration (C_{last}) was determined by the linear trapezoidal rule. The area was extrapolated to infinity ($AUC_{t-\infty}$) by dividing C_{last} by the terminal elimination rate constant, where C_{last} is the concentration at t_{last}. $AUC_{0-\infty}$ was the sum of AUC_{0-t} and $AUC_{t-\infty}$. Area under the first moment curve ($AUMC_{0-t}$) from the start of anesthesia to C_{last} was determined by the linear trapezoidal rule applied to C $\cdot$ t *versus* time data as

$$AUMC_{t_1-t_n} = \sum_{i=1}^{n-1} \frac{(t_{i+1} - t_i) \cdot (C_{i+1} \cdot t_{i+1} + C_i \cdot t_i)}{2}. \quad (3)$$

The area was extrapolated to infinity ($AUMC_{t-\infty}$) according to

$$AUMC_{t-\infty} = \frac{C_{last} \cdot t_{last}}{K_e} + \frac{C_{last}}{K_e^2}. \quad (4)$$

Total $AUMC_{0-\infty}$ equals the sum of $AUMC_{0-t}$ and $AUMC_{t-\infty}$. Mean residence time (MRT) was approximated according to

$$MRT = \frac{AUMC}{AUC} - \frac{\text{Duration of anesthetic administration}}{2}. \quad (5)$$

Apparent systemic clearance (CL) was computed as the sevoflurane dose divided by sevoflurane $AUC_{0-\infty}$. This was performed using both the MAC-hour and total pulmonary uptake dose estimates. Apparent volume of distribution (V_{ss}) was computed as the product of MRT and CL.

Net plasma fluoride concentrations were obtained by subtracting the preanesthetic baseline value from all subsequent values and were used for pharmacokinetic calculations unless otherwise indicated. HFIP concentrations were zero in all preanesthetic baseline samples. Fluoride and HFIP half-lives were determined by log-linear regression of the terminal portion of the net concentration-time curves. Area under the net plasma fluoride-time curve (AUC_{0-t}) from the start of anesthesia to the last measured concentration (C_{last}) was determined by the linear trapezoidal rule. Areas were extrapolated to infinity ($AUC_{t-\infty}$) by dividing $\hat{C}$ by the terminal elimination rate constant, where $\hat{C}$ was the concentration at t_{last} estimated from the regression. $\hat{C}$ rather than the actual concentration C_{last} was used to decrease the variability introduced by extrapolation. Fluoride C_{last} values were highly variable, because of factors such as variation in baseline, urine *p*H, and diurnal variation. $AUC_{0-\infty}$ was the sum of AUC_{0-t} and $AUC_{t-\infty}$. Plasma HFIP area under the curve was determined by the linear trapezoidal rule from time zero to 96 h after the end of anesthesia.

Urinary fluoride and HFIP excretion for each 12- or 24-h urine collection interval was calculated as the product of urine metabolite concentration and urine volume (amount excreted, AE). Urinary metabolite excretion rates were the amount excreted divided by the collection interval. Renal fluoride and HFIP clearances were determined from plasma concentrations and urinary excretion data according to

$$CL_r = \frac{AE}{AUC}, \quad (6)$$

where AE is the amount excreted in the urine, and AUC is the area under the plasma concentration curve. Renal fluoride clearances were calculated from the first three urine collections (0–36 h) and plasma AUC (unadjusted for background) from 0–39 h. Renal HFIP clearances were calculated using the intervals of 0–96 h and 0–99 h for AE and AUC, respectively. The total fluoride excreted during the study period (AE_{tot}) was comprised of endogenous fluoride excretion (AE_{endog}) and fluoride derived from sevoflurane (AE_{sevo}) according to

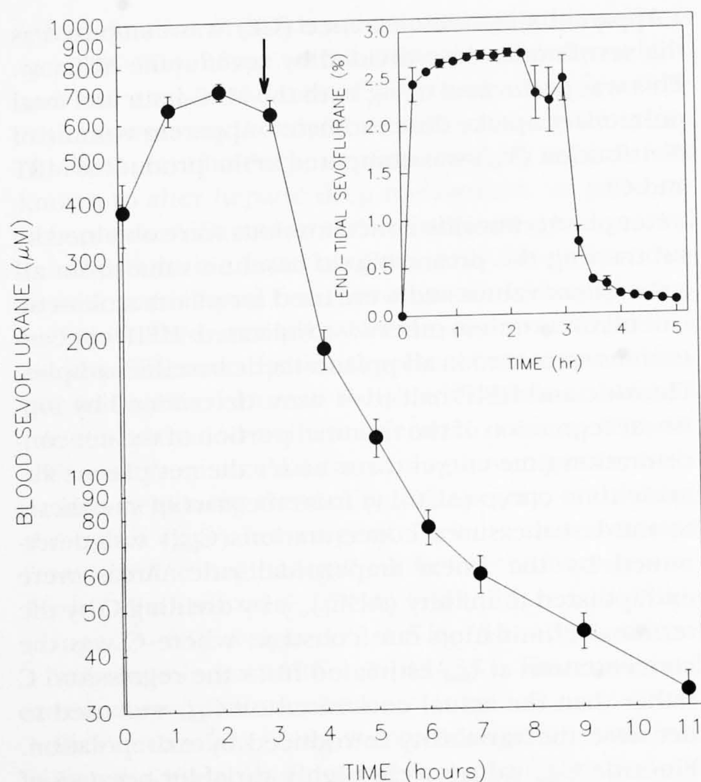


Fig. 1. Blood sevoflurane concentrations (mean ± SE, n = 10). Sevoflurane was administered from 0–3 h, unless the surgical procedure ended before 3 h. The arrow shows the average time that sevoflurane administration was discontinued. (*Inset*) End-tidal sevoflurane concentrations.

$$AE_{tot} = AE_{endog} + AE_{sevo}. \qquad (7)$$

Because prestudy baseline 24-h urine fluoride excretion rates were not determined, the contribution of AE_{endog} to AE_{tot}, and thus AE_{sevo}, could not be measured directly. Nevertheless, AE_{sevo} was calculated as the difference between the total amount of fluoride excreted over the study period (T) and the amount excreted from the endogenous pool:

$$AE_{sevo} = AE_{total} - AE_{endog}. \qquad (8)$$

The prestudy baseline fluoride concentration (C_{pre}) was assumed to represent endogenous fluoride throughout the study. Thus AE_{sevo} could be determined as the product of renal fluoride clearance (CL_r) and the net plasma fluoride AUC as

$$AE_{sevo} = CL_r \cdot (AUC_{total} - C_{pre} \cdot T). \qquad (9)$$

All results are expressed as the mean ± SE.

Results

The mean duration of sevoflurane exposure in the ten patients studied was 174 ± 4 min. Average F_I, F_A, and calculated F_M were 3.2 ± 0.1, 2.6 ± 0.1, and 2.9 ± 0.1%, respectively. Total average pulmonary uptake rate (V_U) of sevoflurane vapor during anesthesia was 12.9 ± 1.1 ml/min, equivalent to 0.50 ± 0.04 mmol/min. Total sevoflurane dose, calculated from the pulmonary uptake rate, was 88.8 ± 9.1 mmol. This corresponded to 11.7 ± 1.2 ml sevoflurane liquid taken up during the entire period of anesthetic exposure. Total sevoflurane dose, calculated from end-tidal data, was 3.7 ± 0.1 MAC-h.

Sevoflurane concentrations in whole blood were measured during anesthesia and for 8 h thereafter (fig. 1). Sevoflurane pharmacokinetics are summarized in table 1. The mean C_{max} was 772 μM, reached approximately 1.75 h after the start of anesthesia. Sevoflurane blood concentrations decreased from an average of 669 μM at the end of sevoflurane anesthesia to 192 μM 1 h after the end of anesthetic administration. Sevoflurane blood concentrations were 5% of the end-anesthetic concentration (36 μM) 8 h after the termination of anesthesia. It is likely, however, that concentrations initially decreased more rapidly than described here,[5,8,14] because of the hourly sampling scheme used,

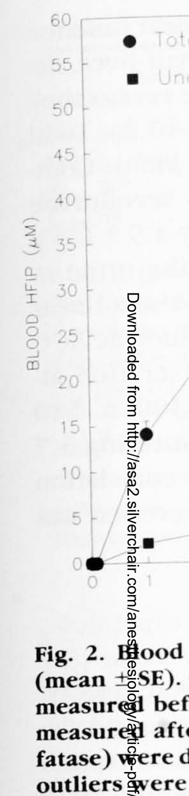
Table 1. Pharmacokinetic Parameters for Sevoflurane

Parameter	
Duration (min)	174 ± 5 (136–180)
Total pulmonary uptake	
L of vapor	2.26 ± 0.22 (1.42–3.60)
mmol	88.8 ± 8.6 (55.6–141.3)
ml liquid	11.7 ± 1.2 (7.3–18.6)
Sevoflurane $AUC_{0-\infty}$ (mM · min)*	167 ± 8 (69–245)
Sevoflurane $AUMC_{0-\infty}$ (mM · min²)†	27,620 ± 1,640 (13,394–37,493)
C_{max} (μM)	772 ± 42 (610–986)
T_{max} (min)	104 ± 15 (6–184)
MRT (min)	77 ± 3 (58–91)
$t_{1/2\beta}$ (h)	2.8 ± 1.0 (0.9–11.3)
CL (L/min)	0.54 ± 0.20 (0.32–0.97)
V_{SS} (L)	42.4 ± 5.9 (22.9–79.7)

Values are mean ± SE (range).

* The average extrapolated portion of the AUC ($AUC_{t-\infty}$) was 0.1% of the total AUC.

† The average extrapolated portion of the AUMC ($AUMC_{t-\infty}$) was 1% of the total AUC.



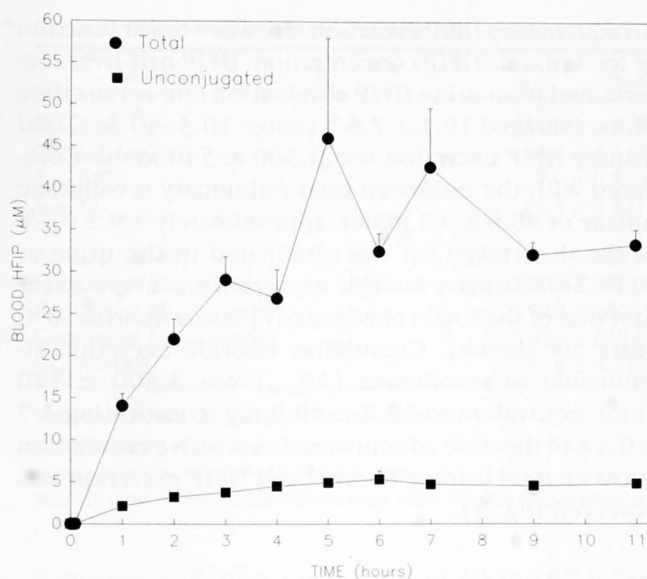


Fig. 2. Blood hexafluoroisopropanol (HFIP) concentrations (mean ± SE). Concentrations of unconjugated HFIP (squares, measured before sample hydrolysis) and total HFIP (circles, measured after sample hydrolysis with β-glucuronidase/sulfatase) were determined in a subset of four patients. Apparent outliers were not excluded from the mean data.

which precluded detection of a more rapid decrease. The average overall half-life, using a loglinear approximation for the terminal portion of the blood concentration-time curve, was 2.8 h, but this does not describe the most relevant portion of the curve, immediately after exposure. The average sevoflurane MRT was 77 min, heavily influenced by the low concentrations associated with the terminal portion of the curve.

Blood HFIP concentrations were measured during anesthesia and for 8 h thereafter in all patients. HFIP is excreted in urine as a glucuronide conjugate,[2,17] indicating the potential for conjugated as well as unconjugated HFIP to be present in the systemic circulation. Therefore, in a subset of patients (n = 4), unconjugated HFIP and total HFIP (representing unconjugated and conjugated HFIP) were measured (fig. 2). Sevoflurane metabolism was rapid. HFIP was detected in blood 5 min after the start of sevoflurane. Unconjugated HFIP in blood was observed, but the amounts were small. Unconjugated HFIP concentrations averaged only 15% of total HFIP, and the mean unconjugated HFIP C_{max} was 5.9 μM compared with the mean sevoflurane C_{max} of 665 μM, constituting less than 1% of the parent drug concentration.

Total HFIP concentrations were compared in plasma and whole blood (fig. 3). There was a significant linear correlation between plasma and blood concentrations ($r = 0.93$, $P < 0.001$). Plasma HFIP concentrations averaged 23% greater than those in whole blood.

Plasma HFIP concentrations were determined in all samples obtained during anesthesia and for up to 96 h after the end of sevoflurane administration (fig. 4 and table 2). Because unconjugated HFIP concentrations averaged only ≤15% of total HFIP, total HFIP exclusively was measured in plasma. Peak plasma HFIP concentrations occurred 2–10 h after the end of sevoflurane anesthesia, with an average T_{max} of 5.5 h and an average C_{max} of 39.8 μM. Individual plasma HFIP concentration-time curves exhibited monophasic elimination kinetics in all patients, with a mean terminal elimination half-life of 20.1 ± 8.2 h (harmonic mean ± pseudo SD). A virtually identical half-life of 19.1 h was obtained (see below) from urinary HFIP elimination-rate analysis. The apparent renal clearance of HFIP was 52.6 ± 6.1 ml/min.

Plasma fluoride concentrations were measured during anesthesia and for 96 h thereafter (fig. 4). Metabolite pharmacokinetics are summarized in table 2. Peak fluoride concentrations occurred within 3 h of the termination of sevoflurane administration in all patients, with an average C_{max} of 36.2 μM. The average T_{max} of 2 h was substantially earlier than the T_{max} for HFIP. Examination of individual fluoride concentration-time

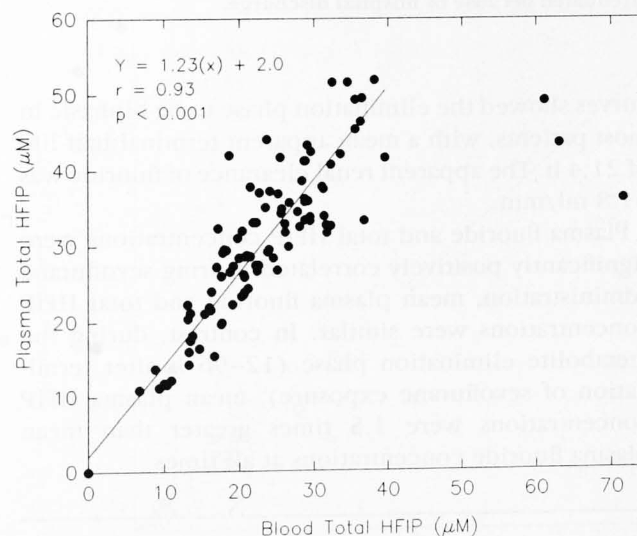


Fig. 3. Comparison of total hexafluoroisopropanol (HFIP) concentrations in whole blood and plasma in all ten patients. HFIP was measured hourly during anesthesia and 1, 2, 3, 4, 6, and 8 h after the end of sevoflurane administration. Three apparent outliers were omitted from the regression analysis.

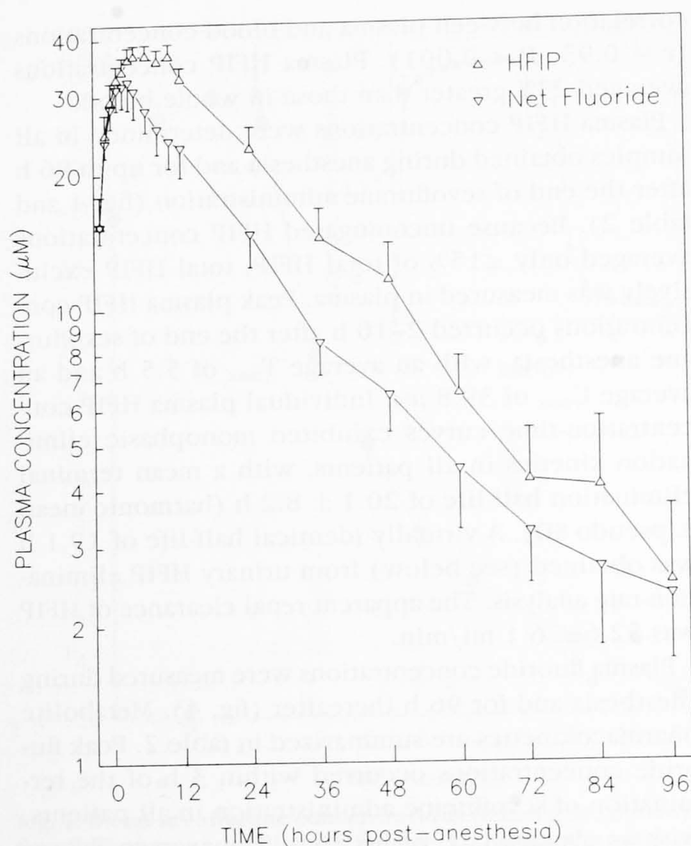


Fig. 4. Plasma hexafluoroisopropanol (HFIP; right-side-up triangles) and net fluoride (upside-down triangles) concentrations (mean ± SE). Sevoflurane was administered from 0–3 h, unless the surgical procedure ended before 3 h. Ten patients were studied, although the number of patients after 48 h was attenuated because of hospital discharge.

curves showed the elimination phase to be biphasic in most patients, with a mean apparent terminal half-life of 21.4 h. The apparent renal clearance of fluoride was 51.8 ml/min.

Plasma fluoride and total HFIP concentrations were significantly positively correlated. During sevoflurane administration, mean plasma fluoride and total HFIP concentrations were similar. In contrast, during the metabolite elimination phase (12–96 h after termination of sevoflurane exposure), mean plasma HFIP concentrations were 1.5 times greater than mean plasma fluoride concentrations at all times.

Total urinary HFIP excretion rate was a linear function of total plasma HFIP concentration. HFIP half-lives, determined from urine HFIP elimination rate *versus* time plots, averaged 19.1 ± 2.6 h (range 10.3–40.3). Total urinary HFIP excretion was 4,300 ± 540 μmol. Compared with the estimated total pulmonary sevoflurane uptake of 88.8 ± 9.1 mmol, approximately 4.9 ± 0.5% of the dose taken up was eliminated in the urine as HFIP. Total urinary fluoride excretion was also a linear function of the total (unadjusted) plasma fluoride AUC (data not shown). Cumulative fluoride excretion attributable to sevoflurane (AE_{sevo}) was 3,300 ± 540 μmol, equivalent to 62.8 ± 10.2 mg, constituting 3.7 ± 0.4% of the dose administered. A positive correlation between total urinary fluoride and HFIP excretion was observed (fig. 5).

Discussion

Sevoflurane blood concentrations increased rapidly, were maintained constant during anesthesia, and decreased rapidly after anesthetic administration ceased. Plasma concentrations of the primary metabolites HFIP and fluoride were detectable within minutes of the start of anesthesia, reflecting the rapid rate of sevoflurane metabolism.[18] The stoichiometry of fluoride and HFIP formation was 1:1, in agreement with a previous clinical investigation[2] and *in vitro* experiments using rat liver microsomes.[19]

The current investigation demonstrates for the first time that HFIP in humans is glucuronidated immediately after formation and circulates predominantly (85%) in plasma as the glucuronide conjugate. Rapid HFIP glucuronidation also has been observed in rats.# Plasma HFIP concentrations averaged 23% greater than those in whole blood. This was less than the 50% greater plasma concentration predicted from blood HFIP if there was negligible HFIP-binding to erythrocytes and using the mean perioperative hematocrit of 35%. In contrast, equal HFIP partitioning into erythrocytes would have yielded similar plasma and blood HFIP concentrations. Thus there is partial HFIP partitioning into erythrocytes, as the alcohol and/or glucuronide conjugate.

HFIP was eliminated in urine as the glucuronide conjugate, consonant with previous investigations in humans[2,17] and animals.[20] Elimination kinetics of HFIP were monoexponential, with a mean apparent HFIP elimination half-life of 20.1 h based on plasma concentrations and 19.1 h based on urinary excretion. This

Yoshimura M, Saga M, Imai M, Tajima T, Tamura T, Sato N: Time course of free HFIP and HFIP glucuronide concentrations in blood after intravenous administration of HFIP in rats. Sevoflurane Study ADME-17, Central Research Laboratories, Maruishi Pharmaceutical Co., Ltd., 1988.

Table 2. Pharmacokinetic Parameters for Sevoflurane Metabolites

Parameter	Fluoride	Total HFIP
C_{max} (μM)	36.2 ± 3.9 (23.3–61.5)	39.8 ± 2.6 (26.2–51.9)
net C_{max} (μM)	34.0 ± 4.0 (21.7–59.5)	NA
T_{max} (h)*	2.0 ± 0.4 (0–3.4)	5.5 ± 0.9 (2–10)
$t_{1/2\beta}$ (h)	21.4 ± 2.8 (13.1–39.8)	20.1 ± 2.6 (13.1–59.0) (plasma data)
		19.1 ± 2.6 (10.3–40.3) (urine data)
$AUC_{0-\infty}$ (μM · h)†	1,110 ± 160 (442–1,970)	1,370 ± 110 (997–1,950)
Cumulative AE_{total} (μmol)	3,950 ± 565 (1,530–6,950)	4,350 ± 530 (1,790–6,600)
Cumulative AE_{endog} (μmol)	640 ± 160 (140–1,760)	NA
Cumulative AE_{sevo} (μmol)	3,300 ± 540 (1,210–6,230)	4,350 ± 530 (1,790–6,600)
CL_r (ml/min)	51.8 ± 4.5 (36.2–72.6)	52.6 ± 6.1 (29.2–88.4)

Values are mean ± SE (range). NA = not applicable.

* Relative to the end of anesthesia.

† The extrapolated portion of the fluoride AUC ($AUC_{t-\infty}$) was 12.8 ± 3.3% of the total AUC. For HFIP, $AUC_{0-99\,h}$ was determined and the curve was not extrapolated because most plasma concentrations were below the limit of quantification by 99 h postanesthesia.

compares with previous reports of 30 and 67 h based on urinary excretion of organic fluoride[8,17] and 55 h based on urinary excretion HFIP glucuronide.[17] Potential reasons for these apparent differences are not evident.

In contrast with HFIP, the elimination kinetics for fluoride were biexponential. Multiexponential fluoride kinetics are well known and influenced in part by the fluoride dose excreted.[21] The mean renal fluoride clearance (51.8 ml/min) in our patients with an average age of 44 yr was consistent with the 64.9 ml/min in young subjects (21–26 yr) and 43.7 ml/min in older subjects (65–75 yr) reported by Jeandel *et al.* after administration of sodium fluoride.[22] The mean apparent fluoride elimination half-life in the current investigation, calculated from plasma concentration data, was 21.4 h. Fujii *et al.* reported 35 h after 1.2 MAC-h.[7] Fluoride half-lives calculated from urinary excretion data were longer: 34 h after 0.4 MAC-h[8] and 58 h after 11 MAC-h.[10] All estimates of fluoride kinetics, however, are subject to considerable variability. Plasma fluoride concentrations after anesthesia will be influenced by ongoing trace anesthetic metabolism; by pseudoequilibrium with calcified tissues; by renal clearance, diurnal variation, and gastric *p*H; and by daily fluoride intake in food and water, which is rarely standardized.[21] Renal fluoride clearance in turn is highly dependent on urine flow and *p*H.[23]

Quantitation of urinary metabolite excretion and the dose of sevoflurane taken up permits calculation of the extent of sevoflurane metabolism. Based on HFIP excretion, approximately 4.9 ± 0.5% of the absorbed sevoflurane dose was metabolized. Calculations based on fluoride excretion are more intricate, however, because fluoride pharmacokinetics are complex. Fluoride undergoes both renal and nonrenal clearance, the latter into bone, sweat, and feces.[23] Elimination into sweat is negligible under normal temperatures, and fecal elimination is low (5–10%); thus nonrenal clearance represents primarily absorption into bone.[23] Previous investigations describing the metabolism of sevoflurane[2] and other[24] anesthetics have routinely cited 50% fluoride uptake into bone. However, it is

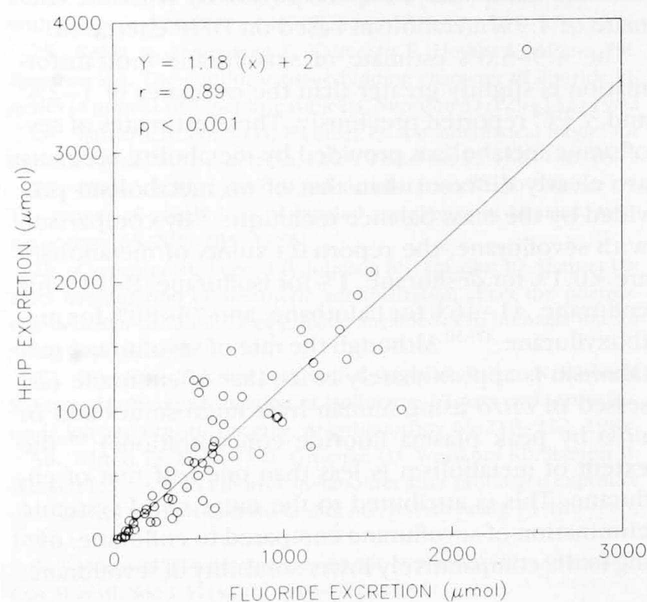


Fig. 5. Urinary total hexafluoroisopropanol and fluoride excretion. Urine metabolite concentrations were multiplied by urine volume for each collection interval (12 or 24 h).

appreciated that fluoride pharmacokinetics are nonlinear, due to saturable uptake by bone.[25,26] Although 50–58% of fluoride is bound to bone in adults at low fluoride doses (<5 mg),[21,23] bone incorporation is less effective at higher doses.[26] For example, fluoride content in newly formed bone becomes nonlinear at plasma concentrations exceeding 25 μM and doses >10 mg/day.[26] In the current investigation, plasma fluoride concentrations commonly exceeded 25 μM, and the average recovered dose of fluoride was 63 mg. Using the model of Turner *et al.*,[26] bone uptake at 40 μM is calculated to be approximately one-third of the fluoride dose, which is less than the 50% commonly cited. Assuming, therefore, that one-third of fluoride produced from sevoflurane is cleared to bone, one would predict plasma fluoride concentrations 1.5 times less than those of HFIP. This prediction was confirmed by the observed results (fig. 4), showing mean plasma fluoride concentrations 1.5 times less than those of HFIP. This cannot be attributed to differences in metabolite elimination, because apparent plasma and renal clearances were comparable for fluoride and HFIP. Thus, under the conditions of this investigation, fluoride clearance to bone is most likely one-third rather than one-half the total fluoride clearance. Using this figure, the recovered fluoride attributable to sevoflurane metabolism, which constitutes 3.7% of the dose taken up, corresponds to a total estimated fluoride formation of 5.6% of the sevoflurane dose. This compares favorably with the estimate of 4.9% metabolism based on HFIP excretion.

The 4.9–5.6% estimate of sevoflurane biotransformation is slightly greater than the estimates of 1–2%[2] and 3.3%[4] reported previously. These estimates of sevoflurane metabolism provided by metabolite recovery are clearly different than that of no metabolism provided by the mass balance technique.[5] By comparison with sevoflurane, the reported extents of metabolism are <0.1% for desflurane, 1% for isoflurane, 8–11% for enflurane, 41–46% for halothane, and 75–80% for methoxyflurane.[27–30] Although the rate of sevoflurane metabolism is approximately twice that of enflurane (assessed *in vitro* using human liver microsomes and *in vivo* by peak plasma fluoride concentrations),[18] the extent of metabolism is less than one-half that of enflurane. This is attributed to the more rapid systemic elimination of sevoflurane compared to enflurane, owing to the comparatively lower solubility of sevoflurane.

Clinical Significance

Biotransformation to potentially toxic metabolites is a concern with any volatile anesthetic agent. Methoxyflurane metabolism can result in nephrotoxicity, associated with plasma fluoride concentrations exceeding 50 μM.[31] In the current investigation, one patient exhibited a peak plasma fluoride concentration of 61.5 μM, which was not associated with any abnormality of renal function as assessed by serum blood urea nitrogen and creatinine. Previous investigations also have demonstrated the absence of sevoflurane renal effects despite fluoride concentrations in excess of 50 μM.[10,12,32]

HFIP has not been associated with toxicity in clinical sevoflurane investigations published to date. We found that total HFIP formation averaged 0.06 mmol/kg, based on urinary excretion data, and the unconjugated portion was 0.008 mmol/kg, based on systemic glucuronidation data. In comparison, the toxic HFIP dose in rats is 0.6 mmol/kg.** No evidence of HFIP toxicity was observed in the current investigation. It is unlikely that unconjugated HFIP concentrations occurring during sevoflurane anesthesia are of clinical significance.

Limitations

The anesthetic protocol was designed to provide a maximally uniform sevoflurane dose while minimizing potential drug interactions that could alter the disposition of sevoflurane or its metabolites. Propofol was used for induction and maintenance of anesthesia after sevoflurane was discontinued. Although possible, it is unlikely that propofol altered sevoflurane metabolism to fluoride and HFIP because propofol has minimal effects on P450 2E1,[33] the P450 isoform responsible for sevoflurane metabolism.[18] Both HFIP and propofol undergo glucuronidation, and the influence of propofol on HFIP glucuronidation is unknown. Propofol may have influenced the glucuronidation and, hence, elimination of HFIP. Nevertheless, more than 85% of HFIP in blood underwent glucuronidation.

Both fluoride and HFIP formation were used to calculate the extent of sevoflurane metabolism. The intervals used to estimate renal fluoride clearance (0–36 h for urine and 0–39 h for plasma) and renal HFIP clearance (0–96 h for urine and 0–99 h for plasma), although not the same, were considered approximately equivalent. This calculation caused a slight downward bias in the estimate of renal clearances. In the calculation of fluoride half-lives, preanesthesia fluoride concentrations were assigned as baseline values and subtracted from fluoride concentrations obtained during

** Abbott Laboratories: Data on file. 1988.

and after anesthesia. Error in baseline estimates and/or systematic fluctuation in baseline fluoride concentrations may have influenced the half-life estimates. In general, HFIP data probably provide more reliable estimates of sevoflurane biotransformation because of the lack of interference from endogenous HFIP.

In summary, the results of this investigation show that sevoflurane undergoes rapid metabolism in humans to the principal metabolites fluoride and HFIP-glucuronide, which circulate in plasma and are eliminated in the urine. The overall extent of sevoflurane metabolism was approximately 5%.

The authors thank the various anesthesiology residents and nursing personnel who participated in this investigation.

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Appendix: Analytical Methods

Blood Sevoflurane

Sevoflurane concentrations in whole blood were determined by gas chromatography (GC) with headspace sampling and flame ionization detection (FID) using 2-methoxyethanol as an internal standard. The capillary column was a Stabilwax.DA (15 m × 0.32 mm × 0.5 μm film thickness; RESTEK, Bellafonte, PA). The GC injector was operated in the split mode at 200°C, and the detector temperature was 240°C. The carrier gas was helium (16 psi), and nitrogen was the makeup gas. The GC oven was held at 70°C for 2 min, then increased at 6.25°C/min to 120°C and held for 1 min. Typical retention times for sevoflurane and the internal standard 2-methoxymethanol were 1.2 and 4.9 min, respectively. Quantitation was performed by integrating peak areas. Standard curves were prepared by adding known amounts of sevoflurane and the internal standard to blank whole blood and were linear ($r^2 = 0.999$) over the range 5–800 μM with the limit of quantification 5 μM.

Plasma Fluoride

Fluoride concentrations in plasma were determined using an ion-selective electrode. Aliquots of plasma (0.25 ml) were added to 0.75 ml 0.1 M HCl in a Teflon cell equipped with a stirring bar. Fluoride concentrations were measured using an Orion 901 Ionanalyzer (Boston, MA) with a fluoride specific electrode and a combination *p*H electrode.[34] Standard curves of fluoride in plasma (1–48 μM) were prepared each day by adding known amounts of sodium fluoride to pooled blank plasma and analyzing as described. The assay was linear over the range 1–48 μM fluoride with correlation coefficients of 0.999, and the limit of quantification was 1 μM.

Urine Fluoride

Fluoride concentrations in urine were determined as described for plasma. Standard curves were prepared daily using blank urine and were linear ($r^2 = 0.999$) over the concentration range 4–640 μM, and the limit of quantification was 1 μM. Urine fluoride concentrations were multiplied by the urine volume and fluoride excretion expressed as micromoles fluoride/collection interval.

Plasma HFIP

HFIP concentrations in plasma were determined by headspace GC-FID using 2,2,3,3,3-pentafluoro-1-propanol (PFnP) as the internal standard. Total plasma HFIP was quantitated after converting conjugates to the free alcohol by incubating plasma with β-glucuronidase/sulfatase (2,000 U of Type H1, Sigma, St. Louis, MO) for 15 h at 37°C. Vials were cooled to ambient temperature, and 200 μl of 3.5 M phosphoric acid was injected through the septum to decrease the *p*H from 5 to 2. Vials were vortexed and loaded into the headspace autosampler. Standard curves were prepared by adding known amounts of HFIP (2.5–160 μM) and the internal standard to blank human plasma and analyzing as described.

Analyses were performed on the GC-FID instrument described above. The capillary column was a RESTEK RTX 1701 (30 m × 0.53 mm × 3.0 μm film thickness). Other instrument parameters were similar to those described above for analysis of sevoflurane in blood, except the headspace sample temperature was 100°C and the helium carrier gas pressure was 20 psi. Typical retention times for HFIP and the internal standard were 7.6 and 4.6 min, respectively. No interference from endogenous plasma compounds was observed. Quantitation was performed by integrating peak areas. Standard curves were linear over the range 2.5–160 μM HFIP with correlation coefficients of 0.999, and the limit of quantification was 2.5 μM. Values reported as below the limit of quantification were taken as zero for purposes of pharmacokinetic parameter determinations.

Blood HFIP

HFIP concentrations in whole blood were determined by GC-FID for the unconjugated alcohol and as total HFIP after deconjugation. Total HFIP was determined as described above for plasma, and unconjugated HFIP was determined by omitting the deconjugation step. Instrument conditions were identical to those used for HFIP in plasma. The assay was linear over the ranges 2.5–80 and 5–80 μM for unconjugated and total HFIP, respectively, with correlation coefficients of 0.999 for both.

Urine HFIP

HFIP concentrations in urine were determined by headspace GC-FID. Urine HFIP, excreted as the glucuronide conjugate, was measured as HFIP alcohol after glucuronide hydrolysis. To a 22-ml headspace vial were added 0.5 ml urine, 1.5 ml 10 M sulfuric acid, and 25 μl of the internal standard PFnP. The vial was immediately capped, vortexed, and loaded into the headspace autosampler. Samples were maintained at 100°C for 30 min, after which glucuronide hydrolysis was 99% complete. Preliminary experiments showed that glucuronide hydrolysis using β-glucuronidase (overnight) or sulfuric acid (30 min) provided equivalent results, and the latter method was used routinely. Standard curves were prepared each day by adding known amounts of HFIP (10–1,600 μM) and the internal standard to blank human urine and analyzing as described.

Analyses were performed on the GC-FID instrument described above. The capillary column was a RESTEK Stabilwax.DA (15 m × 0.32 mm × 0.5 μm film thickness). Other instrument parameters were similar to those described above for analysis of HFIP in plasma. The GC oven temperature program was identical to that used for analysis of sevoflurane in blood. Typical retention times for HFIP and the internal standard PFnP were 5.3 and 2.1 min, respectively. Standard curves of peak area ratios (HFIP/PFnP) *versus* HFIP added were prepared using HFIP calibration standards and used to quantify HFIP concentrations in unknowns. The assay was linear over the range 10–1,600 μM HFIP with correlation coefficients of 0.999, and the limit of quantification was 10 μM. Urine HFIP concentrations were multiplied by the urine volume, and HFIP excretion expressed in micromoles fluoride/collection interval.