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Pharmacokinetic Study on Excretion of Inorganic Fluoride Ion, a Metabolite of Sevoflurane

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ABSTRACT

Blood and urinary inorganic fluoride ion concentration was determined in six healthy volunteers after inhalation of 2% sevoflurane for one hour.

The serum inorganic fluoride ion concentration increased 30 min after discontinuation of inhalation to 14.8 ± 3.0 μmol/liter, which was about 10 times higher than the level before inhalation. The serum elimination constant of inorganic fluoride was calculated to be 0.000467 and the half-life was 1,487 min.

The urinary excretion rate of inorganic fluoride ion was the highest (452 nmol/min) after 12-24 hr. The urinary excretion rate constant of inorganic fluoride was calculated to be 0.000268 and the half-life was 2,583 min.

The distribution volume of inorganic fluoride excreted in the urine was calculated to be 127 liters. This value showed that fluoride ion produced in the cell cannot readily pass through the cell membrane due to its polarity, resulting in a delay of the maximum excretion rate of inorganic fluoride until the first or second day after inhalation of the anesthetic.

Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether, a newly developed inhalation anesthetic, is an ether containing seven fluorine atoms[2,5] and is stable chemically[3,4,8]. Fluorine is released when a fluoride-containing anesthetic is metabolized in the body, and may cause renal damage if its serum concentration exceeds 50 μmol[1].

The maximum serum concentration and urinary excretion rate of fluoride after inhalation of a fluoride-containing anesthetic is obtained between one and two days after the inhalation[6] when the blood anesthetic concentration is extremely low. This delay in fluoride excretion has been considered to be either sustained metabolism of the anesthetic incorporated in adipose tissues or to accumulation of fluorine in the tissues and its slow excretion. By the former reason, we cannot explain why blood fluoride concentration is higher after inhalation than during inhalation. We have some idea of the possibil mechanism for the latter reason. Since fluorine is produced in the cell, it must cross the cell membrane to be excreted in the urine. Ionized fluorine, however, may not readily pass through the cell membrane, resulting in the delay in excretion, if there is no active transport system for fluoride ion.

We examined this hypothesis by evaluating the serial changes in serum concentration and urinary excretion of fluorine after sevoflurane inhalation.

METHOD

This study was a part of Phase I study of sevoflurane which has been done in Department of Anesthesiology, Hamamatsu Medical College.

Sevoflurane was provided by Maruishi Pharmaceutical Co (Osaka, Japan). The other reagents were commercial products of special grade.

Six male volunteers who inhaled 2% sevoflurane for one hour were studied. Urine was collected before inhalation and at 12 hr-intervals after inhalation for seven days. Blood was collected before inhalation, every 15 min during inhalation and 15, 30, 45, 60, 360, 1,440, and 2,880 min after inhalation.

The blood concentration of sevoflurane was measured by head-space gas method. Head-space gas was analyzed by gas-chromatography (Shimadzu GC4A PTF) equipped with a flame ionization detector. 20% Dioctylphtalate packed in 4 mm × 3 m stainless steel column was used as liquid-phase and kept at 100°C.

Fluoride ion was measured by ionchromatograph (Yokogawa IC-100) equipped with a suppressor and electroconductivity detector. An anion exchange resin (SAX-1) was used as a separator, packed in 25 cm × 4.6 mm stainless steel column. As an eluent solution and scavenger, 5 mM of sodium tetraborate and 50 mM of dodecylbenzensulfonic acid were, respectively, used at a flow rate of 2 ml/min.

Prior to ionchromatography, the urine and serum were diluted 10 times with deionized water and treated with the cation exchange resin column and the serum was deproteinized by ultrafiltration using Amicon^{R} CF25.

From the data of excreted amount of inorganic fluoride in the urine (urine volume × concentration of inorganic fluoride) was calculated the urinary excretion rate. The excretion half-life ($T_{1/2}$) and excretion rate constant (ke) were calculated from excretion rate-time data. The serum elimination half-life and elimination rate constant were calculated in the same way from concentration-time data. The distribution volume of inorganic fluoride was calculated from the total excreted inorganic fluoride in urine (excretion rate at time zero / rate constant) and serum inorganic fluoride concentration at time zero.

All pharmacokinetic calculations were made by means of the net concentration, i.e., the measured level of fluoride substracted by background level from the control experiments.

Means and standard deviations of different groups of data were calculated. Regression analysis was performed according to the least square method. Student t-test was used to assess the significant difference between the data. Difference with random probability of 5% or less was considered significant.

RESULTS

1. Blood Sevoflurane Concentration (Table 1)

Table 1. Concentration of Blood Sevoflurane

	time min	Concentration of sevoflurane μmol/liter M ± SD
During Inhalation	0	0
	15	359.8 ± 107.2
	30	341.2 ± 95.3
	45	330.3 ± 87.9
	60	314.7 ± 85.9
after inhalation	5	90.5 ± 14.1
	10	60.2 ± 14.9
	15	39.2 ± 10.9
	30	26.3 ± 4.3
	45	18.3 ± 3.4
	60	14.5 ± 2.9

The sevoflurane concentration in the whole blood reached a plateau (359.8 ± 107.2 μmol/liter) 15 min after the beginning of inhalation and remained at nearly a constant level during inhalation. The concentration decreased to 90.4 ± 14.1 μmol/liter five min after discontinuation of inhalation of sevoflurane. The elimination of half-life of serum sevoflurane was calculated to be 22 min.

2. Serum Inorganic Fluoride Concentration (Table 2)

The mean concentration (1.25 ± 0.59 μmol/liter) before sevoflurane inhalation increased to a maximum level of 14.8 ± 3.0 μmol/liter, which was about 10 times higher than the value before inhalation, at 30 min after inhalation and it decreased thereafter.

The elimination half-life of inorganic fluoride in serum was 1,487 min and the rate constant was 0.000467. The concentration of inorganic fluoride at time zero was calculated to be 11.7 μmol/liter.

3. Urinary Excretion of Inorganic Fluoride (Ta-

Table 2. Blood Concentration of Inorganic Fluoride

	time min	Concentration μmol/liter (m ± SD)
before inhalation		1.25 ± 3.6
during inhalation	15	4.0 ± 1.9
	30	6.9 ± 2.0
	45	9.2 ± 3.3
	60	10.6 ± 3.1
after inhalation	15	12.5 ± 3.5
	30	14.8 ± 3.0
	45	13.1 ± 3.4
	60	13.9 ± 2.7
	360	10.2 ± 4.5
	1440	7.0 ± 2.3
	2880	4.4 ± 1.3

Table 3. Urin excretion rate of inorganic fluoride

	time min	rate nmol/min
before inhalation		11.3 ± 5.0
after inhalation	1080	452.1 ± 157.5
	1800	329.4 ± 220.1
	2520	232.6 ± 108.3
	3240	137.9 ± 107.9
	3960	78.8 ± 83.3
	5400	84.2 ± 37.8

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Urinary excretion rate of inorganic fluoride was 11.3 nmol/min before inhalation, increased to 323 nmol/min 12 hr after inhalation of sevoflurane, and reached a maximum rate of 452 nmol/min after 24 hr. The excretion half-life of urinary inorganic fluoride and the rate constant was 2,583 min and 0.000268, respectively. The total amount of inorganic fluoride was calculated to be 1.49 mmol. The volume of distribution was calculated to be 127 liters.

DISCUSSION

The concentration of sevoflurane in the blood increased and decreased promptly by initiation and termination of inhalation of sevoflurane, respectively. The blood/gas partition coefficient of sevoflurane (0.6)[7] is smaller than that of other volatile anesthetics[8] and is close to that of gas anesthetics, suggesting a rapid induction of and recovery from anesthesia. The results of our studies show one of the advantages of this drug.

The serum fluoride concentration increased to 14.8 μmol/liter 30 min after discontinuation of the inhalation, when blood sevoflurane concentration was less than one-tenth that during inhalation of sevoflurane. Therefore, degradation of sevoflurane might be negligible in extent. The serum elimination half-life of inorganic fluoride was 2,100 min and agrees with another report[8].

The urinary excretion half-life was longer than that of serum. It suggests that inorganic fluoride was eliminated not only in the urine but also in the bile and/or digestive fluid.

The volume of distribution was calculated to be 127 liters. This value indicates that fluoride ion is stored in the intracellular fluid at a high concentration. We consider that fluoride released by biodegradation of sevoflurane in the endoplasmic reticulum cannot readily pass through the cell membrane due to its polarity, resulting in a delay after inhalation of the anesthetic.

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REFERENCE

1. **Cook, T.L., Beppu, W.J., Hitt, B.A. and Mazze, R.I.** 1975. A comparison of renal effects and metabolism of sevoflurane and methoxyflurane in enzyme-induced Rats. Anesth. Analg. **54**: 829–835.
2. **Cook, T.L., Beppu, W.J., Hitt, B.A., Kosec, J.C. and Mazze, R.I.** 1975. Renal effects of and metabolism of sevoflurane in Fisher 344 rats. Anesthesiology **43**: 70–77.
3. **Fujii, K., Morio, M., Kikuchi, H., Nakatani, K. and Ikeda, K.** 1987. An application of ion chromatography on glucuronide, metabolite of sevoflurane. Hiroshima J. Anesth. **23**: (in press).
4. **Hanaki, C., Fujii, K., Morio, M. and Tashima, T.,** 1987. Decomposition of sevoflurane by sodalime. Hiroshima J. Medical Sciences **36**: 61–67.
5. **Holaday, D.A. and Smith, F.R.** 1981. Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology **54**: 100–106.
6. **Mazze, R.I., Beppu, W.J. and Hitt, B.A.** 1979. Metabolism of Synthane; Comparison with in vivo and in vitro decomposition of other halogenated hydrocarbon anesthetics. Br. J. Anesth. **51**: 839–844.

7. **Sato, N.** Personal comunucation.
8. **Wallin, R.F., Regan, B.M., Napoli, M.D. and Stern, I.J.** 1975. Sevoflurane: A new inhalational anesthetic agent, Anesth. Analg. **54**: 758—765.