Hiroshima Journal of Medical Sciences
Vol.36, No.1, 99~104, March, 1987
HIJM 36-14

Urinary Excretion of Inorganic and Organic Fluoride after Inhalation of Sevoflurane

Tatiana Ivanova DAVIDKOVA, Kohyu FUJII, Hirosato KIKUCHI, Mayumi HORIBE, Keiko MUKAIDA, Nobuyoshi SATO and Michio MORIO

Department of Anesthesiology, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan

(Received December 18, 1986)

Key words: Anesthetics, volatile: sevoflurane. Biotransformation: fluorometabolites. Pharmacokinetics: excretion. Toxicity: metabolites.

ABSTRACT

This study was designed to investigate the defluorination of sevoflurane in patients. Five patients, scheduled for orthopedic surgery, were administered sevoflurane for 60 min during NLA-nitrous oxide-oxygen. The end-tidal concentration of sevoflurane was adjusted at 0.6% throughout the entire inhalation period.

The serum concentration of inorganic F^- increased significantly 15 min after the onset of inhalation and reached a plateau at 45 min with a mean value about 15 μM. The serum organic fluoride level increased significantly 45 min after the onset of inhalation and did not change significantly 4 hr later with a mean value of about 140 μM.

The elimination half-lives and rate constants were calculated from urinary data to be 2040 min and 0.00034 for inorganic fluoride and 1800 min and 0.00038 for organic fluoride respectively. The ratio organic/inorganic fluoride was calculated to be 2.3.

Sevoflurane, fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether, is a new volatile inhalation anesthetic. This agent is known as a potent, non-explosive, pleasant smelling liquid and has a vapour pressure of 200 torr at 25°C. Because of its low blood/gas partition coefficient of 0.6[10], an equilibrium of sevoflurane between alveoli and blood is expected to be achieved in a short period of time. In clinical application, the biotransformation of sevoflurane was evaluated especially inorganic and organic fluoride in serum and urine.

METHODS AND MATERIALS

Five patients, ASA physical status 1 or 2 (age 44.8 ± 14.2, height 164 ± 14.2 cm, body weight 61.8 ± 8.9 kg, M ± SD), scheduled for orthopaedic surgery, were studied. The study was approved by the Ethical Committee on Human Studies of Hiroshima University Hospital and the Japanese Ministry of Health. Written informed consent to the study was obtained from all patients.

All patients were premedicated with atropine sulfate, 0.4 — 0.5 mg i.m., 45 — 60 min prior to anesthesia. Flunitrazepam, 1 mg, iv, and fentanyl, 10 μg/kg, iv, were used for induction and intubation was performed under muscle relaxation with pancuronium bromide of 0.1 mg/kg. The anesthesia was maintained with 70% nitrous oxide in oxygen. All patients were ventilated using Anespirator^R with tidal volume of 8 ml/kg and respiratory rate of 12/min, these parameters were altered, if necessary, according to blood gas analyses. Thirty minutes from the initiation of surgery, sevoflurane was administered for 60 minutes through gas chromatographically calibrated vaporizer. The endtidal concentration

was monitored by NORMAC^R (Datex, Finland) equipped with an infra-red sensor and also calibrated with gas chromatography and recorded on chart simultaneously with arterial blood pressure. The vaporizer was adjusted so as to keep the end-tidal sevoflurane concentration at 0.6% (approximately 1/4 — 1/3 of MAC in oxygen) during the entire period of inhalation.

Arterial blood samples were taken for measurement of inorganic and organic fluoride and sevoflurane concentration before inhalation, every 15 min during inhalation, 15, 30, 60, 120 and 240 min after discontinuation of sevoflurane and on the third postoperative day.

Urine samples were collected 12 hr before surgery, during inhalation and every 24 hr for 6 postoperative days.

Arterial blood gases, blood sugar, and sodium, potassium and calcium ions were analyzed before inhalation and after discontinuation of sevoflurane. Before the inhalation of sevoflurane and on the first and third postoperative days, blood samples were drown for measurement of total protein, bilirubin, GOT, GPT, cholinesterase, BUN and creatinine.

1. Measurement of blood concentration of sevoflurane

The blood concentration of sevoflurane was measured by gas chromatograph Simadzu GC - 4A PTF equipped with a flame ionization detector. A 3 m × 4 mm stainless steel column was packed with 20% dioctylphtalate and kept at 100°C. The injection port and flame ionization detector were maintained at 110°C. As carrier gas, helium (30 ml/min) was used.

2. Measurement of fluoride ion

Fluoride ion was measured by Ion Chromatographic Analyzer IC0-100, (Yokogawa Electric Co., Japan) equipped with a suppressor and an electro-conductive detector. An anion exchange resin (SAX-1) was used as separator, packed in 25 cm × 4.6 mm column. As an eluent solution and a scavenger, 5 mM of sodium tetraborate and 50 mM of dodecylbenzensulphonic acid were used respectively, at a flow rate of 2 ml/min. Sodium fluoride was used as a standard solution.

i) Inorganic serum and urine fluoride

For measuring the concentration of serum inorganic fluoride, 50 μl of serum was diluted 10 times with deionized water and centrifuged for 10 min at 500 × G for deproteinization, using an AMICON^R ultrafiltration membrane cone. The ultrafiltrate, 100 μl, was injected into the ion chromatographic analyzer through the cation exchange filter.

The urine samples were prepared in the same manner but diluted 100 times without deproteinization.

ii) Organic serum and urine fluoride

Total fluoride was measured by modified oxygen-flask combustion method[9].
The difference between the total nonvolatile fluoride and the inorganic fluoride was defined as fluoride ion from organic compounds.

iii) Parameters of pharmacokinetics[8]

From the data of urine volumes and urine concentrations of inorganic and organic fluoride were calculated their excretion rates. The excretion rates against the midpoint of the collection time of urine were plotted on semilogarithmic paper. From the slope of the regression lines were calculated the elimination half-lives ($T_{1/2}$) and the elimination rate constants (k). Assuming that urinary excretion rate is proportional to the serum concentration[2], it can be related to the amount of the substance in the body by the following equation:

$$\text{Excretion rate} = Cl_R/V \cdot Ab \quad (1)$$
$$Cl_R/V = ke, \text{ thus}$$
$$\text{Excretion rate} = ke \cdot Ab \quad (2)$$

where Cl_R is renal clearance; V, volume of distribution; Ab, amount of the substance in the body; and ke, excretion rate constant.

From the equation (2) at time zero were calculated the total amounts of organic and inorganic fluoride excreted in the urine.

4. Reagents

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

5. Statistics

Mean 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 significance of differences between the data. Differences with random probability of 5% or less were considered significant.

RESULTS

Arrhythmia, abnormal ECG, and change in blood pressure were not observed during inhalation of sevoflurane. Postoperative laboratory findings showed no unexplainable abnormality. All patients were discharged uneventfully.

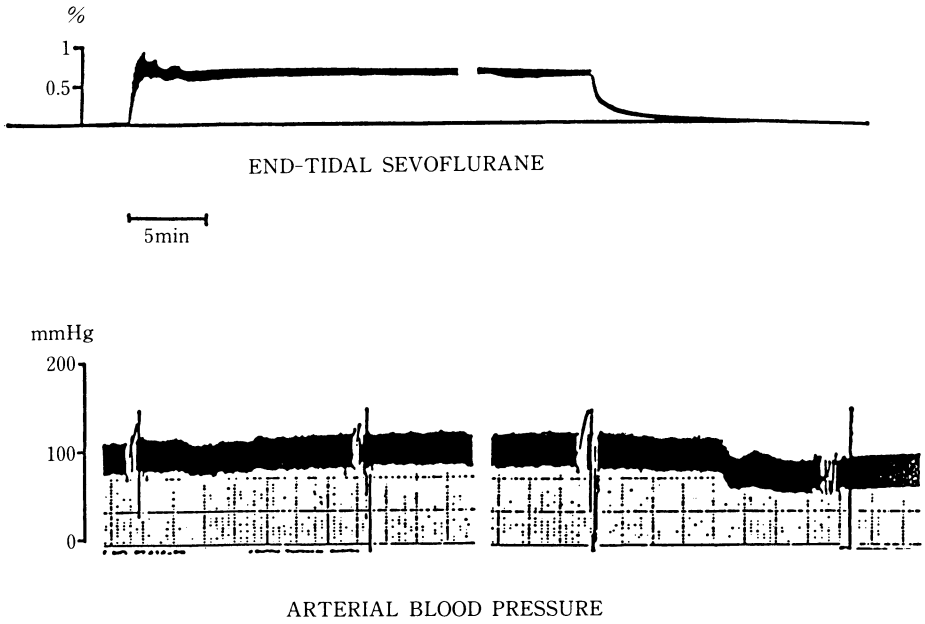

Fig. 1. Simultaneous record of an end-tidal sevoflurane concentration 0.6% (approximately 1/4 — 1/3 MAC in oxygen) and corresponding arterial blood pressure.

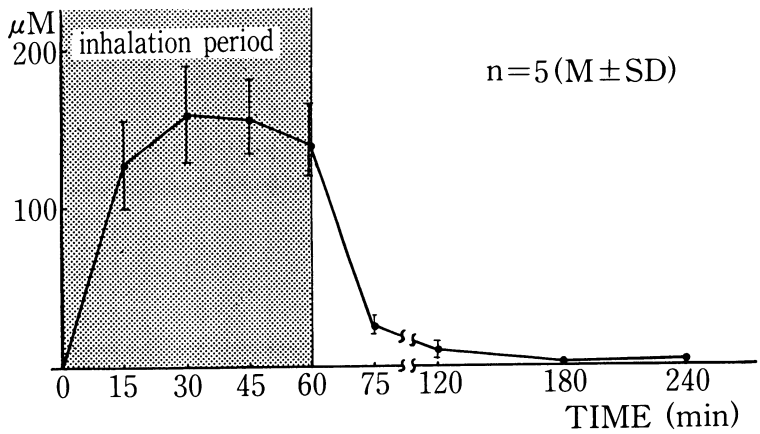

Fig. 2. Blood concentrations of 0.6% end-tidal sevoflurane during 1 hr of inhalation and 4 hr after termination of inhalation. n=5 (M ± SD)

1) The end-tidal and blood concentration of sevoflurane

The end-tidal sevoflurane concentration of 0.6% was achieved in a very short period of time as shown on Fig. 1. A considerable manipulation of the vaporizer was required for a few

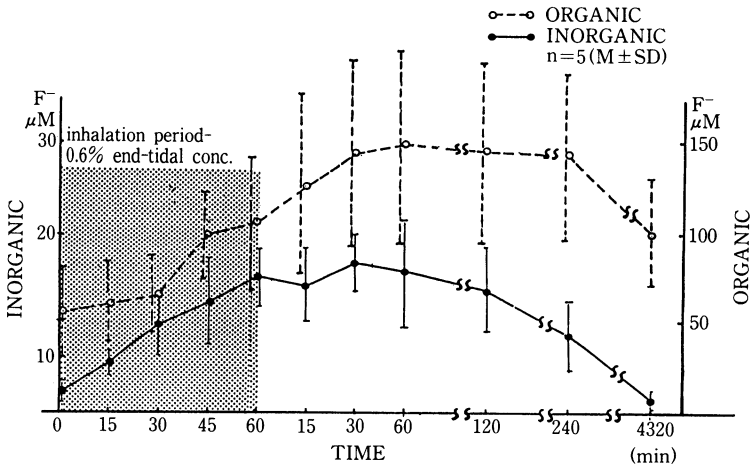

Fig. 3. Serum concentrations of inorganic and organic fluoride during 1 hr of inhalation, 4 hr after termination of inhalation and on the third postoperative day. n=5 (M ± SD)
●—●: inorganic fluoride ○----○: organic fluoride

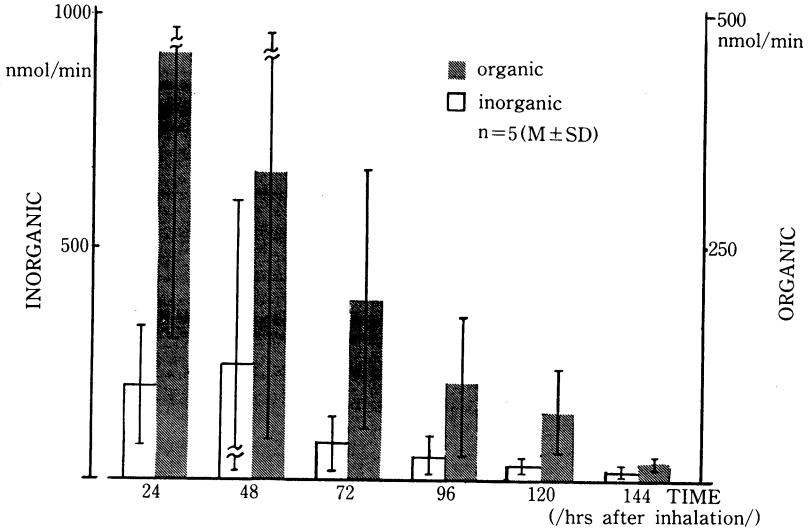

Fig. 4. Excretion rates of inorganic and organic fluoride every 24 hr in 6 postoperative days after inhalation of 0.6% end-tidal sevoflurane for 1 hr. n=5 (M ± SD)
□: inorganic fluoride ▒: organic fluoride

minutes, but thereafter a stable concentration was maintained only with minute readjustments. After termination of inhalation, the end-tidal sevoflurane concentration dropped sharply to the base line.

The blood concentration of sevoflurane, as can be expected from the traces of the end-tidal concentration (Fig. 1), was almost constant during the period of inhalation. The values ranged from 130 μM to 160 μM, and decreased sharply after discontinuation of the anesthetic (Fig. 2).

2) Serum concentration of inorganic and organic fluoride (Fig. 3)

The serum concentration of inorganic fluoride increased significantly 15 min after the onset of inhalation and reached plateau at 45 min. This did not change significantly 4 hr after the termination of inhalation. The mean values were about 15 μM, ranging from 6.7 — 28 μM. The highest mean value of 16.6 μM was observed 30 min after termination of inhalation. On the third postoperative day the level of inorganic fluoride

returned to normal.

The serum concentration of the organic fluoride increased significantly 45 min after the onset of inhalation and did not change significantly 4 hr after discontinuation of sevoflurane. The mean values were about 140 μM. ranging from 93.8 μM to 234.2 μM. The highest mean value of 149.3 μM was observed 60 min after the end of inhalation. The serum concentration of organic fluoride tended to decrease on the third postoperative day, but did not return to the preoperative value.

3) Urinary inorganic and organic fluoride

In Fig. 4 are shown the excretion rates of inorganic and organic fluoride every 24 hr after inhalation of sevoflurane. The largest amount of fluoride was excreted during the first 72 hr and decreased significantly thereafter.

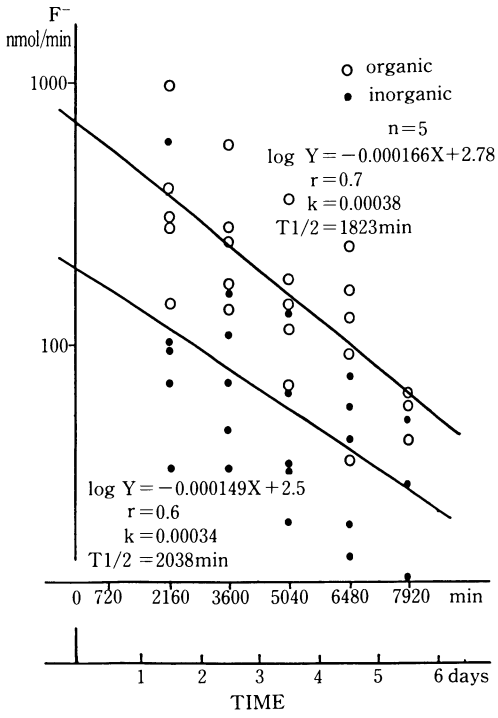

Fig. 5. Excretion rates of inorganic and organic fluoride against the midpoint of collection time of urine plotted on semilogarithmic paper. n=5
●: inorganic fluoride ○: organic fluoride

Fig. 5 shows the excretion rates of inorganic and organic fluoride against the midpoint of the collection time of urine, plotted on semilogarithmic paper. From the slope of the regression lines were calculated the elimination half-lives and the elimination rate constants for both organic and inorganic fluoride. The T1/2 of the inorganic fluoride was 34 hr and the T1/2 of the organic fluoride was 30 hr.

The amounts of organic and inorganic fluoride in the body were calculated to be 2,286.5 μmoles and 987.5 umoles respectively. The ratio between the two was 2.3.

DISCUSSION

The requirements of inhalational anesthetics include rapid induction and recovery and absence of organ toxicity. As expected from the low blood-gas partition coefficient of sevoflurane[10], equilibrium of the anesthetic between the alveoli and blood was achieved in a very short period of time, promising a rapid induction and recovery. The toxicity of inhalational anesthetics depends largely on the extent of their biotransformation and the effects of the metabolites in the body. Inorganic fluoride is a common metabolite of several halogenated anesthetics[3], including sevoflurane. It has been established that high serum concentrations result in renal concentrating defect[1,6]. In the present study the inhalation of 0.6% end-tidal sevoflurane for 1 hr resulted in serum inorganic fluoride concentration far below the nephrotoxic level of 50 μM[1]. On the other hand, glucuronide of hexafluoroisopropanol is a unique metabolite of sevoflurane but not much is known about the toxicity of the compound[5]. It accounts for 80% of the organic fluorinated metabolites of sevoflurane[4]. Hydrolysis of the ether linkage takes place to produce fluoride ion, carbon dioxide and hexafluoroisopropanol[4]. Therefore, the ratio organic/inorganic fluoride should be theoretically about 6. In this study it was 2.3. It could be speculated that glucuronide of hexafluoroisopropanol is the major product. The glucuronide could be excreted in the bile and cleaved to hexafluoroisopropanol and glucuronic acid by glucuronidase. Then hexafluoroisopropanol might be reabsorbed and brought to the lung by the systemic circulation. Because hexafluoroisopropanol is volatile compound, it can be excreted with the expiratory gas. Therefore, the value of ratio might be

smaller than six.

The elimination half-life of inorganic fluoride was 34 hr and close to the value for enflurane of 37 hr[3], but shorter than the value for methoxyflurane of 48 hr[3]. Due to its low blood/gas and oil/gas partition coefficients, sevoflurane is subjected to metabolism for a shorter time when compared to methoxyflurane. Therefore, in the case of sevoflurane less time is needed for the inorganic fluoride to decline to one-half.

The half-life of organic fluoride was calculated to be 30 hr. The value for enflurane is 88 hr and for methoxyflurane 35 hr[3]. The organic fluorinated metabolites of sevoflurane, enflurane and methoxyflurane are different compounds, thus showing different half-lives. This could be explained by their difference in protein binding or in mechanisms of membrane transport.

ACKNOWLEDGEMENT

This study was supported in part by a Grant-in-aid for Science Research from the Ministry of Education, Science and Culture of Japan.

REFERENCES

1. **Cousins, M.J. and Mazze, R.I.** 1973. Methoxyflurane nephrotoxicity: A study of dose-response in man. JAMA. **225**: 1611—1616.
2. **Ekstrand, J. and Ehrnebo, M.** 1983. The Relationship Between Plasma Fluoride, Urinary Excretion Rate and Urine Fluoride Concentration in Man. J. Occup. Med. **25**: 745—748.
3. **Holaday, D.A. and Fiserova-Bergerova, V.** 1979. Fate of Fluorinated Metabolites of Inhalation Anesthetics in Man. Drug. Metab. Rev. **9(1)**: 61—78.
4. **Holaday, D.A. and Smith, F.R.** 1981. Clinical Characteristics and Biotransformation of Sevoflurane in Healthy Human Volunteers. Anesthesiology **54**: 100—106.
5. **Martis, L., Lynch, S., Napoli, D., et al.** 1981. Biotransformation of Sevoflurane in Dogs and Rats. Anesth. Analg. **60**: 186—191.
6. **Mazze, R.I., Calverley, R.K. and Smith, N.T.** 1977. Inorganic Fluoride Nephrotoxicity: Prolonged Enflurane and Halothane Anesthesia in Volunteers. Anesthesiology **46**: 265—271.
7. **Norgate, C.E., Sharp, J.H. and Cousins, M.J.** 1976. Metabolism of Enflurane in Man Following a Second Exposure. Anesth. Intens. Care **4**: 186—191.
8. **Rowland, M. and Tozer, T.** 1980. Clinical Pharmacokinetics: Concepts and Applications, Lea & Febiger, Philadelphia.
9. **Schoeniger, W.** 1955. Rapid microanyalytical determination of halogen in organic compounds. (Ger) Mikrochim Acta: 123—129.
10. **Wallin, R.F., Regan, B.M. and Napoli, M.D.** 1975. Sevoflurane: A New Inhalational Anesthetic Agent. Anesth. Analg. **54**: 758—765.