Hiroshima Journal of Medical Sciences
Vol.36, No.1, 93~97, March, 1987
HIJM 36-13

Clinical Evaluation and Metabolism of Sevoflurane in Patients

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(Received December 18, 1986)

Key words: Anesthetics, volatile: Sevoflurane: Fluoride, inorganic: Fluoride, serum;

ABSTRACT

Sevoflurane was submitted to Phase II studies in patients following Phase I studies. Sevoflurane, 2% inspired during maintenance, was administered with 50% N_2O in oxygen to produce surgical anesthesia in 9 orthopedic patients of ASA Physical Status I. Under controlled ventilation, endotracheal concentration of sevoflurane was recorded. The blood concentration of sevoflurane was measured during and after the inhalation. Serum, urinary inorganic fluoride, and glucuronide of hexafluoroisopropanol were analysed with ion chromatographic analyzer.

The patient inhaled sevoflurane for 3.5 ± 1.6 hr. All the patients were anesthetized and operated uneventfully. Postoperative laboratory findings showed no unexplainable abnormality. The end expiratory concentration of sevoflurane reached a plateau in 4.0 ± 0.8 min and fell rapidly after discontinuation of sevoflurane. Blood concentration of sevoflurane was about 500 μM during inhalation. It decreased promptly after termination of sevoflurane and was not correlated with anesthetic time. The time for verbal response after discontinuation was 11.8 ± 4.2 min. The serum concentration of inorganic fluoride increased after inhalation and reached a plateau (13.7 ± 8.2 μM) in 120 min. The level lasted for 120 min after anesthesia and fell by half at 12 hr after anesthesia. Urinary fluoride concentration varied from 20 to 3,000 μM during the first 12 hr urine, and showed its maximum in the first postoperative 12 or 24 hr urine.

The findings that sevoflurane with nitrous oxide and oxygen produced surgical anesthesia without any sequelae and that the serum fluoride level did not exceed the nephrotoxic level warrent the further clinical evaluation in a wider range of subjects.

Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether), a new volatile inhalational anesthetic, was submitted to Phase II studies following Phase I studies[3,7] in Japan. Since healthy volunteers in Phase I study were successfully anesthetized without any sequelae[3,6], sevoflurane could serve as a clinical anesthesia as well. Among the physicochemical, pharmacological and toxicological properties of this agent[13], the characteristic low blood/gas partition coefficient of 0.60, similar to nitrous oxide, implies a rapid induction of anesthesia and a fast recovery.

Like other inhalational anesthetic agents, sevoflurane also has some chemical[5,13] and metabolic instability[1,4,6,9]. One of the metabolites of this agent is an inorganic fluoride which is known to cause renal dysfunction[2,10,11]. In clinical application, it is, therefore, important to estimate an extent of biotransformation of the anesthetic, especially on toxic substance(s).

The present Phase II studies of sevoflurane

were undertaken to evaluate its clinical safety and efficacy, and an extent of biotransformation in surgical patients.

MATERIALS AND METHODS

Nine ASA Physical Status 1 orthopedic patients (6 males and 3 females, age; 17-52 yr) were studied. They had no history of anesthesia within 6 months or history of hepatorenal dysfunction.

The study was approved by the Ethical Committee on Human Studies of the Hiroshima University Hospital and the Japanese Ministry of Health and Welfare, and written informed consent was obtained from each patient or from the parents when the patient was under 20 years of age.

Patients were premedicated with atropine sulfate (0.5 mg) and hydroxyzine (50 mg) given intramuscularly one hr before anesthesia. A radial artery cannula was inserted for blood pressure recording, for sampling for arterial blood gas analysis (ABL II^R, Radiometer, Denmark) and for measurement of serum inorganic fluoride.

After induction of anesthesia with thiamylal (4 mg/k, iv) and intubation with pancuronium bromide (0.1 mg/kg, iv), a mixture of 2% of sevoflurane and 50% of nitrous oxide in oxygen was inhaled. Sevoflurane was delivered through a sevoflurane vaporizer (Acoma, Japan) which was calibrated by a gas chromatograph. The endotracheal (close to carina tracheae) concentration of sevoflurane was measured with NORMAC^R equipped infra-red sensor (Datex, Finland) which was also calibrated by gas chromatography, and recorded on a chart with arterial blood pressure. The patient was ventilated artificially (Acoma Anespirator^R, Japan) at 8 ml/kg of tidal volume with respiratory rate of 10 to 12/min, which was adjusted within physiological conditions on arterial blood gases. At the end of the operation, sevoflurane and nitrous oxide were discontinued simultaneously.

Routine laboratory examinations were followed up to the 7th to 10th postoperative day.

A simple verbal command was conducted immediately after discontinuation of inhalation anesthetics in all the patients.

The blood sampling for measurement of inorganic fluoride concentration was obtained at the first 30 min and at every 60 min during and after discontinuation of sevoflurane. The urine for measurement of inorganic fluoride and glucuronide of hexafluoroisopropanol was collected every 60 min for several hours and was stored daily for several postoperative days.

Inorganic fluoride and glucuronide of hexafluoroisopropanol were measured with ion-chromatographic analyzer (IC-100, Yokogawa Electric Co., Japan) equipped with a suppressor and an electro-conductive detector, which is described elsewhere[3,4].

The blood concentration of sevoflurane was analysed at 15 and 30 min and every 60 min thereafter during anesthesia, and at 15, 30 and 60 min after anesthesia by a gas chromatograph (GC-4A PTF equipped with a flame ionization detector, Shimadzu, Japan) as described elsewhere[3].

Sevoflurane used was donated from the Maruishi Pharmaceutical Co., Osaka, Japan.

Mean and standard deviations of different groups of data were calculated. Student t-test was used to assess the significance of differences between data. Differences with random probability of 5% or less were considered significant.

RESULTS

The Patient was administered sevoflurane for 3.5 ± 1.6 hr (M ± SD), ranging from 2.2 to 5.5 hr. Blood pressure (Fig. 1.) and heart rate were kept relatively stable. No arrhythmia was evident on ECG. All the patients were anesthetized and operated with 2% inspired concentration of sevoflurane and 50% of nitrous oxide in oxygen. Postoperative laboratory findings showed no unexplainable abnormality. All patients were discharged uneventfully.

1) Endotracheal concentration of sevoflurane

As shown on Fig. 1, the end expiratory concentration of sevoflurane, which indicates the lower concentration on the trace of endotracheal concentration, reached a plateau in 4.0 ± 0.8 min after the exposure. A sudden fall of concentration was also observed immediately after discontinuation of sevoflurane in all the patients.

2) Blood concentration of sevoflurane

As shown on the trace of endotracheal concentration of sevoflurane, the blood concentration of the agent after initiation of inhalation

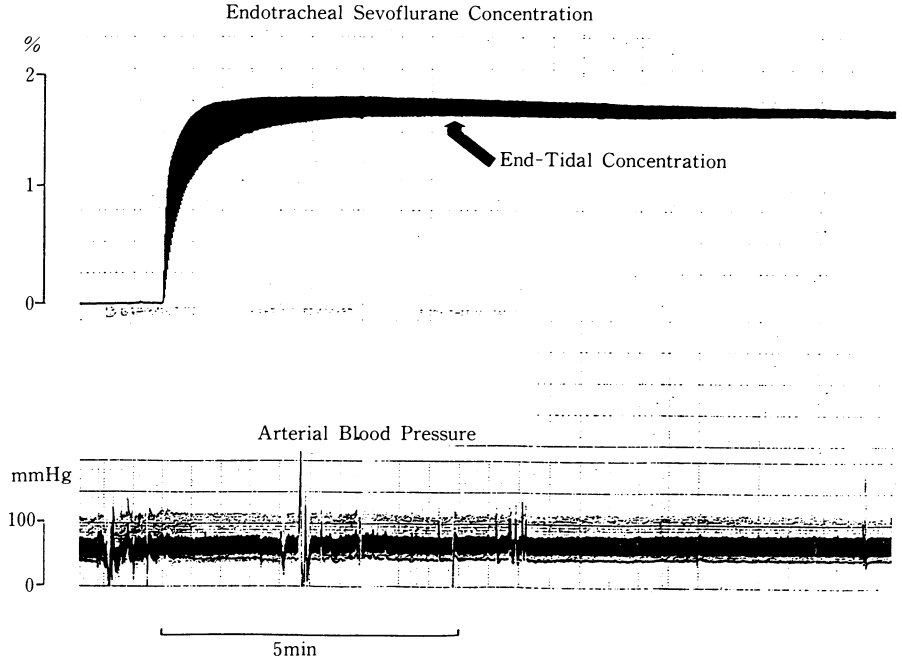

Fig. 1. Endotracheal concentration of sevoflurane and arterial blood pressure
The endotracheal concentration of sevoflurane was measured by NORMAC^{R} and recorded on a chart with arterial blood pressure. The patient was ventilated artificially with Acoma respirator^{R} at 8 ml/kg of tidal volume with respiratory rate of 10 to 12 /min which was adjusted to obtain the physiological limits based on arterial blood gases.

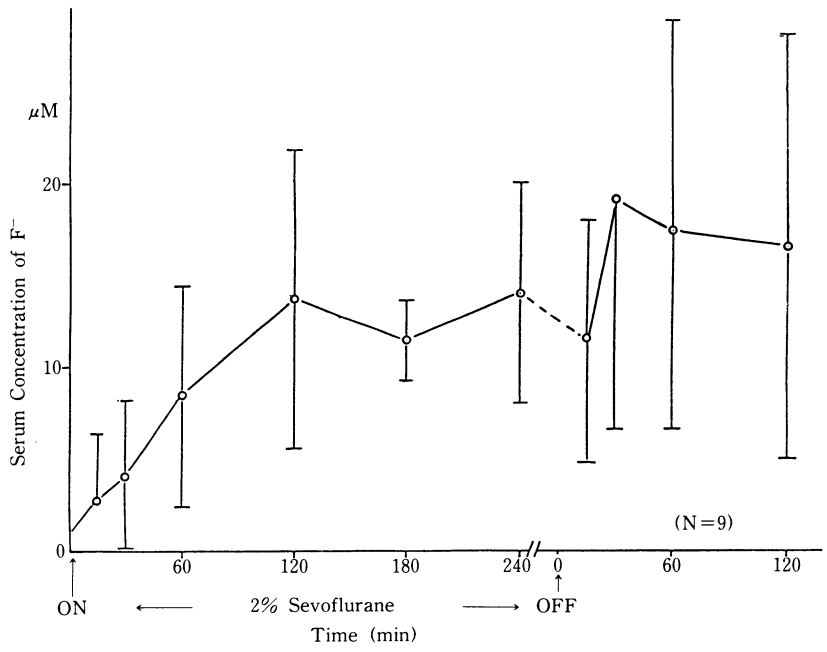

Fig. 2. Serum concentration of inorganic fluoride
Serum concentration of inorganic fluoride in patients was measured during and after inhalation of 2% sevoflurane and 50% nitrous oxide in oxygen, using an ion chromatographic analyzer. Values are expressed as mean ± standard deviations. The serum concentrations at 180 and 240 min during inhalation indicate the data from five and three patients, respectively.

rose also rapidly and was maintained at about 500 μM during inhalation (e.g. 499.8 ± 65.0 μM at 60 min after inhalation). Fall of blood concentration after termination of inhalation was also fast in all the patients and was not correlated with anesthesia time of sevoflurane.

3) Verbal response

The time for verbal response after discontinuation of sevoflurane was 11.8 ± 4.2 min, ranged from 7 to 19 min, and was also not correlated with anesthesia time of sevoflurane.

4) Serum concentration of fluoride

As shown on Fig. 2, serum concentration of inorganic fluoride rose significantly to 13.7 ± 8.2 μM (range: to 19.6 μM) at 120 min after the start of sevoflurane administration and was almost constant. After termination of sevoflurane, serum fluoride levels were maintained at an average of about 10 to 20 μM. In one patient, the maximum level reached 38.3 μM which was obtained 30 min after discontinuation of 3 hr sevoflurane. Serum fluoride was measured 12 hr after anesthesia in three patients and showed almost half of their maximum.

5) Urinary inorganic fluoride and glucuronide of hexafluoroisopropanol

Urinary fluoride concentration varied widely to range from 20 to 3,000 μM during inhalation and in the first 12 hr after anesthesia. The peak concentration was observed during the first 12 or 24 hr of the postoperative period in all the patients.

The total amount of inorganic fluoride excreted in the urine varied also from 405 to 4,664 μmoles with a mean value of 1,690. The total amount of inorganic fluoride was not correlated with anesthesia time of sevoflurane.

A glucuronide of hexafluoroisopropanol was detected in urine from the initial 12 hr urine in the postoperative period and showed its maximum concentration. In the following 12 hr urine, it decreased. On the 3rd or 4th postoperative day, it became undetectable.

DISCUSSION

As in Phase I study of healthy volunteers[3,7], sevoflurane served as clinical anesthesia without any adverse effects.

In a very short period of time, the stable end tidal concentration of sevoflurane was obtained though 2% inspired concentration of sevoflurane was administered immediately after intubation (Fig. 1). This was reflected in a stable and constant blood concentration of the anesthetic from the early period to the end of inhalation as also shown in Phase I study[3]. The differences between each inspiratory and expiratory (end-tidal) concentrations during the inhalation (Fig. 1) suggest that the apparent uptake of sevoflurane decreases soon after the start of inhalation, assuming that there was no volume change in inspiration and expiration. From these data, as expected from its physical property, the equilibrium of the anesthetic between the alveoli and blood could be obtained in a very short period of time. The rapid fall of blood concentration after termination of inhalation also suggests that the uptake of this agent was small. Clinically, this reflects the finding that the time of verbal response after discontinuation of the inhalation was fast in onset, and it promises an early recovery from anesthesia.

It is noteworthy that serum fluoride concentration increased soon after initiation of inhalation of sevoflurane and reached a plateau 120 min after exposure. A constant level of serum fluoride lasted for 120 min after discontinuation of sevoflurane. Pharmacokinetic studies of sevoflurane and its metabolite(s) would elucidate the mechanism.

One of the most important findings in this studies, however, is that unlike methoxyflurane the serum fluoride level did not exceed 50 μM of the nephrotoxic level[2]. The serum fluoride level by sevoflurane anesthesia showed almost the same or slightly lower value as by enflurane[8,11,12], though it is higher than that by other inhalational anesthetic agents such as halothane or isoflurane[10].

This Phase II study of sevoflurane shows that the new volatile anesthetic agent, sevoflurane, warrents further laboratory study and clinical evaluation in a wider range of subjects.

ACKNOWLEDGEMENTS

A part of this work was supported by a Research Grant from the Japanese Ministry of Education, Science and Culture and presented at the 8th European Congress of Anaesthesiol-

ogy, Vienna, Austria, in September, 1986.

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