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Comparison of Plasma Inorganic Fluoride Concentration with Sevoflurane-N_2O and Enflurane-N_2O Anesthesia

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Plasma inorganic fluoride concentrations were measured in adult patients without hepatic or renal disease following sevoflurane-N_2O anesthesia (n=7) or enflurane-N_2O anesthesia (n=6). The anesthetic dosage of sevoflurane and enflurane was 6.48±2.15 %-hours and 6.57±2.50 %-hours, respectively. The mean peak plasma inorganic fluoride concentration in the sevoflurane group was 19.5±13.4 μmol/L 1 hour after anesthesia, which decreased to preanesthetic levels 24 hours after anesthesia. In the enflurane group the values were 13.2±5.8 μmol/L at the end of anesthesia and decreased, but remained, still twice as high as the preanesthetic level 24 hours after anesthesia. The relationship of plasma inorganic fluoride concentration and anesthetic dosage was more pronounced in the sevoflurane group (r=0.68, slope= 4.2) than in the enflurane group (r=0.39, slope=1.2). In conclusion, sevoflurane-N_2O anesthesia results in similar subnephrotoxic levels of plasma inorganic fluoride as enflurane-N_2O anesthesia, and although the fluoride concentration had a better correlation to anesthetic dosage in the sevoflurane group than in the enflurane group, its excretion was faster in the sevoflurane group than in the enflurane group.

Key Words: Sevoflurane, inorganic fluoride concentration

Sevoflurane {fluoromethyl 2,2,2-trifluoro-1-(trifluoro methyl) ethyl ether} has a blood-gas partition coefficient of 0.6. This allows a rapid induction of anesthesia and emergence. However, it is well known that one inorganic fluoride ion is produced per one sevoflurane molecule that is metabolized (Cousins and Mazze 1973; Mazze *et al.* 1977). Compared to other anesthetic agents, this is a large amount of fluoride production and could potentially lead to nephrotoxicity if large amounts of this anesthetic were metabolized.

A previous in-vivo study in animals have shown that the plasma inorganic fluoride concentrations following 2~3% inspired concentration of sevoflurane for one hour and for a duration of 1.0 to greater than 7.0 MAC hours, respectively, were similar to those of enflurane anesthesia and both of these anesthetics did not result in renal impairment (Cook *et al.* 1975a,b). The previous studies in human volunteers (Holaday and Smith 1981; Frink *et al.* 1992) following sevoflurane anesthesia reported peak plasma inorganic fluoride concentrations to be 22 μmol/L and 29.3 μmol/L.

In this study, we evaluated the plasma inorganic fluoride concentrations following sevoflurane-N_2O anesthesia compared with enflurane-N_2O anesthesia in healthy patients who needed moderately prolonged anesthesia for more than three hours.

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MATERIALS AND METHODS

Thirteen, either sex, adult surgical patients with ASA physical status I or II, who were without hepatic or renal disease, and were scheduled for time-consuming operations such as microsurgery or reconstructive surgery etc., were randomly assigned into sevoflurane (n=7) and enflurane (n=6) groups. But cancer patients were excluded. All the patients were premedicated with glycopyrrolate (0.004 mg/kg) and midazolam (0.05 mg/kg) intramuscularly 1 hour before induction of anesthesia.

At patient's arrival to the operation room, a radial arterial catheterization was done for continuous blood pressure measurement and blood sampling to measure inorganic fluoride. Servomed (Hellige, Hamburg, W-Germany) was applied to monitor continuous EKG and blood pressure. After induction of anesthesia with thiopental 5 mg/kg and succinylcholine 1 mg/kg intravenously for endotracheal intubation, sevoflurne or enflurane with nitrous oxide 50% in oxygen was given through a semiclosed circuit with soda lime for CO_2 absorption(total gas flow, 4 L/min.). Ventilation was controlled to maintain $PaCO_2$ at 30~40 mmHg. The inhaled concentration of each anesthetics was adjusted for each surgical situation, and with completion of operation, inhalation anesthetics including nitrous oxide were discontinued simultaneously.

Blood samplings for plasma inorganic fluoride measurement were obtained prior to anesthesia, every 1 hour during anesthesia, at the end of anesthesia, and 1, 2, and 24 hours after anesthesia. At each time of blood sampling during anesthesia, the anesthetic dosage (%-hour) was calculated and recorded according to vaporizer dial setting concentration (Enflurane vaporizer, Ohio, USA and sevoflumatic TCV-7, Aika, Tokyo, Japan). Plasma inorganic fluoride was measured by fluoride selective electrode model 94-01 and ion analyzer 901 (Orion Research, Mass, U.S.A.) after calibration with NaF (0.01~100 ppm).

For statistical analysis of data, the independent t-test was applied for intergroup analysis and the repeated measured ANOVA was applied to intragroup comparison. Correlation of anesthetic dosages (%-hour) and plasma inorganic fluoride concentrations was also obtained to measure the relationship between the two variables. P value less than 0.05 were considered as significant.

Table 1. Demographic data

Group	Enflurane (n=6)	Sevoflurane (n=7)
Age (years)	37±21	26±6
Sex (M/F, No)	3/3	4/3
Weight (kg)	55±8	55±9
Height (cm)	163±18	166±12
Operation time (min)	255±119	259±128
Anesthesia time (min)	294±116	291±127
Anesthetic dosage (%-hour)	6.57±2.50	6.48±2.15

Values are mean ± SD, except sex.
No significant difference between two groups.

Table 2. Hemodynamic changes during perioperative periods

Group	Preoperation		Intraoperation		Postoperation	
	Enf	Sevo	Enf	Sevo	Enf	Sevo
SBP (mmHg)	119±23	130±18	115±11	109±17	128±17	126±18
DBP (mmHg)	75±12	75±16	71±9	67±10	73±8	77±10
HR (beats/min)	85±22	79±11	68±31	86±9	88±11	87±12

Values are mean ± SD.
Enf; enflurane, Sevo; sevoflurane, SBP; systolic blood pressure, DBP; diastolic blood pressure, HR; heart rate.
No significant difference between two groups.

Table 3. Mean peak plasma inorganic fluoride concentration during perianesthetic periods

Group	Anesthesia			Post-anesthesia		
	Before	During	End	1 Hour	2 Hour	24 Hour
Enf	4.0±4.9	9.8±5.8	13.2±5.8	10.6±3.9	11.3±6.8	8.6±5.6
Sevo	2.8±3.8	16.7±8.9	16.2±6.9	19.5±13.4	11.0±3.2	3.8±2.6

Values are mean ± SD(in μmol/L).
Enf; enflurane, Sevo; sevoflurane.
Not significant in intergroup and intragroup comparison ($p>0.05$).

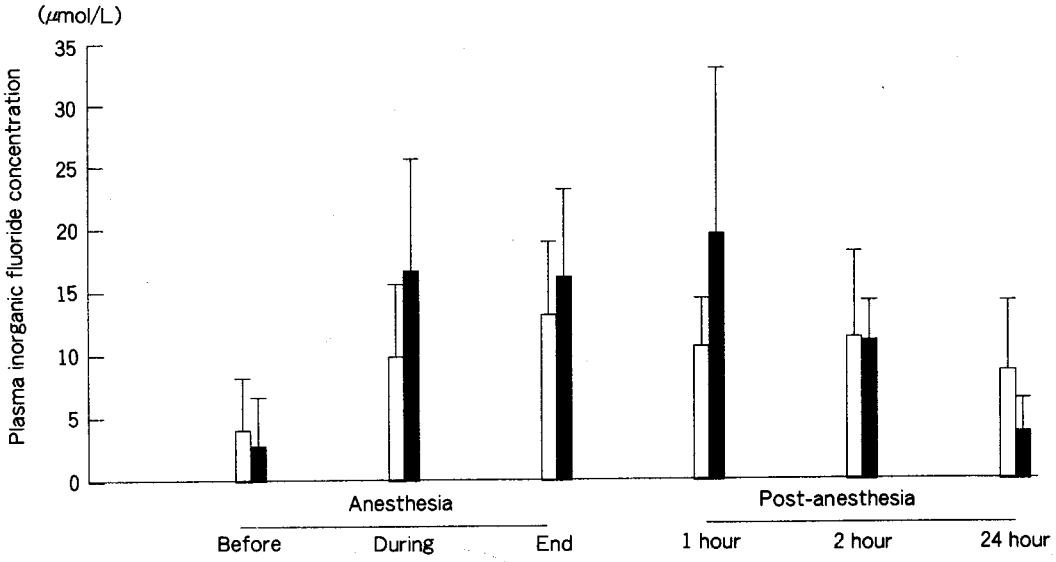

Fig. 1. *Plasma inorganic fluoride concentrations during the perianesthetic periods of the sevoflurane (■) and the enflurane (□) group. All values are mean ± SD. Not significant in intergroup and intragroup comparison($p>0.05$).*

RESULTS

Table 1 represents mean age, sex, height, weight, operation and anesthetic duration of patients in the sevoflurane and enflurane group. These values were all statistically insignificant between the two groups. Sevoflurane and enflurane were administered for 291 ±127 and 294±116 min., respectively. Their anesthetic dosages were 6.48±2.15 %-hours and 6.57±2.50 %-hours, respectively. Arterial blood pressure and heart rate were maintained and remained stable throughout anesthesia (Table 2) due to the adjustment of anesthetic depth for each surgical situation.

When compared to the preanesthetic level, the respective mean plasma inorganic fluoride concentration during anesthesia in the enflurane and sevoflurane groups showed a 2- and 6-fold increased. The peak mean concentration of inorganic fluoride was 13.2±5.8 μmol/L at the end of anesthesia in the enflurane group, and 19.5±13.4 μmol/L 1 hour after anesthesia in the sevoflurane group. At 24 hours after anesthesia, these values declined to preanesthetic levels in the sevoflurane group, while still remaining at about a two fold increase of the preanesthetic level in the enflurane group (Table 3 and Fig.1). But these concentrations did not show any significance statistically in intergroup and intragroup com-

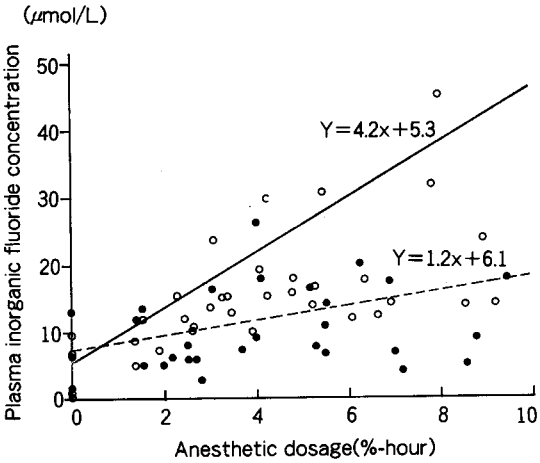

Fig. 2. *Scattergram and regression plot of the anesthetic dosages (%-hour) and plasma inorganic fluoride concentration in the sevoflurane (open circle, solid line) and the enflurane (closed circle, dashed line) group.*
r=0.68, p<0.01 in the sevoflurane group and r =0.39, p<0.05 in the enflurane group.

parison. There was a linear correlation between the anesthetic dosages and plasma inorganic fluoride concentrations in both anesthetics (r=0.39, slope=1.2, p<0.05 in the enflu-rane group and r=0.68, slope=4.2, p<0.01 in the sevoflurane group) (Fig. 2).

DISCUSSION

Most fluorinated inhalational anesthetics produce fluoride ions through their metabolism which are known to potentially cause organ toxicity. Since Crandell *et al.* (1966) first reported nephrotoxicity related with methoxyflurane, there have been many studies about methoxyflurane-nephrotoxicity in animals (Mazze *et al.* 1972 and 1973; Cousins *et al.* 1974) and in humans (Taves *et al.* 1970; Mazze *et al.* 1971; Cousins and Mazze 1973). Nephrotoxicity following methoxyflurane anesthesia, which is unresponsive to ADH resulting in inability to concentrate urine, could occur especially when plasma inorganic fluoride exceeds 50 μmol/L (Cousins and Mazze 1973). In in-vivo and in-vitro animal studies, Barr *et al.* (1974) and Cook *et al.* (1975a,b), showed that inorganic fluoride excretion following sevoflurane anesthesia was similar to that of enflurane anesthesia. No subsequent renal function impairment was noted after use of either anesthetic. In a human volunteer study, Holaday and Smith (1981) reported 22 μmol/L of plasma inorganic fluoride with 2~3 % sevoflurane inhalation for one hour. In human study, Smith *et al.* (1992) reported plasma inorganic fluoride of 23.2 and 26.4 μmol/L with 0.77% or 0.86% sevoflurane and 60% N_2O for 154 and 157 minutes, respectively. The extent of exposure to sevoflurane in this study was correlated with inorganic fluoride production. In yet another human study, Frink EJ *et al.* (1992) used only sevoflurane anesthesia resulting in a peak plasma inorganic fluoride level of 29.3 μmol/L, 2 hours after anesthesia, which was reduced to less than 10 μmol/L 24 hours after anesthesia.

In this study, the plasma inorganic fluoride concentration following sevoflurane or enflurane anesthesia was similar to previous studies (Holaday and Smith 1981; Smith *et al.* 1992), and there were no statistical differences of plasma inorganic fluoride concentrations between the two anesthetics and the highest levels were 45.2 μmol/L in the sevoflurane group and 26.2 μmol/L in the enflurane group. Our study did not reveal the postanesthesic levels of inorganic fluoride from more than two hours till 24 hours after anesthesia. Holaday and Smith (1981) and Frink *et al.* (1992) found that the peak plasma inorganic fluoride concentration occurred within two hours after sevoflurane anesthesia and declined to preexposure level 24 hours after anesthesia. Meanwhile, Mazze (1984) found that plasma inorganic fluoride level remained above 20 μmol/L for approximately 18 hours after enflurane anesthesia. Therefore, the authors thought that there might be some differences of inorganic fluoride concentration between sevoflurane and enflurane anesthesia 24 hours after anesthesia. The mean peak inorganic fluoride reached 13.2 μmol/L at the end of enflurane anesthesia and 19.5 μmol/L 1 hour after sevoflurane anesthesia. Two hours

following anesthesia, a level of 11 μmol/L was recorded in both groups. Inorganic fluoride concentration in the enflurane group was twice as high as in the sevoflurane group 24 hours after anesthesia. These find-ings can be well explained by Cook *et al.* (1975a), who indicated that sevoflurane was defluorinated at a rate similar to methoxyflurane but plasma inorganic fluoride levels were one sixth of methoxyflurane because low tissue solubility of sevoflurane facilitated its rapid postanesthetic excretion through the lung, whereas the high solubility of methoxyflurane retarded its elimination. Meanwhile, although enflurane is defluorinated at about one seventh the rate of sevoflurane, its greater tissue solubility induce slow elimination and, consequently, a similar extent of defluri-nation when compared to sevoflurane. Cook *et al.* (1975b) reported no renal impairment after as long as ten hours' of sevoflurane anesthesia in rats. Still it is possible that nephrotoxicity might be related to the duration for which high concentration of inorganic fluorides are present as well as the peak level itself, which was mentioned by Cook *et al.* (1975a,b) and Mazze (1984).

Our study revealed that moderately prolonged anesthesia for more than three hours with sevoflurane or enflurane resulted in similar subnephrotoxic concentrations of plasma inorganic fluoride, but the correlation of anesthetic dosages and inorganic fluoride concentrations was more apparent in the sevoflurane group than in the enflurane group, and the excretion of the inorganic fluoride was faster in the sevoflurane group than in the enflurane group.

Additional studies should be done to confirm our finding for the establishment of the safety of sevoflurane use in patients with underlying renal impairment.

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