Plasma Fluoride Concentration and Urinary Fluoride Excretion in Obese and Non-Obese Patients Following Enflurane Anesthesia

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Plasma fluoride concentrations and urinary fluoride excretions were measured following enflurane anesthesia (1.5%, 2 hours) in obese (8 cases) and non-obese (9 cases) patients.

At the end of anesthesia, there was no significant difference in plasma fluoride concentrations between the two groups. In the several days following anesthesia, however, plasma fluoride concentrations in obese patients were higher than those in non-obese patients.

Urinary fluoride excretions after anesthesia were greater in obese patients than those in non-obese patients, and the period of increased fluoride excretion was prolonged in obese patients.

These results suggested that obese patients metabolized more enflurane than non-obese patients during the postanesthetic period. In obese patients, their excess fatty tissue may cause a greater and more prolonged elevation of blood enflurane concentrations after anesthesia. (Key words: enflurane, flurometabolites, obesity, fluoride)

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It has been well-documented that obese patients have a higher risk of suffering from the characteristic renal dysfunction following methoxyflurane anesthesia than non-obese patients. The cause of renal dysfunction is attributed to the metabolite of methoxyflurane, inorganic fluoride[1–3]. Obese patients can accumulate a larger amount of methoxyflurane because of its high lipid solubility, and consequently, they metabolize a larger amount of methoxyflurane than non-obese patients. As a result, plasma fluoride concentration in obese patients following methoxyflurane anesthesia tend to be higher than that in non-obese patients[1,4].

Enflurane is also metabolized and releases inorganic fluoride, but to a lesser extent[5]. In this study, plasma fluoride concentration and urinary fluoride excretion were measured to determine whether obese patients metabolize more enflurane than non-obese patients. In addition, urinary output and urinary specific gravity were measured to evaluate the renal function following enflurane anesthesia.

Materials and Methods

Seventeen adult patients without renal dysfunction, undergoing elective surgical procedure which were expected to take about 2 hours with little bleeding, were studied. Informed consent for sampling blood and urine was obtained from each patient. Before the induction of anesthesia, body weight, height and girth (at the umbilical level, at

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the end of expiration in supine position) were measured. Percent fat was calculated from the following formula[6]:

Percent fat = 90 − 0.788 (height (cm) − girth (cm))

Patients with more than 30% of percent fat were defined as the obese group and patients with less than 30% of percent fat were defined as the non-obese group.

Premedication which consisted of 50 mg of hydroxyzine pamoate and 0.5 mg of atropine sulfate were administered intramuscularly 45 min before the inducation of anesthesia. Following preoxygenation, anesthesia was induced with thiopental (250–300 mg) followed by 1 mg/kg of succinylcholine chloride to fascilitate the endotracheal intubation. Anesthesia was maintained with 1.5% of enflurane in 60 percent nitrous oxide and oxygen for 2 hours, even if the surgical procedure had been performed before. After 2 hours, enflurane was discontinued and subsequent anesthesia was maintained with 66 percent nitrous oxide in oxygen and droperidol-fentanyl or diazepam-pentazocine until the completion of the surgical procedure. Pancuronium bromide was utilized for muscle relaxation during the surgical procedure.

Enflurane was delivered by a well-calibrated enflurane vapolizer (Enfluratec®). Blood samples for plasma fluoride concentration analysis were drawn in a heparinized plastic syringe before the induction of anesthesia, at the end of enflurane administration and at points 24, 48, 72 and 168 hours after the end of enflurane administration. Daily urinary output and the urinary specific gravity were measured on the day before the operation and on the 1st, 2nd, 3rd, 5th and 7th postoperative days. Simultaneously, urine specimens were obtained to determine a 24-hour fluoride excretion on the same days described above.

Blood samples and collected urinary specimens were deposited, not in a glassware, but in a plasticware throughout the study. Plasma fluoride concentrations were measured by ion-specific electrode (Fluoride Selectrode F-1052F®, Radiometer, Copenhagen) according to the method described by Fry[7]. The Student's t-test was used for statistical analysis. $P<0.05$ was considered statistically significant.

Table 1. Patient characteristics

		obese	non-obese
number of patients		8	9
Age	(y.o.)	53.8±11.8*	39.8±13.6
Height	(cm)	152.8±5.0*	161.9±9.4
Weight	(kg)	65.5±7.4	60.6±13.7
Girth	(cm)	90.4±5.7**	75.4±9.4
BSA	(m^2)	1.63±0.11	1.64±0.22
% fat	(%)	40.8±4.1**	21.8±5.1

Values are Mean±S.D.
* $P<0.05$
** $P<0.005$

Results

Eight patients were defined as the obese group and 9 patients were defined as the non-obese group (table 1). Although there was no significant difference in the body weight of the two groups, percent fat of the obese group was significantly larger than that of the non-obese group, and was twice as large as that of the non-obese group. No significant difference was observed between the two groups in the bleeding volume or in the infused fluid volume.

1) Plasma fluoride concentration (fig. 1)

Mean plasma fluoride concentrations before induction in the obese and non-obese groups were 1.04 μEq/l and 0.70 μEq/l, respectively. The difference between the two groups was not statistically significant. After enflurane anesthesia, plasma fluoride concentrations increased markedly reaching a peak (obese group, 11.3±2.6 μEq/l; non-obese group, 10.5±1.6 μEq/l) at the end of anesthesia, and then gradually decreased. In both groups, plasma fluoride concentrations after anesthesia were higher than preoperative values until the 3rd postoperative day, and then returned to the preoperative values on the 7th postoperative day. No significant difference in plasma fluoride concentrations was observed between the two groups at the end of anesthesia,

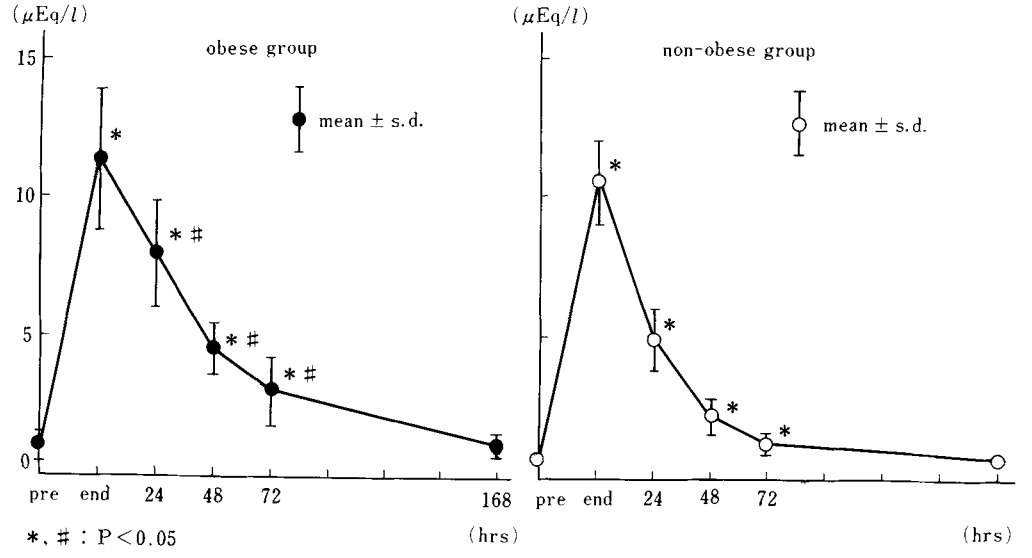

Fig. 1. Plasma fluoride concentrations

After enflurane anesthesia, plasma fluoride concentrations were markedly elevated reaching a peak at the end of anesthesia. (* means significant difference from preanesthetic value in each group.)

At the end of anesthesia, a significant difference was not observed between the two groups. At 24, 48, 72 hours after anesthesia, however, plasma fluoride concentrations in the obese group were higher than those in the non-obese group. (# means significant difference between the two groups.)

however, plasma fluoride concentrations in the obese group were significantly higher than those in the non-obese group at 24, 48 and 72 hours after anesthesia.

2) Urinary fluoride excretion (fig. 2)

After enflurane anesthesia, daily urinary fluoride excretion was remarkably increased in both groups, Maximum daily fluoride excretion was observed on the 1st postoperative day (obese group, 423.6±182.6 μEq/m^2/day; non-obese group, 261.1±135.0 μEq/m^2/day). In the non-obese group, the daily fluoride excretion returned to the preoperative value on the 5th postoperative day. On the other hand, in the obese group, it was greater than the preoperative value even on the 7th postoperative day. Daily fluoride excretion in the obese group was larger than that in the non-obese group on the 1st, 2nd, 3rd and 7th postoperative days. On the 5th postoperative day, the obese group excreted more urinary fluoride than the non-obese group, however, the difference was not statistically significant. Ultimately, the obese group excreted larger amounts of fluoride than the non-obese group during the postoperative period.

3) Daily urinary output and urinary specific gravity (fig. 3)

Daily urinary output and specific gravity were kept in a normal range and no statistical differences were observed between the two groups throughout the study.

Discussion

An increased methoxyflurane or halothane biotransformation was reported in obese patients compared with non-obese patients[1,4]. Bentley et al. demonstrated that reductive metabolism of halothane, following anesthesia, increased in obese patients compared with non-obese. Metabolism during anesthesia, however, was similar to that in non-obese patients[8]. They also reported an increased enflurane metabolism in obese patients not only after anesthesia but also during anesthesia[9].

The present study demonstrated that

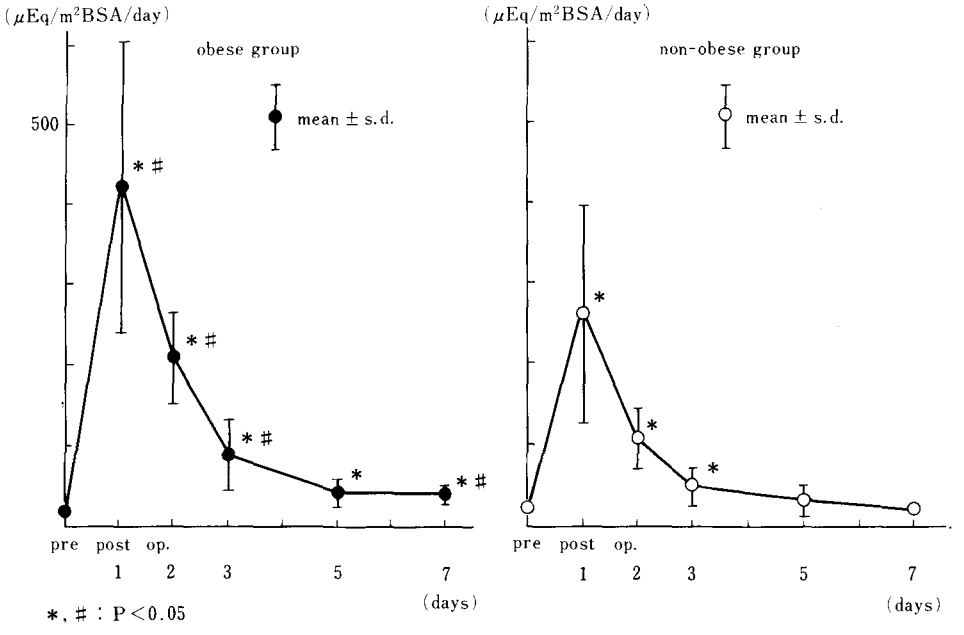

Fig. 2. Daily urinary fluoride excretions

After enflurane anesthesia, daily urinary fluoride excretions increased markedly. (* means significant difference from preanesthetic value in each group.) In the non-obese group, it returned to the preanesthetic value on the 5th postoperative day. On the other hand, in the obese group, it was greater than the preoperative value even on the 7th postoperative day.

Daily fluoride excretions in the obese group were larger than those in the non-obese group on the 1st, 2nd, 3rd, and 7th postoperative day. (# means significant difference between the two groups.)

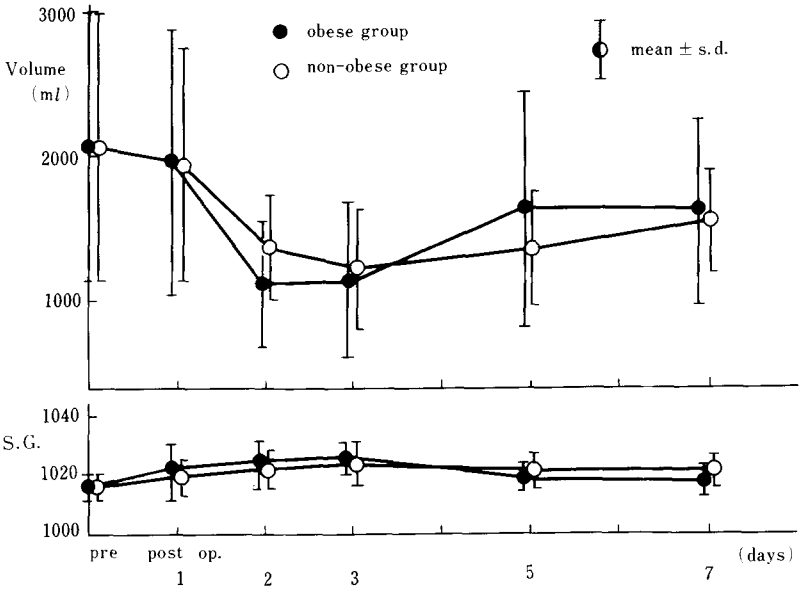

Fig. 3. Daily urinary outputs and urinary specific gravities

Daily urinary outputs and urinary specific gravities were kept in a normal range. No statistical difference was observed between the two groups throughout the study.

there was not a significant difference in plasma fluoride concentration between the two groups during enflurane anesthesia. This result, which apparently contradicts the result reported by Bentley et al.[9], suggests that there is not a significant difference in the metabolic rate of enflurane between the obese and non-obese group during anesthesia, when enflurane must be metabolized at a maximum rate in both groups.

Plasma fluoride concentration and urinary fluoride excretion following anesthesia should reflect the enflurane metabolic rate after anesthesia, rather than during, because the biological half-life of fluoride is very short (approximately 1 hour)[10,11]. In other words, if enflurane was to be metabolized only during anesthesia, plasma fluoride concentration and urinaty fluoride excretion would decrease and return to a normal level in a few hours following anesthesia. The prolonged elevation of plasma fluoride concentration and increase of urinary fluoride excretion in our study suggest a persistent enflurane metabolism for several postoperative days following anesthesia. Hitt and White also reported that the great majority of enflurane metabolism occurred after anesthesia, rather than during anesthesia[12,13].

In the obese group plasma fluoride concentration was higher than that in the non-obese group in the postoperative period. Increased daily urinary fluoride excretion after anesthesia lasted longer in the obese group than in the non-obese (7 vs. 3 days). Additionally, the degree of the increase of daily urinary fluoride excretion in the obese group was larger than that in the non-obese group. These results indicate that enflurane metabolism in the obese group is larger, and more prolonged, than that in the non-obese group.

Why is enflurane metabolized greater after anesthesia rather than during anesthesia, and why is the metabolism in the obese patients larger and more prolonged? The mechanism may be explained as follows:

Michaelis constant "Km" of enflurane metabolism is 30–50 μM/l in vivo and 70 μM/l in vitro[12]. Those concentrations correspond to 0.02–0.05 MAC. When blood enflurane concentration is more than 2"Km", in other words, at 0.1 MAC, the metabolic rate is nearly Vmax regardless of the enflurane concentration. Therefore, during clincal anesthesia, enflurane is metabolized at a maximum rate, and the amount of metabolized enflurane is proportional to the duration of the anesthesia.

When blood enflurane concentration is between "Km" and 2"Km", enflurane is metabolized at a parallel rate to the concentration. Blood enflurane concentration reaches "Km" several hours after the end of anesthesia. At this moment, enflurane has already been released from vessel-rich tissue and muscular tissue. As a result, most of the enflurane in the blood is derived from fatty tissue. The bulk of enflurane metabolism occurs in this postanesthetic period and the amount of metabolized enflurane depends upon the dose released from the fatty tissue.

Enflurane absorption and distribution in the fatty tissue should be considered at this point. Since the fatty tissue has a large enflurane storage capacity (λ fat/gas is 111, while λ tissue other than fat/gas is 1.9–3.8), large amounts of enflurane are absorbed and stored in the fatty tissue during anesthesia. Chase reported that 42% of enflurane absorbed during anesthesia was released from fatty tissue after anesthesia[5]. Fatty tissue can not become saturated within a short time period because of its very large time constant[5,14–16]. Therefore, prolonged anesthesia increases the enflurane storage in the fatty tissue. Since obese patients have a large amount of fatty tissue than non-obese patients, they accumulate larger amount of enflurane in these tissues.

Enflurane absorbed in the body tissues during anesthesia is released into the blood after anesthesia. The speed of this release is influenced by three factors: (1) λ tissue/blood (T/B), (2) tissue blood flow, and (3) tissue volume. In the fatty tissue, λ T/B is large and tissue blood flow is small, therefore, the release from the tissue

is slow and prolonged. Chase demonstrated that $T\frac{1}{2}$ of enflurane release in fatty tissue was 36 hours, while $T\frac{1}{2}$ in vessel-rich tissue and muscular tissue were 17.8 minutes and 3.2 hours, respectively[5]. In obese patients, it has been reported that λ blood/gas is smaller than that in non-obese patients[17–19]. Therefore, λ T/B in obese patients might be larger than that in non-obese patients. Furthermore, blood flow to the unit volume of the fatty tissue is smaller in obese patients than that in non-obese patients[20], although total blood flow to the fatty tissue is larger in obese patients than that in non-obese patients[21]. For these reasons, enflurane release from the fatty tissue is expected to be prolonged, especially in obese patients. During the postanesthetic period, blood enflurane concentration in obese patients is also expected to be higher than that in non-obese patients. Consequently, in obese patients, enflurane metabolism would last longer at a maximum metabolic rate.

The another important factor which determines the metabolic dose is the duration of anesthesia. Prolonged anesthesia increases the amounts of metabolized enflurane during and after anesthesia. Therefore, the longer the duration of anesthesia is, the higher and more prolonged the elevation of plasma fluoride concentration becomes. Lawry and Cousins reported that peak serum fluoride concentration is determined, not by the anesthetic concentration, but by the anesthetic duration[22,23]. White's observation also supported this speculation[13].

Aso reported that serum inorganic fluoride concentrations were higher in elder patients than in younger patients before and after enflurane anesthesia[24]. Although patients in our obese group were elder than those in our non-obese group, they were younger than Aso's patients and had similar preanesthetic plasma fluoride concentrations to our non-obese group. Therefore, in our study, we don't believe the difference of the age between the two groups had a great influence on the plasma fluoride levels.

Plasma fluoride concentrations following enflurane anesthesia were almost the same as the results reported previously[23–31]. Peak plasma fluoride concentrations were well below the level which can produce renal dysfunction[26,31]. In fact, urinary specific gravity and urinary output remained in the normal range throughout the study. This suggests that 1.5% of enflurane is administered for 2 hours without apparent renal dysfunction, however, subclinical renal dysfunction was not excluded in this study, since vasopression test was not conducted. In our study, plasma fluoride concentrations tend to stay in high level in the obese patients. This tendency is expected to be accelerated by the prolongation of enflurane administration. Even so, a risk of renal dysfunction still may exist in obese patients, especially following prolonged enflurane anesthesia.

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