Salivary Excretion of Trifluoroacetic Acid (TFAA) after Halothane Anesthesia

Michio KAWAHARA, Susumu AKITA, Takahisa TAKESHITA, Kohyu FUJII* and Michio MORIO*

Trifluoroacetic acid (TFAA) in the saliva, blood and urine after halothane anesthesia was determined by ionchromatography in surgical patients. The mean salivary concentration of TFAA was 1115.5 ± 516.2 μM on the 1st, 732.4 ± 543.9 μM on the 3rd and 406.6 ± 258.7 ± μM on the 7th post-operative day. The mean serum concentration of TFAA was 390.1 ± 115.7 μM on the 1st, 220.8 ± 73.2 μM on the 3rd and 133.8 ± 84.8 μM on the 7th post-operative day. The concentration of TFAA in saliva was approximately three times as high as that in the blood, but their time courses were almost parallel. The excretion of TFAA in urine changed in a similar manner. It was concluded from the findings that the salivary gland plays a role as one of the routes for the elimination of TFAA. (Key words: salivary gland, trifluoroacetic acid, biotransformation, anesthetics, halothane)

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Trifluoroacetic acid (TFAA) is the main metabolite of halothane, the most prevalent volatile anesthetic employed in clinical anesthesia. Analysis of TFAA after anesthesia is very useful in investigating the metabolism of halothane. However, there have been few reports on the quantitative study of TFAA after halothane anesthesia because of the difficulty involved in the analysis. Takiyama et al.[1] measured urinary excretion of TFAA by using isotachophoresis in postoperative patients.

We applied ionchromatographical analysis to determine TFAA in saliva, blood and urine after halothane anesthesia in surgical patients. The purpose of this study was to determine whether TFAA is excreted in saliva, and, if so, to compare that with the concentration of TFAA in blood and urine.

Division of Dental Anesthesia, Hiroshima University Dental Hospital, Hiroshima, Japan

**Department of Anesthesiology, Hiroshima University School of Medicine, Hiroshima, Japan*

Address reprint requests to Dr. Kawahara: Division of Dental Anesthesia, Hiroshima University Dental Hospital, 1-2-3, Kasumi, Minami-ku, Hiroshima, 734 Japan

Materials and Methods

Eight patients (ASA physical status 1, 6 males and 2 females, age 8–41 yrs), scheduled for oral surgery, were studied (table 1). They had no past history of general anesthesia, hepatorenal dysfunction and administration of drugs which are considered to induce enzyme induction. Patients were premedicated by administering atropine sulfate (0.5 mg) and hydroxyzine (50 mg) intramuscularly 45 min before anesthesia. Anesthesia was induced with thiopental (5 mg/kg, iv) and endotracheal intubation was performed with pancuronium bromide (0.1 mg/kg, iv). During anesthesia, patients were administered 0.5–2.0% halothane and 60% nitrous oxide in oxygen, and ventilated artificially to maintain the end-tidal CO_2 at 35–40 mmHg.

Blood samples for the measurements of TFAA were collected before anesthesia, and

Table 1. Patients examined for TFAA analysis

Name	Sex	Age (yrs)	Weight (kg)	Height (cm)	Diagnosis	Duration of Anesthesia (min)
KT	M	8	25	131.0	mandibular fracture	115
SH	F	17	56	156.0	hare lip	105
KY	M	31	65	167.5	mandibular fracture	150
SI	M	17	89	175.0	mandibular fracture	125
ST	M	19	50	170.0	mandibular cyst	75
KK	F	41	54	158.0	palate tumor	55
AN	M	18	56	170.0	mandibular fracture	85
KT	M	16	55	168.0	mandibular fracture	150

on the 1st, 3rd and 7th post-operative day. Saliva samples were collected by placing a piece of cotton in the mouth for a few minutes at the same time when blood samples were taken. Urine samples were collected for 24 hours before surgery and for every 24 hours on the 1st, 3rd and 7th post-operative day, and a part of each urine sample was used for measurements of TFAA after recording the daily urinary volume. All the samples were stored in a refrigerator at 4°C until the measurements were performed.

The concentration of TFAA in the samples were measured by Ionchromatographic Analyzer IC-100 (Yokogawa Electric Co., Japan) equipped with a suppresser and an electroconductivity detector. An anion exchange resin (SAX-1), packed in a 25 cm (L) × 4.6 mm (D) stainless steel column, was used as a separator. As an eluent and scavenger, 5 mM of sodium tetraborate and 50 mM of dodecylbenzensulfonic acid were used, respectively, at a flow rate of 2 ml/min.

Prior to the ionchromatographical analysis, samples were diluted with deionized water (saliva: ×100, urine: ×100, and serum: ×50) and treated with a cation exchange resin column and the serum was deproteinized by ultrafiltration using AMICON® CF25.

From the data of the concentration of TFAA in urine samples and the daily urine volume, the total amount of TFAA excreted in urine per day was calculated. Means and standard deviations of the different groups of data were calculated. 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

The duration of halothane inhalation was 107.5 ± 34.4 min. (mean ± SD) and ranged from 55 to 150 min. The concentration of halothane during the surgery was varied from 1.0 to 1.5% depending on the patient's condition. The mean of the product of concentration of halothane and duration of inhalation was 129.4 ± 43.7 %·min (mean ± SD). A stable anesthesia was maintained and the post-operative courses were also uneventful.

(1) Serum concentration of TFAA

Figure 1 shows the time course of the changes of serum TFAA after halothane anesthesia. TFAA was not detected in blood before the administration of halothane. The mean serum concentration of TFAA was 390.1 ± 115.7 μM (mean ± SD) on the 1st post-operative day, which decreased to 220.8 ± 73.2 μM on the 3rd and to 133.8 ± 84.8 μM on the 7th post-operative day.

(2) Salivary concentration of TFAA

Figure 1 shows the time course of the changes of salivary TFAA after halothane

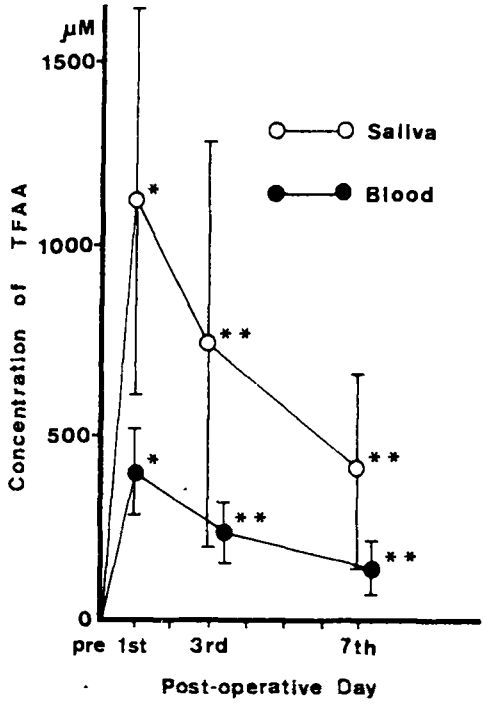

Fig. 1. Time course of the changes of salivary and serum TFAA concentration after halothane anesthesia. Values are mean ± SD. (*$P<0.01$, **$P<0.05$)

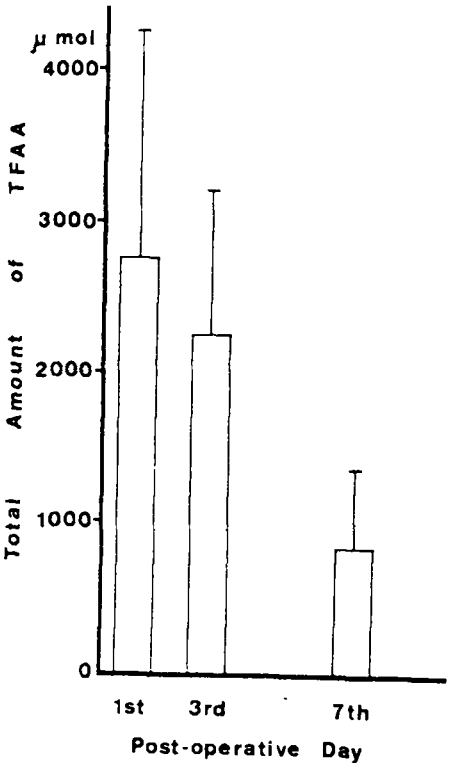

Fig. 2. Total amounts of TFAA excreted in urine per day. Values are mean ± SD.

anesthesia. TFAA was not detected in saliva before the administration of halothane. The mean salivary concentration of TFAA was 1115.5 ± 516.2 μM (mean ± SD) on the 1st post-operative day, which decreased to 732.4 ± 543.9 μM on the 3rd and to 406.6 ± 258.7 μM on the 7th post-operative day.

(3) Urinary excretion of TFAA

Figure 2 shows the changes of the total amount of TFAA excreted in urine in a day. TFAA was not detected in urine before the administration of halothane. The mean daily urinary excretion of TFAA was 2772.3 ± 1521.1 μmol (mean ± SD) on the 1st post-operative day, and 2256.9 ± 972.1 μmol on the 3rd and 837.5 ± 534.3 μmol on the 7th post-operative day.

Discussion

Stier[2] identified TFAA in urine of rabbits as a metabolite of halothane in 1964. Rehder[3] first detected TFAA in urine of humans received halothane anesthesia and demonstrated biotransformation of halothane. Morio[4] and Takiyama[1] observed a much greater excretion of TFAA in urine by quantitative analysis. The metabolic processes of halothane were established following further studies[5,6] and TFAA was shown to be the main metabolite of halothane under aerobic condition and to be eliminated in urine.

We have detected TFAA in saliva and gastric juice of guinea pigs during and after halothane anesthesia and proposed two new routes, saliva and gastric juice, for the elimination of TFAA. In this study, we detected TFAA in saliva, blood and urine in surgical patients after halothane anesthesia. The concentration of TFAA in saliva was approximately three time as high as that in blood and showed a similar time course as serum and urinary TFAA. TFAA was considered to be carried by blood circulation and to accu-

mulate in organs and tissues in almost equal concentration[7]. However, in our study, the salivary concentration of TFAA was several times higher than that in blood.

It can be speculated that there is an active transport system which concentrates salivary TFAA similar as sodium ions in salivary glands[8], or there is a salivary metabolism of halothane since cytochrome P-450 activity has been demonstrated in submandibular glands of rats[9]. Although further experiments are necessary to clarify these mechanisms, the amount of TFAA excreted in the saliva can not be neglected, since the excretion of saliva is as much as 1.0–1.5 liter per day.

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