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Clinical Effects of Halothane Concentration on Trifluoroacetic Acid Excretion in Urine

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ABSTRACT

Excreted amount of urinary trifluoroacetic acid (TFA) during and after halothane anesthesia in twelve surgical patients was determined isotachophoretically. The levels of urinary TFA which amount was zero or a trace during the anesthesia increased after discontinuation of halothane inhalation. The values of daily excreted TFA were the highest on the 2.1±0.3 postoperative day (M±SEM). The urinary TFA values of patients inhaling a low concentration (0.8%) of halothane reverted to zero or a trace level on the 11.2±1.0 postoperative day (M±SEM) and the total amount of averaged 21.53±3.23 mmol (M±SEM). In patients to levels seen on the 7.0±0.6 postoperative day (M±SEM) and the total amount of TFA excreted was 20.20±4.77 mmol (M±SEM). These clinical findings indicate that the aerobic biotransformation of halothane after anesthesia is enhanced by high concentration of halothane.

Halothane is metabolized into trifluoroacetic acid (TFA)[8,9] as an aerobic metabolite and into CF_2CHCl and CF_3CH_2Cl[6,9] as anaerobic metabolites, *in vivo* and *in vitro*. With regard to metabolic rates and alveolar concentrations of this anesthetic agent, Sawyer et al (1971)[12], found that the fraction of halothane removed from the blood by the liver in miniature swines increased with decrease in the alveolar concentration of this compound. As they defined this fraction as the amount of halothane metabolized, the amount metabolized in the liver was assumed to be inversely dependent on the alveolar concentration of the compound. When measuring the concentration of expired halothane, Cahalan and coworkers[3] reported that, in humans, a greater fraction of halothane was taken up at subanesthetizing, as opposed to anesthetizing concentrations. Since they attributed the difference between total delivery and total recovery to the amount of the anesthetic metabolized, it was suggested that a greater fraction of halothane was metabolized at subanesthetizing concentration.

As a common by-product of all metabolites of halothane, Br^- is considered to be a theoretically ideal substance for evaluating the total amounts of halothane which is biotransformed[1,11,13]. However, it is relatively difficult to estimate the exact amount of Br^- produced from halothane, since this compound is a natural component of the human body. The major part of metabolized halothane can be estimated by the measuring TFA, since this compound is not present in the body and the total urinary excretion of TFA is quantitatively the largest among the metabolites of halothane. We now reported the excretion of TFA in patients during and after clinical anesthesia and also the relationship between inspiratory concentrations of halothane and the excreted rates.

METHODS

Urinary TFA levels were measured in 12 halothane anesthetized Japanese patients who underwent a variety of surgical procedures. Twelve A.S.A. class 1 adults without any history of blood transfusion, liver disease, general anesthesia or drug injection that could lead to hepatic microsomal enzyme induction were classified into two groups according to the inspiratory concentrations of halothane. Six patients were administered less than 0.8 per cent of halothane on the average during anesthesia (Group 1). The average age (±SE) was 47.5±4.5 years; mean weight, 57.6±4.7 kg; and mean height, 161±4.5 cm. The other six patients were administered more than 0.8 per cent of halothane on the average (Group 2). In this group, the average age (±SE) was 47.2±6.6 years; mean weight, 57.5±3.4 kg; and mean height, 159.7±3.9 cm. Each patient was premedicated intramuscularly with atropine sulfate 0.5 mg, hydroxyzine 50 mg, and pentazocine 15 mg. Following intubation with thiopental (4-5 mg/kg) and succinylcholine chloride (1 mg/kg), anesthesia was maintained with various concentrations of halothane and 66% of nitrous oxide in oxygen.

Urine was collected before, during and for 14 days after the anesthesia. To determine the peak urinary TFA excretion, 12 hr urine of three patients in Group 1 was collected for 48 hr following anesthesia.

For TFA analysis, 2 to 10 μl of the urine was subjected to a capillary type isotachopherograph (Shimadzu Model IP-2A). The condition of the assay was the same as reported previously (Morio et al, 1980).

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Statistical evaluation was made by using the t test and P values of less than 0.05 were considered significant.

RESULTS

A significant difference was observed in the mean concentration of halothane between Groups 1 and 2 (Table 1). There was statistically no significant difference in the uptake of halothane which was estimated by the product of inhalation period and mean concentration of halothane between the two groups.

The amount of urinary excreted TFA in each patient after discontinuation of halothane increased from zero or a trace of TFA during the anesthesia. Concerning the total excreted amount of TFA, no significant difference was demonstrated between the two groups.

The TFA output was the highest on the 2.1±0.3 postoperative day (M±SEM) when the first day was defined as the operative day (Fig. 1). In three patients from whom urine was collected every 12 hr, the peak of TFA excretion was found in the urine from the second to third 12 hr after discontinuation of the anesthesia. The amount of TFA excreted in the second 12 hr urine was the same as that of the third 12 hr urine.

Urinary TFA values returned to zero or a trace level on the 11.2±1.0 postoperative day (M±SEM) and the 7.0±0.6 postoperative day (M±SEM) in Groups 1 and 2, respectively. Here, there was a statistically significant difference.

Table 1. Inspiratory Concentration of Halothane, Product of Duration and Concentration of Inspired Halothane, and Total Amount of Urinary TFA.

	Inspiratory concentration of halothane (percent)	Product of duration and concentration of inspired halothane (percent min)	Total amount of urinary TFA (mmol)
Group 1	0.50±0.04*	141.38±32.86	21.53±3.23
Group 2	1.06±0.09*	165.57±29.39	20.20±4.77

Group 1: Patients inhaling a low concentration of halothane (n=6).
Group 2: Patients inhaling a high concentration of halothane (n=6).
* significant difference between groups ($P<0.05$).
Numbers are expressed as mean±SEM.

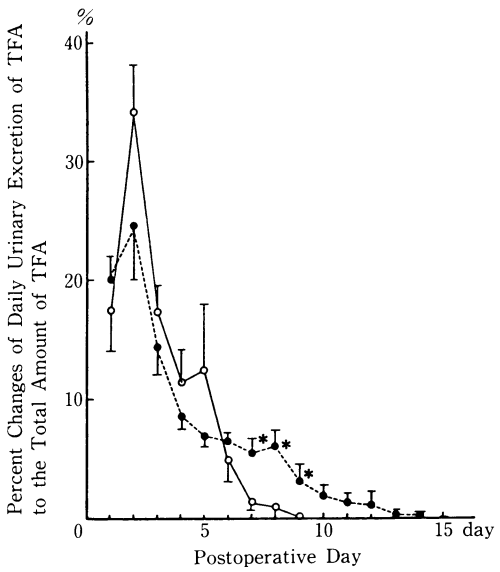

Fig. 1. The daily elimination of urinary TFA in patients with lower halothane concentrations (closed circles) and in those with higher concentrations (open circles). The daily amount of TFA in urine of each patient was normalized and expressed as mean ± SEM.
* significant difference between two groups.

A small second hump was noted in the elimination curve of the daily urinary TFA (Fig. 1). In each curve, a small second hump was found on the 7.6 ± 0.5 postoperative day (M ± SEM) in Groups 1 and 2, respectively. There was a statistically significant difference between the two groups.

DISCUSSION

TFA is biotransformed from halothane in rabbit liver microsomal enzymes supplemented with NADPH and oxygen[7]. Since this activity is increased by pretreatment of the animal with phenobarbital and is inhibited by carbon monoxide, it is strongly suggested that the hepatic microsomal mixed-function oxidase system including cytochrome P-450, catalyzes this reaction. Microsomal cytochrome P-450 in the rat liver was significantly increased by the daily inhalation of halothane[5,14]. Cascorbi et al[4] showed that the total amount of excreted ^{14}C after administration of ^{14}C-halothane was higher in the urine of anesthetists who may chronically inhale halothane, as compared to no such inhalation by pharmacists, this would suggest that halothane acts as an enzyme inducer. In our study, enzyme induction by anesthetics was not taken into consideration, since our patients had no history of halothane or any other anesthesia. The total excreted amount of TFA in the urine did not differ between the two groups, and such is attributed to the finding that the uptake of halothane which was estimated by the product of inhalation period and mean concentrations of halothane was statistically the same in the two groups. This also implies that the total TFA formation is not influenced by the difference of inhaled concentrations of halothane, if the product of duration and concentration of inspired halothane shows no significant difference. However, the excretion rate of TFA in the urine of patients with a higher concentration of halothane was more rapid than that in the lower halothane concentration group and the difference was statistical. Therefore it may be that the enzyme system related to production of TFA from halothane is induced by even a single exposure of halothane and that the extent of this induction may be dependent on the concentration of halothane in the inspiratory gas *in vivo*. If such is indeed the case, then the higher the concentration of inhaled halothane, the larger would be the induction of the enzymes.

Cascorbi et al[4] (administered intravenously trace doses of ^{14}C-labeled halothane to man in the absence or presence of anesthetic concentrations of halothane and found that the urinary excretion of radioactivity when the tracer was injected into unanesthetized subjects was greater than that when injected in anesthetized subjects. Another *in vivo* study suggested that the high alveolar concentration of halothane might inhibit removal of the drug by the liver[12]. On the other hand, by supplementing halothane, the aerobic suspension of rat liver microsomes showed a typical type 1 spectra characterized by a maximum absorption band at 390 nm and a minimum absorption band at 420 nm. The same spectra of type 1 which was induced by hexobarbital were inhibited by halothane[15]. In addition, a study of the influence of halothane on biotransformation of a variety of drugs by rat liver microsomal mixed function oxidase enzymes showed that halothane non-competitively and reversibly depresses the metabolism of type 1

substrates[2]. Therefore, it may be that the formation of TFA from halothane (type 1 substrate) by microsomal enzymes is inhibited by halothane (type 1 substrate) during anesthesia when the concentration of halothane in the blood peaks. It has been reported that the blood concentration of bromide ion is lower during inhalation of halothane than after its discontinuation[1,11]. In the present study, the amount of TFA excreted in the urine was negligible during the inhalation of halothane, and the maximum excretion occurred on and after the 2nd postoperative day. These findings suggest that the formation of TFA from halothane may be inhibited by halothane itself.

Of interest is the presence of a small second hump in the elimination curve of TFA, detected on the 8th postoperative day in the low halothane concentration group and on the 5th postoperative day in high concentration group. The metabolism of halothane may be enhanced or the release of halothane from fat may be increased in the circulation. Regardless of the cause, this second hump suggests that halothane is being metabolized. As there was a difference in the day when the second hump appeared between the two groups, the metabolic rate in the high concentration group is higher than that in the low concentration group.

Our findings suggest that halothane may inhibit the formation of TFA during anesthesia and enhance the aerobic metabolism of halothane by inducing hepatic enzyme after discontinuation of this anesthetic.

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