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Fluoride metabolites after exposure of volunteers and patients to desflurane

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FLUORIDE METABOLITES AFTER EXPOSURE OF VOLUNTEERS AND PATIENTS TO DESFLURANE

by

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A thesis submitted to the Medical Scientist Pathway in partial fulfillment of the requirements for the degree of Doctor of Medicine with Thesis

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Acknowledgements

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Abstract

Previous studies of the metabolism of desflurane in humans have failed to reveal the production of serum or urinary metabolites but the exposure duration was too limited to constitute a sufficient test. We now report a study of the metabolism of desflurane in thirteen healthy volunteers given 7.30 ± 0.81 MAC-hours of desflurane, and twenty-six surgical patients given 3.08 ± 1.84 MAC-hours (mean values ± SD). In both groups, post-anesthesia serum fluoride ion concentrations did not differ from background fluoride ion concentrations. Similarly, post-anesthetic urinary excretion of fluoride ion and organic fluoride in volunteers was comparable to pre-anesthetic excretion rates. However, trifluoroacetic acid levels increased significantly in both serum and urine in volunteers after exposure to desflurane. A peak serum concentration of 0.38 ± 0.17 micromoles/liter of trifluoracetic acid and peak urinary excretion rate of 0.169 ± 0.107 micromoles/hr were detected at 24 hours after desflurane exposure. Trifluoroacetic acid levels in both serum and in urine remained significantly elevated 6 days after desflurane anesthesia. Although desflurane strongly resists biodegradation, a small amount is metabolized in humans.

Introduction

Throughout the earliest decades in which general anesthesia was used for operations in the United States, many physicians believed that volatile anesthetics were metabolically inert. It was not until the mid-1960s when numerous cases were reported of a halothane-associated jaundice, that an anesthetic was first considered a chemical reactant.(1) Subsequent to this change in thought, numerous investigations were launched to determine if halothane was metabolized in humans. The upshot was the description of two pathways of halothane metabolism. The products of the major pathway are trifluoroacetic acid, bromide ion, and chloride ion (2). It is currently suspected that an antibody-mediated hypersensitivity reaction to trifluoroacetic acid covalently bound to protein in hepatocytes is the mechanism for halothane hepatitis (1).

The investigations of halothane biotransformation set a precedent for characterizing other volatile anesthetics not only in terms of their susceptibility to metabolism, but also in terms of the identity and potential tissue toxicities associated with these metabolites. As a result, two other general anesthetics that are occasionally used today were recognized to have metabolites that were potentially toxic in humans. One agent is methoxyflurane, an anesthetic which was demonstrated to yield large amounts of inorganic fluoride secondary to its metabolism (3). Concentrations of fluoride ion in serum greater than approximately 35 micromoles/liter were associated with a transient nephrogenic diabetes insipidus (4).

The second agent is enflurane, an anesthetic that is metabolized to fluoride ion as well as to a variety of organic fluorinated products.(5). Although nephrotoxicity secondary to enflurane anesthesia has not been described, there has been at least one case report of hepatitis attributable to enflurane. In this report, the organic fluorinated products of enflurane metabolism were covalently bound to liver proteins, and these protein-conjugated metabolites were recognized by circulating antibodies in a patient with a history of halothane hepatitis.(6). Although the organic fluorinated product of enflurane is not trifluoroacetic acid, the metabolite is a highly fluorinated compound that closely resembles

trifluoroacetic acid save the addition of an ether bond (1)(Fig 1). Thus, the breakdown of volatile anesthetics to organic fluorinated products has raised the question of a potential basis for cross-sensitization between these anesthetics (1).

With a growing body of knowledge suggesting that metabolites of the inhalational anesthetics are associated with organ toxicities, safety of the general anesthetics in terms of tissue toxicities has become a principal determinant of the acceptability of any new anesthetic agent. At the present time, isoflurane has been accepted as a clinically effective and safe general anesthetic. While this agent is metabolized to a small extent to both trifluoroacetic acid and inorganic fluoride (7), these metabolites are yielded in such small quantities that, clinically, they are thought to be inconsequential (8).

Desflurane is a new general anesthetic that is being investigated for clinical use. This anesthetic closely resembles isoflurane in physical structure. In fact, desflurane differs from isoflurane merely by substitution of a single fluorine atom for chlorine (Fig. 2). This single change results in a compound that is less soluble, and permitting of a rapid recovery from anesthesia in rats (9) and swine (10). Thus, desflurane may have an advantage over isoflurane in operations where rapid recovery from anesthesia is desirable.

The substitution of a fluorine for a chlorine atom also appears to have produced a more stable compound. *In vitro*, this is reflected as an increased resistance to degradation by soda lime compared to isoflurane, particularly at high temperatures (11). *In vivo,* it is reflected as a resistance to metabolism in animals. Indeed, the only demonstration of metabolism was a slight increase in serum inorganic fluoride immediately after anesthesia or a slight increase in urinary excretion in the 24 hours after anesthesia in enzyme-induced rats (12). Humans given about 1 MAC hr of anesthesia with desflurane do not have increases in serum or urinary fluoride (13).

The issue of metabolism of desflurane relative to other anesthetics is of interest because of the potential connection between metabolism and toxicity. A demonstration of the absence of metabolism or a metabolism markedly less than that obtained with other

anesthetics would add to the possible usefulness of desflurane. Although the previous studies in humans have not revealed metabolism, they may not have constituted a sufficient test because of the limited duration and concentration of desflurane that was applied. The present report report gives data for prolonged exposures to desflurane at sometimes high concentrations in both volunteers and patients.

Methods

Subjects

This study was approved by the UCSF Committee on Human Research and all participants gave an informed consent. Thirteen ASA physical status I male volunteers, age 19 to 26 years, and of normal body weight for their height were studied. No volunteers drank more than six alcoholic drinks per week on average, and abstained from all alcohol and over-the-counter medications during the 48 hours prior to the study. Candidates taking acetaminophen within 48 hours of the study, with a history of HBsAg or HIV antibody positivity, or with a history of unusual response to anesthesia or exposure to anesthesia within three months of the study, were excluded. Candidates with a history of parenteral drug abuse, and candidates taking antiinflammatory drugs, antihistamines, or antibiotics within one week of the study, were excluded.

Twenty-six ASA physical status I and II male surgical patients, age 21 to 63 years, were also studied. These patients had elective orthopedic, otolayrngologal, neurosurgical, or general surgical operations. None were obese (weight range 51 - 95 kg), and none had known abnormalities in hepatic function.

Study Procedures and Exposure to Desflurane

Volunteers were anesthetized with desflurane in oxygen. An endotracheal tube was inserted, without facilitation by succinylcholine, and ventilation was controlled with a tidal volume of approximately 10ml/kg, with frequency adjusted to maintain normocarbia as assessed by end-tidal and by arterial gas analysis. Following induction, each volunteer received either desflurane in oxygen or desflurane in 60% nitrous oxide and oxygen at concentrations of 0.83, 1.24, and 1.66 MAC. Volunteers first given desflurane in oxygen were exposed to each concentration of desflurane before being given desflurane in nitrous oxide and oxygen, and vice versa. Controlled ventilation then was discontinued and the three concentrations of desflurane applied during spontaneous ventilation. Ventilation then

was controlled to produce hyperventilation at 1.66 MAC desflurane. Finally, normocarbia was restored, and the original series of three concentrations reapplied. Each concentration was sustained for 15 to 30 minutes. Cardiorespiratory, and neuromuscular measurements were repeated at each anesthetic concentration (14-16).

Surgical patients were anesthetized with desflurane in oxygen with or without nitrous oxide. The trachea was intubated with or without facilitation by succinylcholine, 1mg/kg iv. The concentration of anesthesia administered was that prescribed by the attending anesthetist.

Inspired and end tidal oxygen, carbon dioxide, nitrous oxide, and desflurane were analyzed by infra-red analysis (Datex Model 254). Volunteers were given desflurane for 6.81 ± 0.55 hours and surgical patients were given desflurane for 3.40 ± 2.07 hours. The total dose of desflurane was 7.30 ± 0.8 MAC-hrs in volunteers, and 3.08 ± 1.84 MAC-hrs in surgical patients (mean values ± SD).

Collection of Urine and Serum Samples

Urine samples were collected from volunteers 7-10 days prior to exposure to desflurane, at the end of exposure, and at 24 hours, 4 days, and 6 days following exposure. All urine samples were collected over a 12 hour period (1900-0700) with the exception of the end of anesthesia collections, which were collected over 6.81 ± 0.55 hours. Total urine volumes were recorded for each interval.

Blood samples were collected at the end of the same intervals, with additional samples obtained immediately prior to induction with desflurane and 4 hours after discontinuing desflurane. In surgical patients, blood was collected immediately prior to operation, in the post-anesthesia recovery room, and less frequently at 1 and 3 days after operation.

Serum was isolated from blood after centrifugation at 2000g for 10 minutes. Serum and urine samples were placed in plastic test tubes and kept frozen at -20 to -40° C before analysis for fluoride and trifluoroacetate.

Fluoride Analyses

Fluoride ion levels in serum and urine were determined using a modified method of Fry and Taves (18). Twenty microliters of a 5M sodium acetate buffer (pH 4.50) were added to 180 microliters of undiluted serum or to 180 microliters of a urine sample previously diluted fourfold. The 200 microliter mixture was placed into a machined Teflon cup and the fluoride ion concentration was measured using an Orion fluoride ion electrode (model 96-09) with a Corning model 12 pH meter. Fluoride ion concentrations in serum or urine were obtained by interpolation of a calibration curve prepared by plotting electrode voltage on a linear scale against the concentration of sodium fluoride standards on a logarithmic scale. The polarimetry technique was sensitive to differences in fluoride ion concentration greater than or equal to 1 micromolar.

The content of total fluoride in the urine was determined by the sodium fusion method of Soltis and Gandolfi (19). Nonvolatile organic fluoride from urine samples was calculated by subtracting the free fluoride ion in the original sample from the total fluoride content determined by the sodium fusion technique, after correction for the efficiency of organic fluoride detection. We assumed a 90.4% recovery of organic fluoride based on results from earlier studies (20).

Trifluoroacetic Acid Analysis

Trifluoroacetic acid levels in the serum and urine collected from volunteer subjects was determined by the gas chromatographic-mass spectrometric method of Gruenke and Waskell (21), using pentafluoropropionic acid as the internal standard. The limit of

detection of trifluoroacetic acid using this method ranged between concentrations of 0.10 and 0.20 micromoles/liter.

Statistical Analysis

Comparisons between values obtained prior to and after desflurane exposure were performed by a paired, two-tailed, t - test. We accepted p values of less than 0.05 as significant after using the Bonferroni correction for multiple comparisons.

Results

In both volunteers (Fig. 3) and in patients (Fig. 4), post-anesthesia serum fluoride ion concentrations did not significantly exceed background fluoride ion concentrations. Urinary excretion of fluoride ion and organic fluoride in volunteers also did not significantly increase following exposure to desflurane (Fig 5).

Trifluoroacetic acid appeared in the serum of volunteers exposed to desflurane (Fig. 6). Serum trifluoroacetic acid levels were significantly elevated 24 hours after desflurane exposure and remained elevated (in 6 of 13 volunteers) 6 days after desflurane exposure (Fig. 6). Urinary excretion of trifluoroacetic acid increased significantly above a non-detectable background rate in volunteers (Fig. 7). This increase was detected in 4 volunteers immediately after desflurane anesthesia and was found in all individuals 24 hours after anesthesia. Urinary excretion of trifluoroacetic acid was maximal 24 hours after desflurane anesthesia, and was still evident 6 days after anesthesia (Fig. 7).

Discussion

Because desflurane closely resembles isoflurane in chemical structure, we expected that if desflurane were metabolized, its route and products of metabolism would resemble those of isoflurane. Isoflurane metabolism has been previously described to involve insertion of oxygen by cytochrome P-450 in either of the carbon - hydrogen bonds to yield either an active acylating agent (CF_3COF or $CF_3COOCHF_2$) or trifluoroacetaldehyde, in addition to a one carbon fragment (22). Based on results from previous investigations, trifluoroacetaldehyde is largely converted to trifluoroacetate in humans (23, 24). Thus, if desflurane is metabolized similarly to isoflurane, by either route it would be expected to yield one mole of trifluoroacetate and two moles of fluoride ion for each mole metabolized (Fig. 8).

In the current study we examined desflurane metabolism in humans by comparing pre- and post-anesthetic levels of fluoride ion and organic fluoride (specifically trifluoroacetate) in the urine of volunteers and in the serum of volunteers and patients anesthetized with this drug. Our results in humans are consistent with results from earlier studies in rats (12) and in swine (21), and suggest that although desflurane strongly resists biodegradation, a small amount is metabolized. Mean serum fluoride ion concentrations in volunteers following exposure to 7.30 $\pm$ 0.81 MAC-Hours of desflurane failed to rise above a mean 7-10 day pre-exposure serum fluoride ion concentration of 0.96 $\pm$ 0.42 micromoles/liter. In surgical patients exposed to 3.08 $\pm$ 1.84 MAC-hours of desflurane, mean post-exposure serum fluoride ion concentrations did not rise significantly above a mean pre-anesthesia serum fluoride ion concentration of 0.77 $\pm$ 0.65 micromoles/liter. Similarly, the excretion rate of fluoride ion and organic fluoride in the urine of volunteers following exposure to desflurane did not exceed pre-exposure excretion rates. The present data contrast with elevated concentrations of fluoride ion in serum (Fig. 9) and fluoride ion and organic fluoride in urine (Fig. 10, 11) of surgical patients after exposure to lower average doses of isoflurane (23), and suggest that desflurane resists biodegradation more

than isoflurane, the agent which is the least metabolized of the currently available inhalational anesthetics (24).

Mean serum trifluoroacetic acid concentrations and mean urine trifluoroacetic acid excretion rates in volunteers at 24 hours, 4 days, and 6 days after exposure to desflurane were significantly elevated with a peak mean serum concentration of 0.38 micromoles/liter at 24 hours (Fig. 6). This value is one to three orders of magnitude less than the concentrations of 10 micromoles/liter and 500 micromoles/liter in patients after shorter exposure to isoflurane (19) and halothane (26), respectively. Similarly, the peak mean excretion rate of trifluoroacetic acid in urine after exposure to desflurane (0.169 micromoles/hour, Fig. 7) is greater than two orders of magnitude less than that observed after exposure of patients to lower average doses of isoflurane (approximately 50 micromoles/hour) (24).

Our finding that desflurane is metabolized less than isoflurane is not unexpected given our knowledge of desflurane's solubility properties and chemical formula. Bioavailability and biochemical stability are the two properties of a compound that most affect the extent to which it is metabolized (8). Because desflurane is less soluble than isoflurane in both blood (27,28) and tissues (29), one would expect a rapid redistribution and pulmonary excretion of desflurane compared to isoflurane, thus leaving relatively less anesthetic available to be metabolized. Furthermore, because the bond energy of a carbon to fluoride linkage exceeds that of a carbon to chloride linkage (8), one would predict that desflurane is more stable and, therefore, more resistant to oxidative dehalogenation than isoflurane.

While low blood and tissue solubility predict the small degree of metabolism that we found for desflurane, this property would also predict, given normal renal function, a rapid return of metabolites to background levels after cessation of desflurane anesthesia. Interestingly, although the levels of metabolites steadily decreased from a peak at 24 hours, we detected elevated levels of trifluoroacetic acid in serum and urine as late as six days after

discontinuation of anesthetic. This observation could be explained if complete elimination of trifluoroacetic acid were delayed because this compound was bound to tissue (e.g., liver) or blood proteins and only slowly released into the circulation.

In previous studies, the rate of excretion of organic fluoride in urine collected from patients was used to calculate the elimination half-life of organic fluoride (30). This experiment could be repeated in volunteers anesthetized with desflurane to elucidate why we detected a relatively slow return of trifluoroacetic acid metabolites to background levels in our volunteers. The excretion of trifluoroacetic acid in these subjects could be compared to the excretion of trifluoroacetic acid in volunteers injected with small, but known, quantities of trifluoroacetic acid by intravenous route. If the half-life of trifluoroacetic acid were significantly prolonged in volunteers anesthetized with desflurane, this would suggest the influence of desflurane metabolism rather than the physiologic handling (e.g., tissue binding) of trifluoroacetic acid.

The import of our finding that trifluoroacetic acid levels increase slightly above background after exposure of volunteers to desflurane is that this demonstrates that a small degree of metabolism does occur. That the degree is small presumes that the extent of anesthetic metabolism is proportional to the serum fluoride ion, organic fluoride, and trifluoroacetic acid concentrations. Although this assumption is probably reasonable, it is possible that higher levels of metabolites might have been disclosed if we had made more frequent measurements or if prior to anesthesia our subjects had taken drugs or medications that induce synthesis of hepatic microsomal enzymes (31). Furthermore, it remains possible that fluoride ion could be sequestered (e.g., in bone or liver) and not appear in blood, or that anesthetic metabolism occurs without the appearance of breakdown products in serum or urine. However, mass balance studies performed in human volunteers demonstrate a recovery of desflurane of 100% in end-tidal gas (29). These data corroborate our findings that desflurane is minimally metabolized, and suggest that we have not grossly

underestimated the extent of this metabolism by virtue of an inability to detect sequestered or otherwise unavailable metabolites as is postulated above.

In conclusion, in the present study we investigated the production of fluoride metabolites following prolonged exposure of volunteers and patients to desflurane. We found that metabolism of desflurane was not detectable by any change in the concentration of fluoride ion or organic fluoride in the serum or urine of the participants in this study. Metabolism was determined, rather, by increased levels of trifluoroacetic acid in the serum and urine of participating volunteers.

The low levels of fluoride metabolites in serum and urine following desflurane anesthesia suggest that desflurane is unlikely to produce tissue toxicities. Although trifluoroacetic acid metabolites were detected, and a theoretical potential for desflurane hepatotoxicity by cross -sensitivity with other inhalational anesthetics cannot be excluded (1,6), the possibility appears remote. Such a possibility has yet to be demonstrated for isoflurane, which is metabolized one - tenth the extent of enflurane (32,33), the only agent for which a case report of anesthetic hepatotoxicity by cros-sensitivity reaction has been documented (6). The conversion of isoflurane to trifluoroacetate and other fluoride metabolites is small, amounting to an estimated 0.17% of the isoflurane taken up (22). If the peak serum trifluoroacetate values indicate the relative amounts of metabolism, then probably less than 0.02% of the amount of desflurane taken up is metabolized (i.e., approximately one and two orders of magnitude less than the extent of metabolism of isoflurane and enflurane, respectively). This figure is arrived at by taking the ratio of peak serum trifluoroacetate (0.38/10) (29) times the ratio of blood/gas coefficients (1.4/0.42 ; used to compensate for differences in uptake) (29) times the 0.17% value cited earlier.

Evaluation of the actual organ toxicities secondary to desflurane anesthesia awaits studies of post-desflurane changes in human hepatic and renal function. Preliminary studies in humans suggest that desflurane has no damaging effects on either hepatic or renal function (13). If volunteer or patient studies with more prolonged exposure to desflurane

confirm these results, it would appear that desflurane may be more safe for liver and kidney than any other potent inhalational anesthetic presently available. This conclusion would be in accordance with a prediction that extends from our data of desflurane metabolism.

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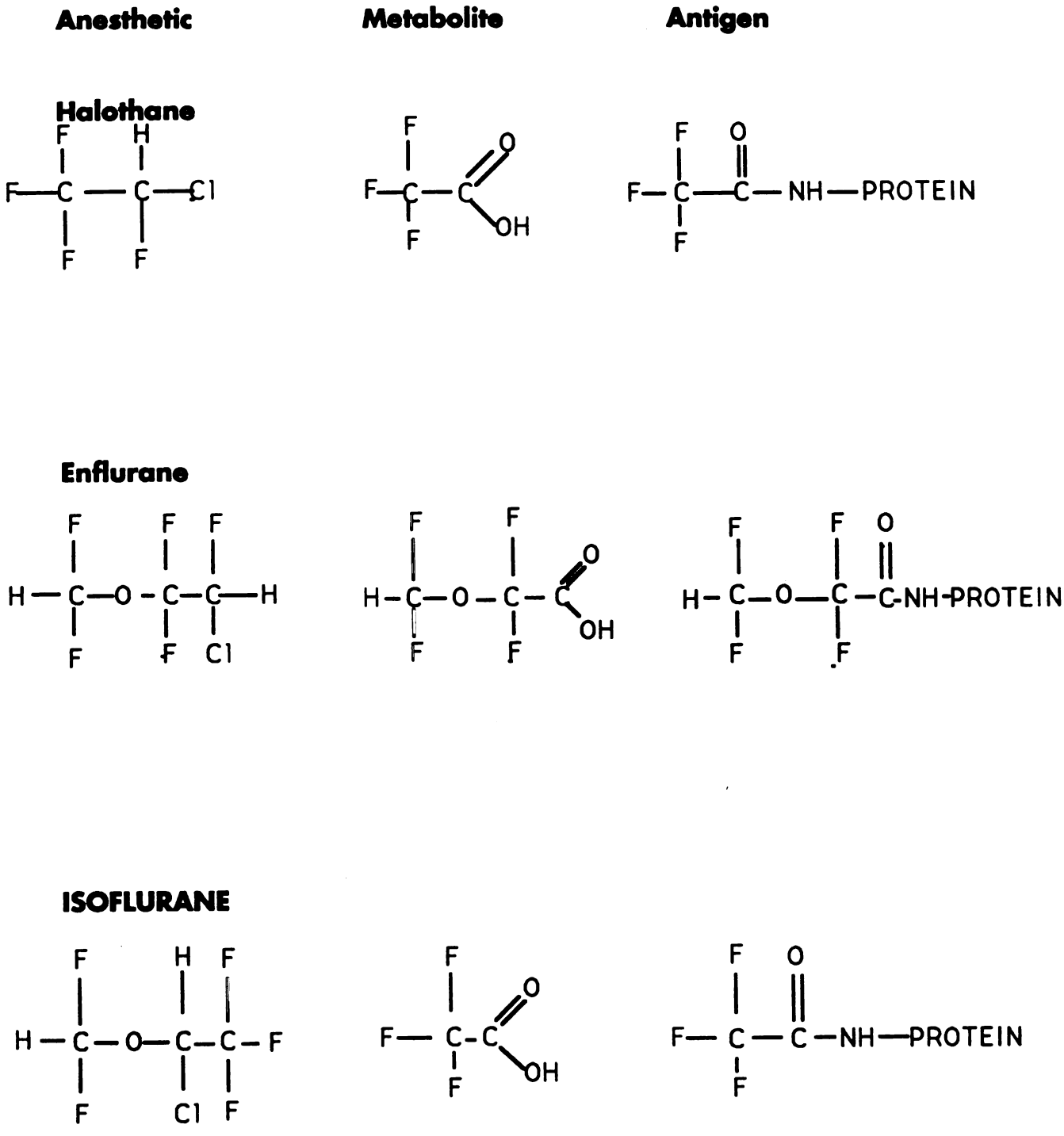
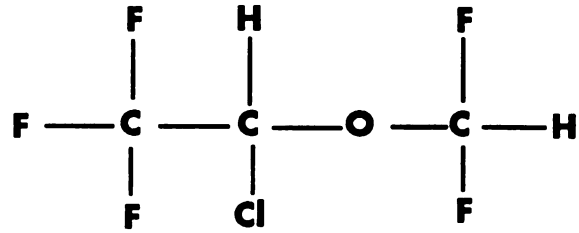
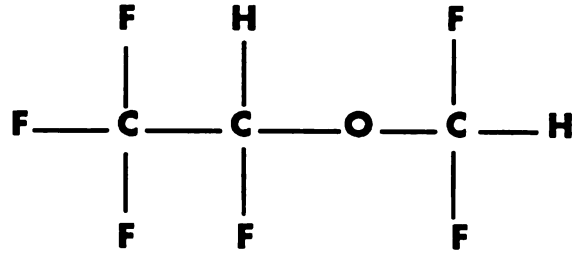


Fig. 1. The three primary inhalational anesthetics, illustrating the major organic metabolite and potent hapten (antigen) of each.



ISOFLURANE



DESFLURANE

Fig. 2. Chemical structures of desflurane and isoflurane. Desflurane differs from isoflurane by substitution of a fluorine for chlorine on the alpha-carbon of the ethyl moiety.

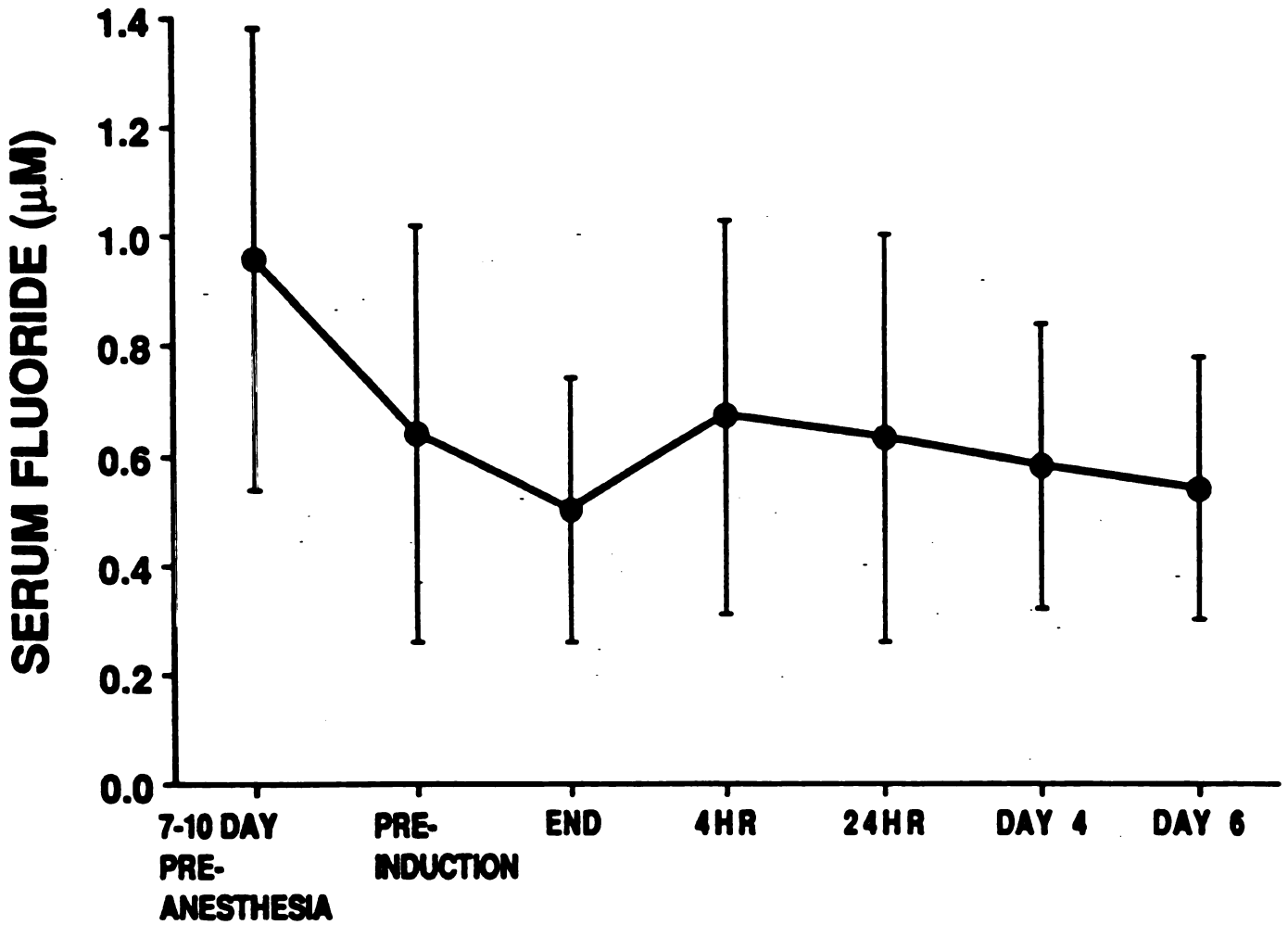


Fig. 3. In volunteers anesthetized with 7.30 ± 0.81 MAC hrs desflurane, serum fluoride ion concentrations 7-10 days prior to anesthesia, or immediately prior to anesthesia, did not differ from values at the end of anesthesia, or at 4 hours, 24 hours, 4 days, or 6 days after anesthesia. The sample number for each value was 13 except for the 7-10 day pre-anesthesia, the end of anesthesia, and the 4 hour post-anesthesia collections, where the sample numbers were 12, 8, and 12 respectively. Error bars indicate ± S.D.

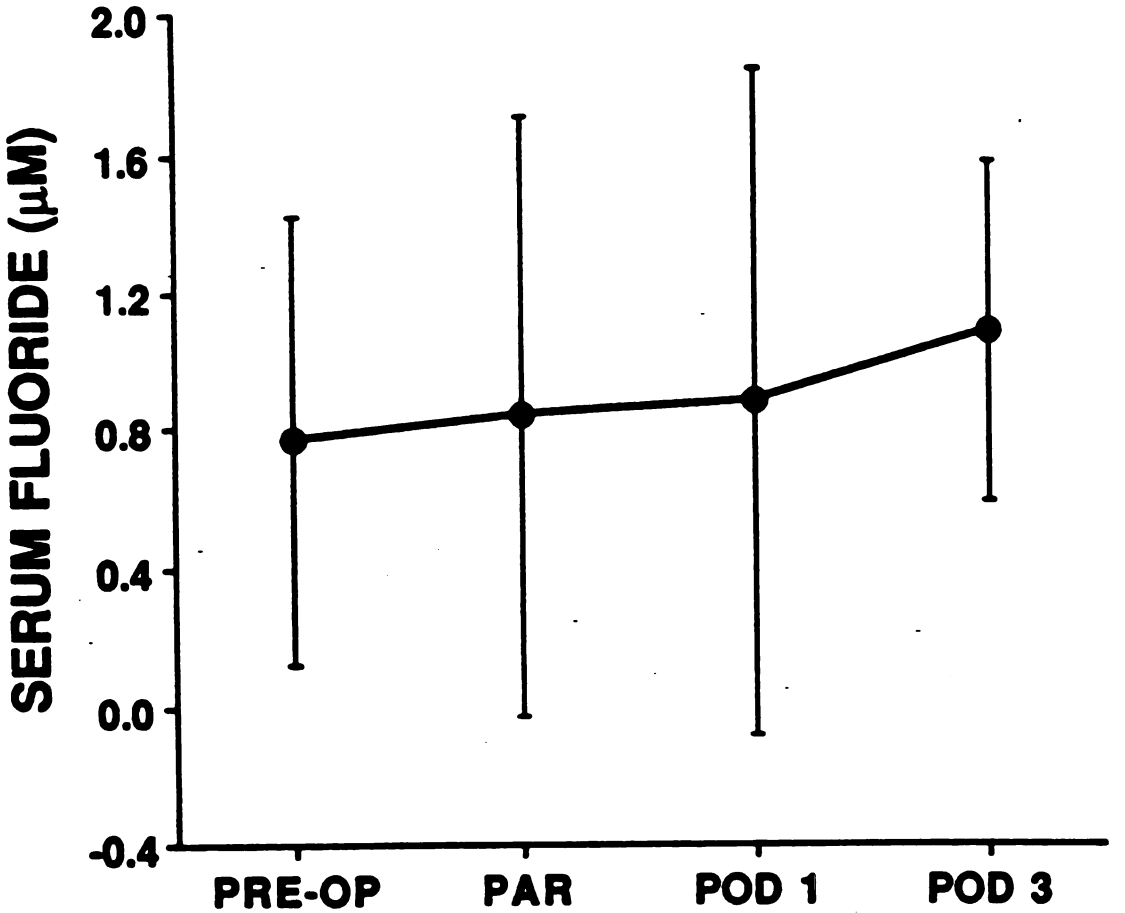


Fig. 4. In patients anesthetized with 3.08 ± 1.84 MAC hrs desflurane, serum fluoride ion concentrations immediately prior to the operation (PRE-OP), did not differ from values in the post-anesthesia recovery room (PAR), or on post-operative days (POD) 1 and 3. The sample numbers were 26 pre-op, 25 in the PAR, 15 on POD 1, and 5 on POD 3. Error bars indicate ± S.D.

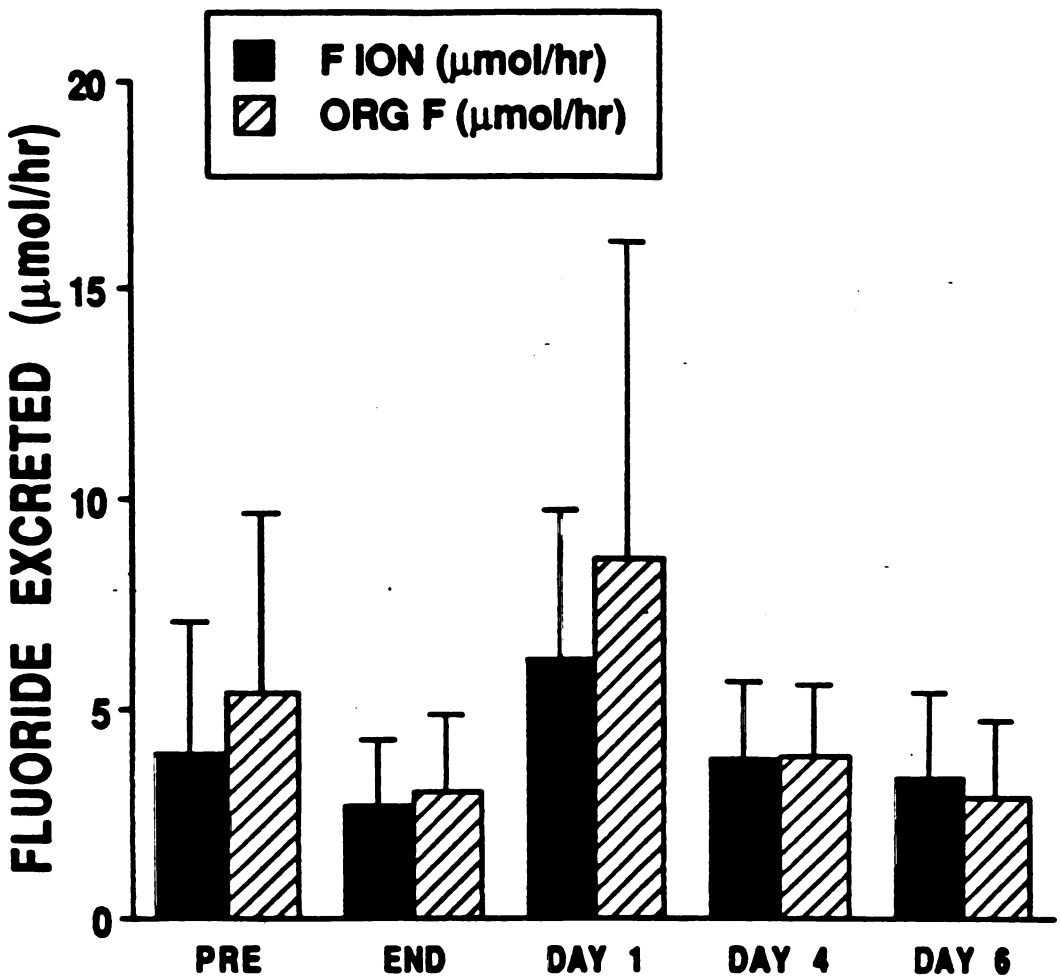


Fig 5. In the volunteers anesthetized with desflurane, urinary excretion rates of fluoride ion and organic fluoride 7-10 days prior to anesthesia did not differ from values at the end of anesthesia, or at 24 hours, 4 days, or 6 days after anesthesia. The sample number for each value was 11, 13, 13, 5, and 12 respectively. Error bars indicate ± S.D.

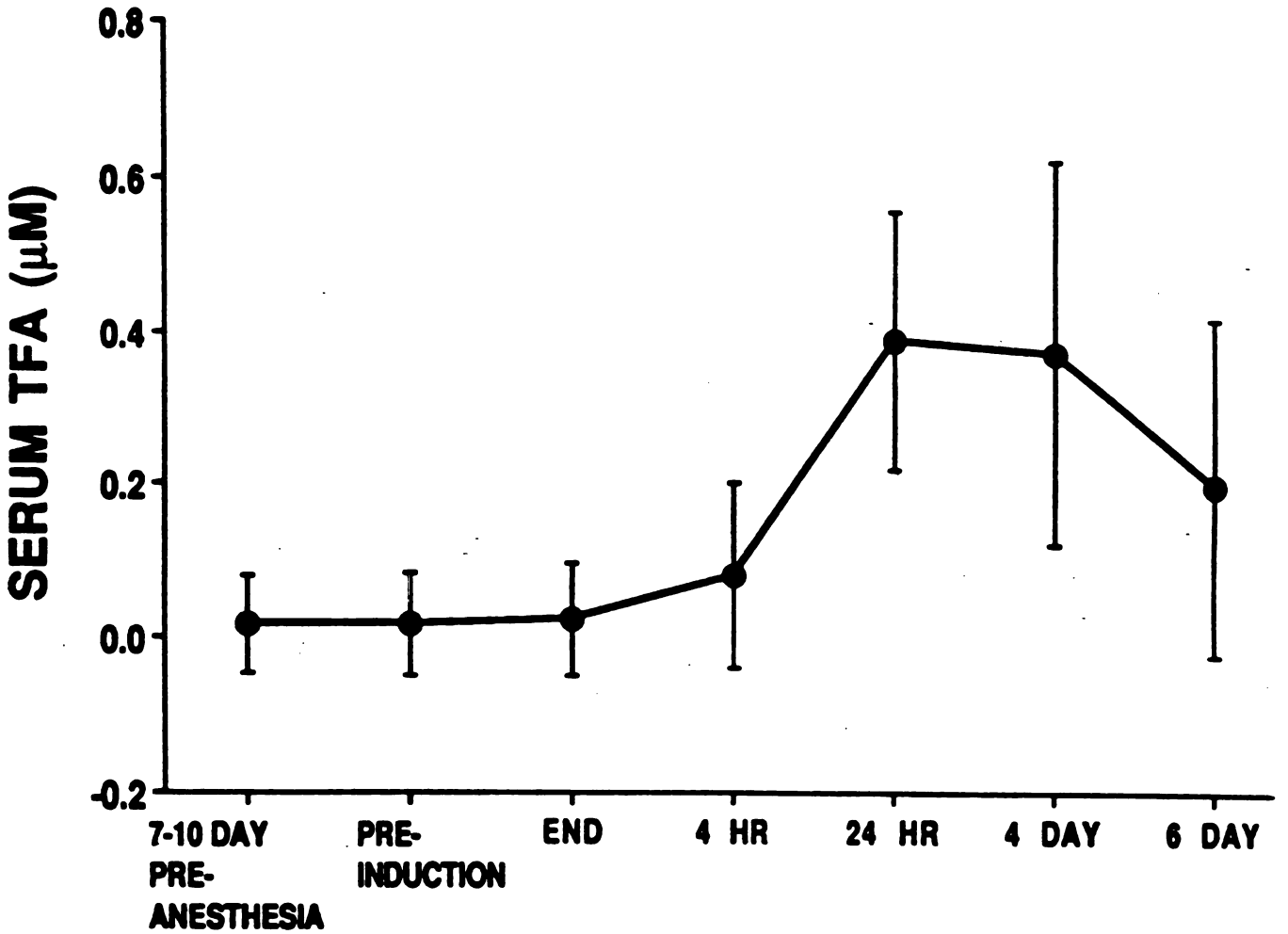


Fig. 6. In volunteers anesthetized with desflurane, serum trifluoroacetic acid concentrations 7-10 days prior to anesthesia ,or immediately prior to induction with anesthetic, did not differ from concentrations at the end of anesthesia, or at 4 hours, 24 hours, 4 days, or 6 days after anesthesia. The sample numbers were 12, 13, 13, 9, and 11 respectively. Error bars indicate ± S.D. Trifluoroacetic acid levels were maximal (0.38 ± 0.17 micrmole/liter) at 24 hours after anesthesia, and remained significantly increased above background at 6 days after anesthesia.

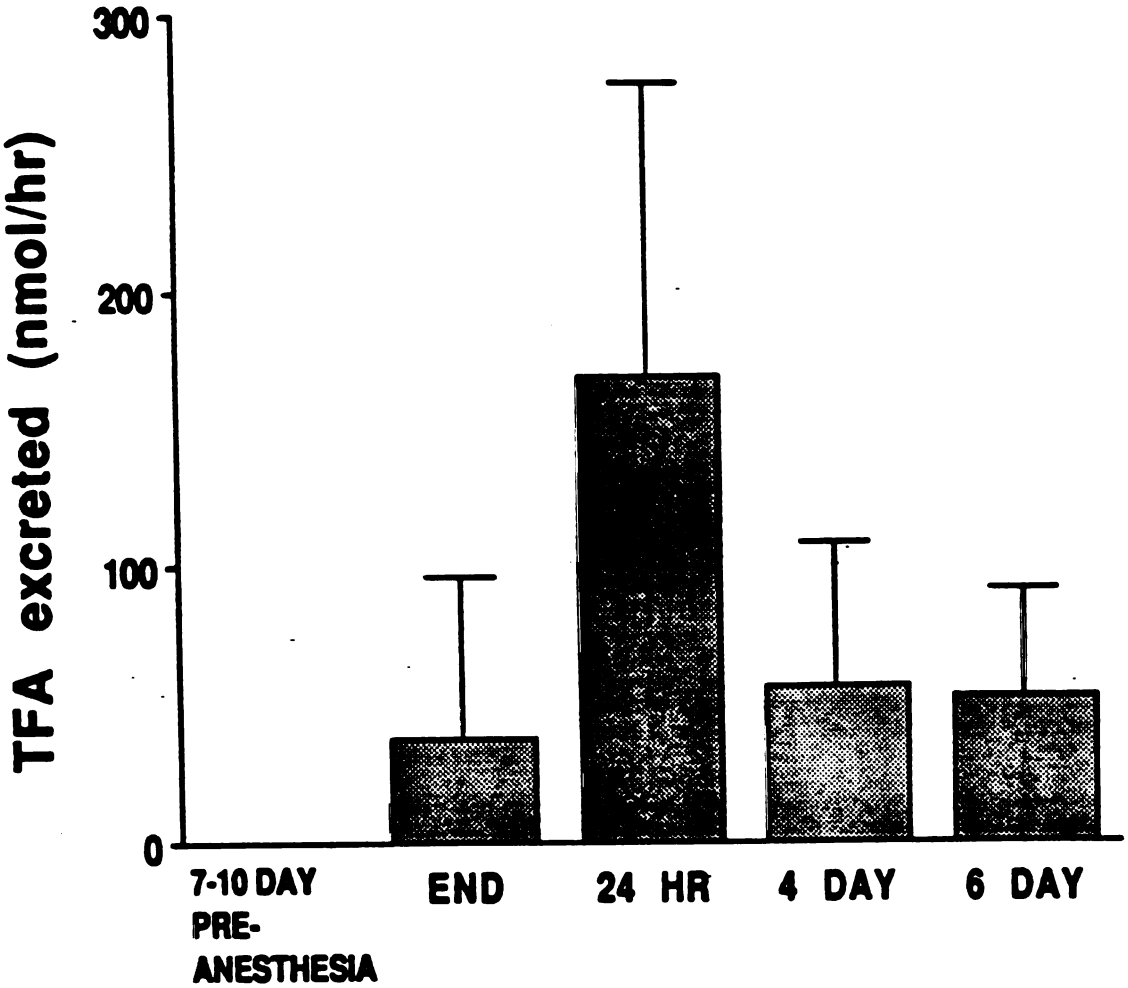


Fig. 7. In volunteers anesthetized with desflurane,urinary excretion rates of trifluoroacetic acid 7-10 days prior to anesthesia, or at the end of anesthesia, differed from rates at 24 hours, 4 days, or 6 days after anesthesia. The sample numbers were 12, 13, 13, 7, and 11 respectively. Error bars indicate ± S.D. The excretion rate was maximal (169 ± 107 micromoles/hour) at 24 hours after anesthesia, and the rate of excretion of trifluoroacetic acid remained significantly increased at 6 days after anesthesia.

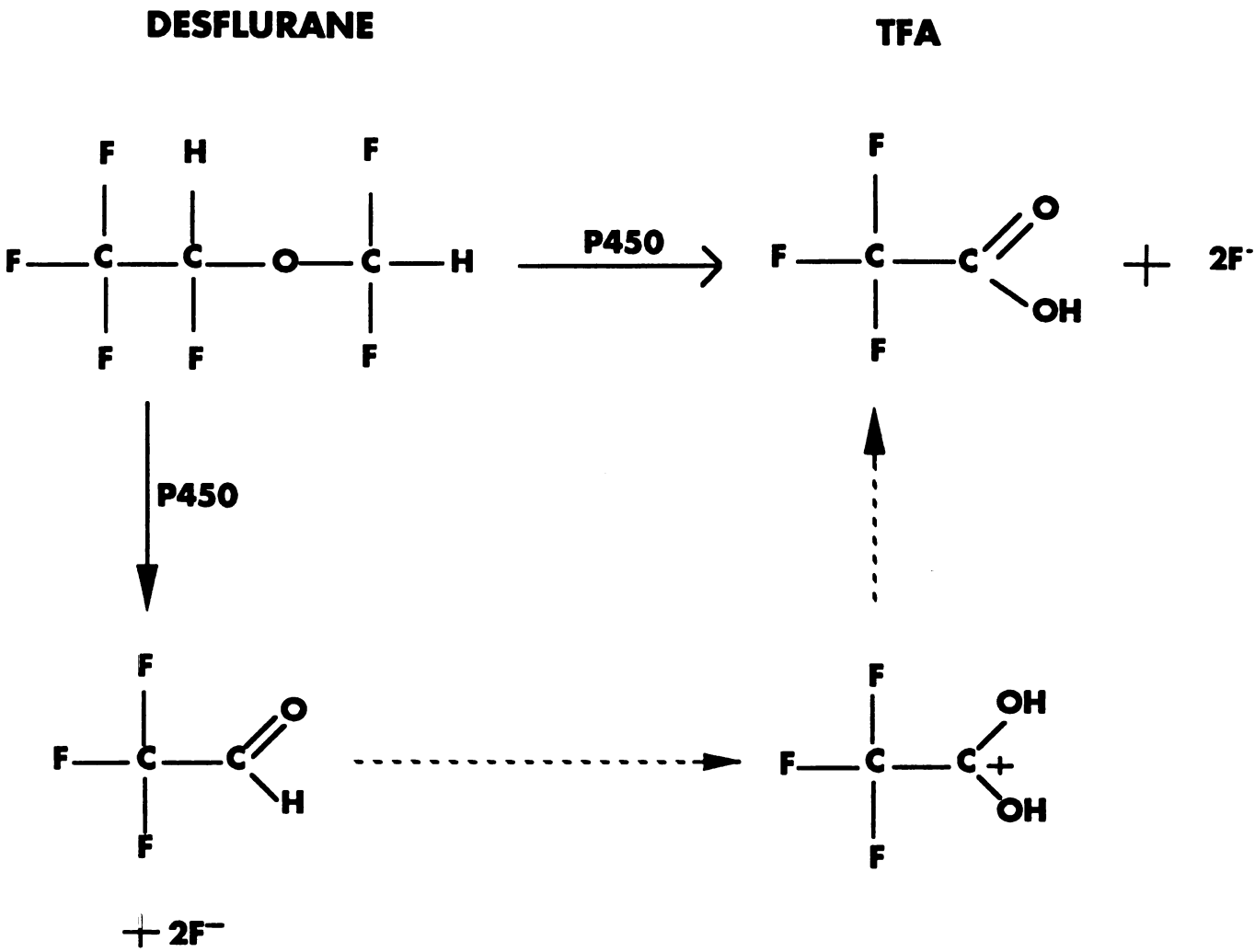


Fig. 8. Possible pathways of desflurane metabolism in humans. By either route, one mole of trifluoroacetate and two moles of fluoride ion would be expected for each mole of desflurane metabolized.

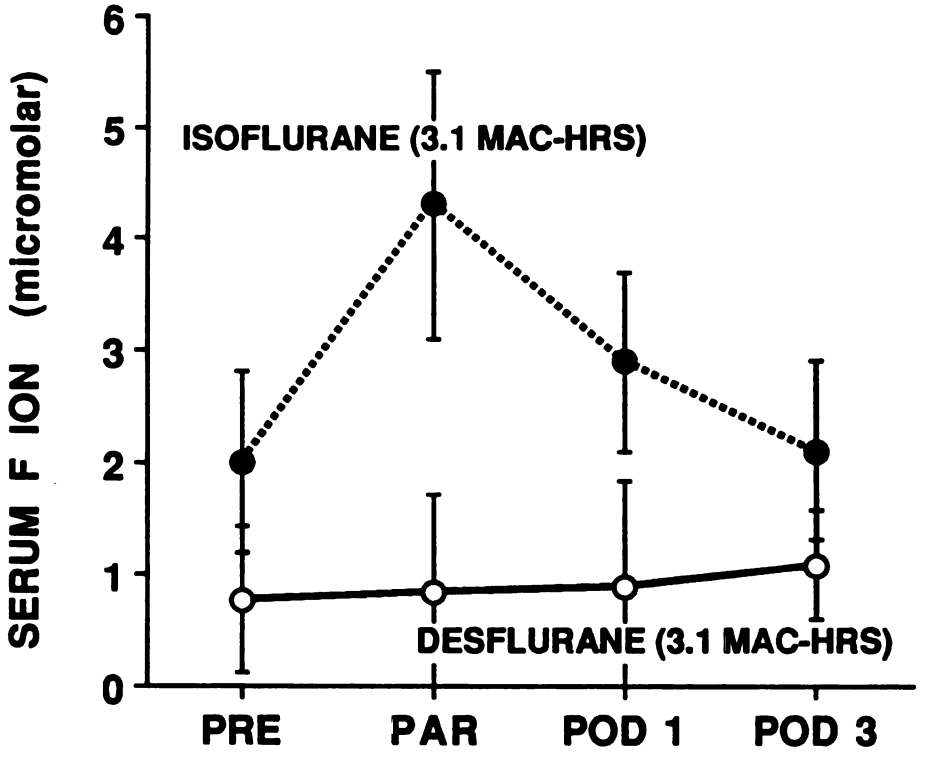


Fig. 9. Concentrations of fluoride ion in the serum of patients are increased after exposure to isoflurane, but not after comparable exposure to desflurane. Error bars indicate ± SD.

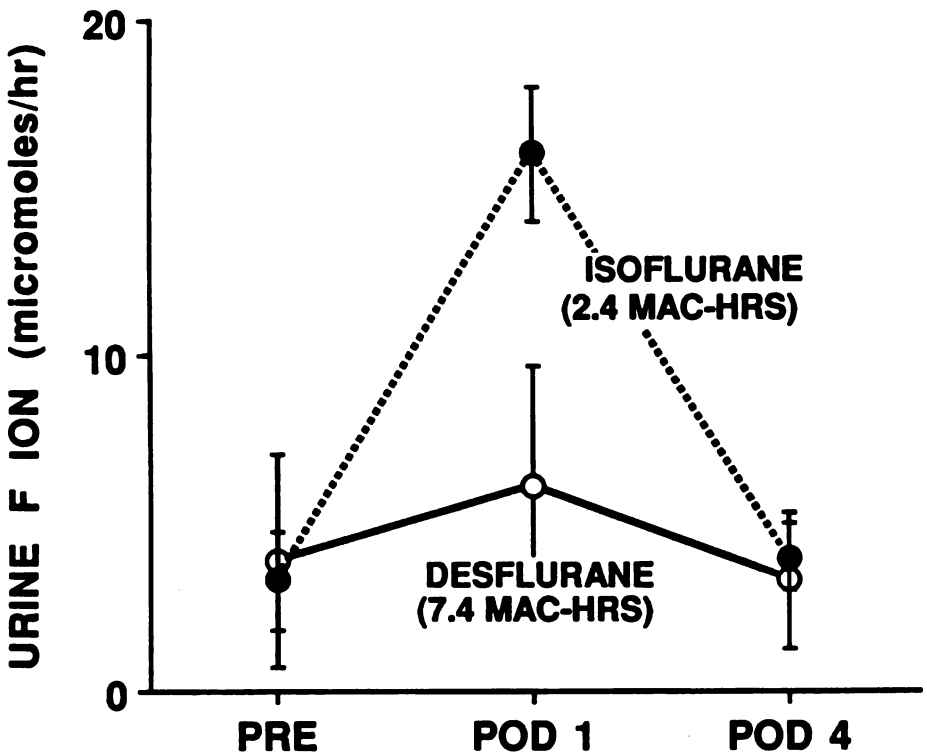


Fig. 10. Excretion rates of fluoride ion in the urine of patients are elevated after exposure to isoflurane, but not in the urine of volunteers after exposure to higher average doses of desflurane. Error bars indicate ± SD.

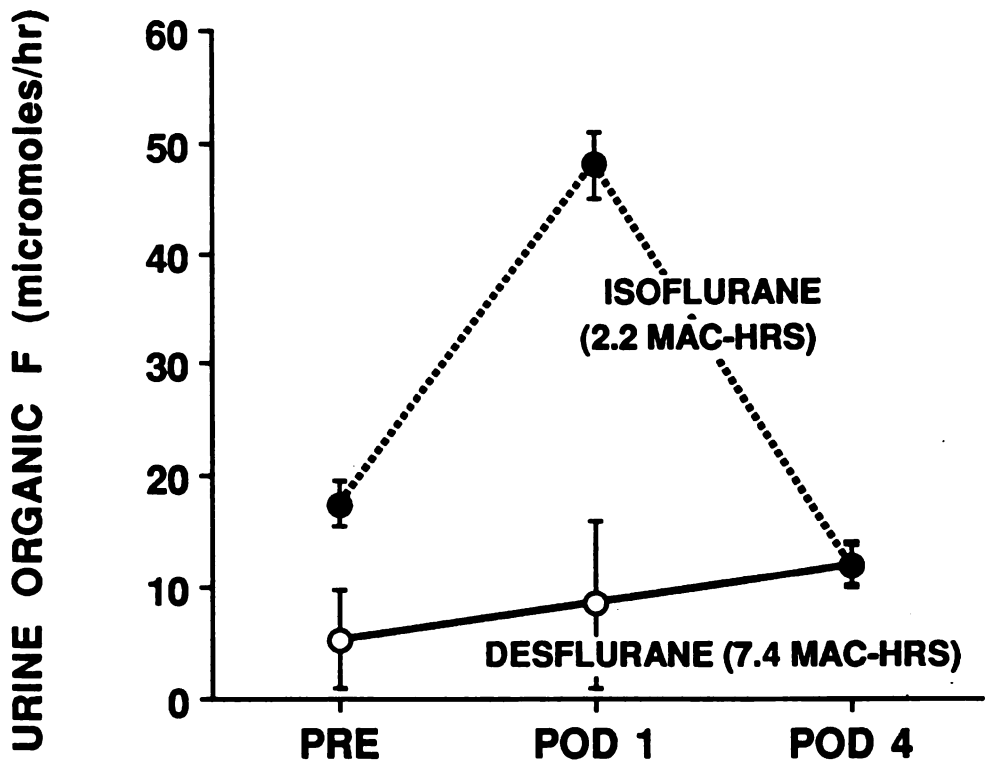
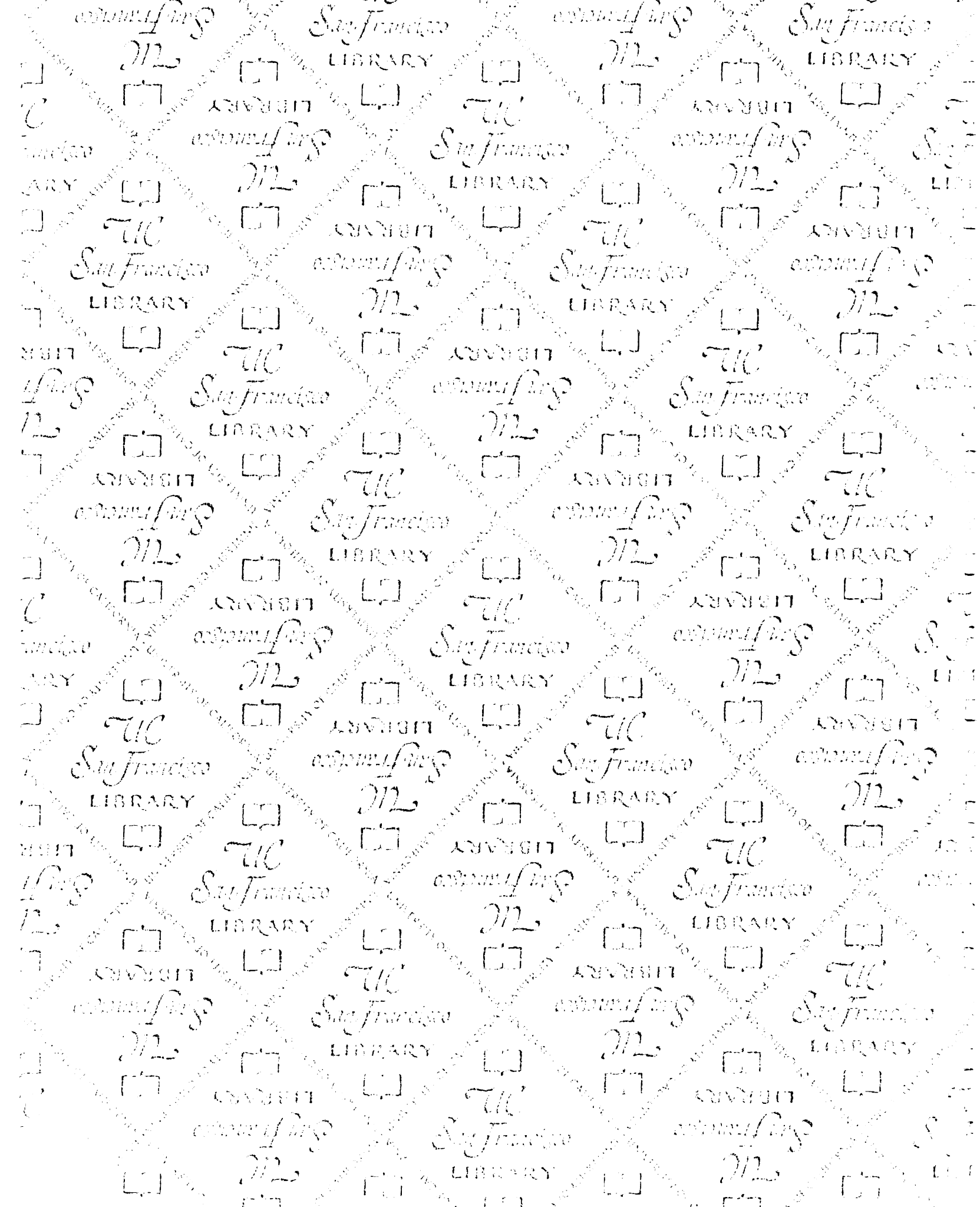


Fig. 11. Excretion rates of organic fluoride in the urine of patients are elevated after exposure to isoflurane, but not in the urine of volunteers after exposure to higher average doses of desflurane. Error bars indicate ± SD.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