Toxicity Following Methoxyflurane Anesthesia

II. Fluoride Concentrations in Nephrotoxicity

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The concentrations of inorganic fluoride and nonvolatile organic fluoride were measured in a patient with nephrotoxic effects following methoxyflurane anesthesia. Concentrations of both were markedly elevated compared to two patients who received methoxyflurane without subsequent nephrotoxic effects. Indirect evidence suggests that the inorganic fluoride concentration was sufficient to account for the nephrotoxic effects. The prolonged elevation of inorganic fluoride observed can be explained on the basis of the breakdown of the nonvolatile organic fluoride to inorganic fluoride and the poor renal clearance of both types.

While methoxyflurane is known to be metabolized to nonvolatile products, no studies have explored the possibility that excessive concentrations of metabolites might cause the polyuric renal failure as described in the previous report by Panner et al (see page 86). There are several possible metabolites of methoxyflurane (CH$_3$O-CF$_2$CCl$_2$H), the most likely being chloride and fluoro ions, methoxydifluoracetic acid, hydroxydifluoracetic acid, and oxalic acid. Fluoride and oxalate are both nephrotoxic and are thus of prime toxicologic importance. The acetic acid derivatives are of interest since they would be nonvolatile intermediates which would not be eliminated by exhalation.

We studied inorganic fluoride and nonvolatile organic fluoride concentrations in patients subsequent to methoxyflurane anesthesia. One patient (patient 2 reported by Panner et al) died with evidence of nephrotoxic effects, and two other patients had uneventful postoperative courses.

Report of Cases

The patient with evidence of nephrotoxic effects was very obese and was anesthetized four hours for cholecystectomy and removal of a common duct stone. Blood samples were drawn on the eighth postoperative day when it was suspected that the patient had nephrotoxic effects secondary to the methoxyflurane anesthesia. Additional samples were obtained 19 and 30 days following surgery. This patient died of renal failure 12 weeks after surgery. Two other patients whose conditions were studied for comparative purposes, were not obese, were anesthetized for two hours, and made uneventful recoveries. Blood samples were obtained from these patients before and after anesthesia and from one patient on two subsequent days.

Methods

We measured inorganic fluoride directly with a fluoride electrode by comparing the voltage readings with those of comparable standards.

We measured the nonvolatile organic fluoride by the difference between acid-labile and inorganic fluoride concentrations.

In the acid-labile fluoride determination the organically bound fluoride is converted to inorganic fluoride by the acid used for the gaseous diffusion of inorganic fluoride from a sample to a trapping solution. After all of the fluoride was separated from the sample the amount was determined by a previously described fluorescent reagent or by the fluoride electrode.
We found no additional fluoride by ashing the samples or by adding methoxyflurane directly to serum. For convenience, the nonvolatile organic fluoride as defined is called organic fluoride.

We determined the electrophoretic mobility of the inorganic and organic fluoride fractions by means of a curtain electrophoresis with use of 0.12% NH₄CO₃ as the buffer.

**Results**

All three patients had elevated inorganic fluoride levels after methoxyflurane anesthesia (Table). However, the levels were considerably higher in patient 1 who had polyuric renal failure. The 275 micromolar (µM) concentration found eight days after anesthesia was ten times the maximum concentration seen in the other two patients. Serum and urine fluoride concentrations from patient 1 were markedly elevated even 19 days after surgery, indicating a very large inorganic fluoride load. The urine volume that day was 1,170 ml. Thus, the clearance of inorganic fluoride from the blood was 5.8 ml/min or 10% of normal. The creatinine clearance was similarly reduced, 6 ml/min.

The organic fluoride concentrations after anesthesia were generally much higher than the inorganic fluoride concentrations except in the urine sample. The renal clearance of the organic fluoride in that specimen was 0.1 ml/min, accounting for only a small fraction of the decrease in organic fluoride concentrations from the eighth to 19th day and implying that considerable metabolism had occurred.

The electrophoretic separations showed that 95% of the fluoride in the blood was present in two distinct forms, one of which was seen as inorganic fluoride only after being treated with acid. Based on the relative mobilities, the organic fluoride was the same whether or not there were nephrotoxic effects (Fig 1 and 2). Figure 3 shows the curtain electrophoretic separation of the urine collected on the same day as the serum in Fig 1. It shows the two same peaks, but the relative heights are different reflecting the difference in renal clearance of the two forms of fluoride.

**Comment**

The consequence of an inorganic fluoride concentration above 200µM in serum has not been directly established, but indirect evidence suggests that it is nephrotoxic. Information from intravenous fluoride injection is most relevant since the fluoride in these patients arises parenterally. Intravenous injections of more than 100 mg of sodium fluoride in experimental studies in the treatment of thyrotoxicosis produced transient abdominal or lumb...
bar pain and when repeated daily for 10 to 15 days the 24-hour urine volume increased to 4 or 5 liters. This syndrome was noted and called "diabete insipidus fluorique" by Goldemberg. He did not report serum fluoride concentrations but they can be estimated. If one assumes that by 10 to 15 days the bones are saturated and no longer clearing fluoride then the daily output of fluoride would be equal to the intake of 100 mg of NaF or 2.38 millimol/day or 1.66 mmol/min. At a normal fluoride clearance of 50 ml/min the average serum concentration can be calculated to be 33 μM. If the 2.38 millimol of fluoride were uniformly distributed in 40 liters of body water (it appears to enter part of the intracellular water space), the serum concentration would be 60 μM. At a clearance of 50 ml/min the serum level would be about 10 μM at 24 hours. The serum values in patient 1 were considerably more than these estimates for "diabete insipidus fluorique" suggesting that the polyuria was caused by excessive fluoride ion concentrations.

Fluoride might cause polyuria simply because the concentrations in the renal tubule reach levels toxic to cells. Concentrations of 1,000 μM have been noted to have a toxic effect on cells in vitro. The inorganic fluoride concentration (850 μM) in the urine of patient 1 after 19 days was nearly this high.

The importance of the organic fluoride metabolites cannot be assessed completely at the present time; however, since they are unstable they are likely to be the immediate sources of inorganic fluoride. The clearance of organic metabolites was very low in patient 1 and the serum concentrations very high providing a possible basis for the prolonged elevation of the inorganic fluoride.

If inorganic fluoride formed from methoxyflurane metabolites is indeed the cause of the polyuria and renal failure, several factors would appear to be important in determining whether the high output failure syndrome will develop in a particular patient: (1) the duration of

2. Electrophoretic pattern on April 1 of serum of patient 2 taken March 6 showing protein (———), inorganic (○○○○○), and acid-labile (・・・・・) fluoride distribution in collected fractions.
3. Electrophoretic pattern on March 13 of urine of patient 1 taken Feb 25 showing protein (---), inorganic (○—○), and acid-labile (●—●—●) fluoride distribution in collected fractions.

anesthesia; (2) the amount of anesthetic retained which, in turn, would be related to obesity and the rate of metabolism of the methoxyflurane to nonvolatile components; (3) the rate of clearance of the inorganic and organic fluoride.

One means of preventing polyuria would be to limit the amount of anesthesia, particularly for obese patients or patients with impaired kidney function. Another means of protection might be by increasing the urine flow rate to dilute the fluoride in the kidney and hence reduce direct toxic effects. This maneuver may be the reason that Gauer et al. found no evidence of nephrotoxic effects after methoxyflurane treatment. They gave large

<table>
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<th>Patient No. and Date of Anesthesia</th>
<th>Sample</th>
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*Average of triplicates which differed by < 5%.

†A measurement of 330 was made 11 days after blood drawn, hence a correction for breakdown in storage was made. All other measurements made within four hours of the time of drawing blood.

Remeasurement with an improved procedure using acetate buffer showed 1 µM. All postanesthetic samples showed increases in the inorganic fluoride concentrations on remeasurement due to breakdown on storage.
amounts of fluids to increase the urine flow rate for accurate renal function studies.

Treatment of methoxyflurane toxic reactions by hemodialysis may be efficacious since the concentration of the fluorine-containing metabolite in serum was high and the clearance by the kidneys was low in one patient in whom it was measured (also see page 96).

Oxalate was not measured in these patients but is not likely to have been the cause of the polyuria seen here. While oxalate is nephrotoxic, it initially causes oliguric renal failure, rather than polyuria. Hepatic damage has been seen after poisoning with a mixture of oxalic and hydrofluoric acid in a human and in rabbits, thus, the hepatic toxic effects noted in case 1 reported by Panner et al (page 86) might have been due to a combination of oxalate and fluoride.

Whether tetracycline affects the metabolism or clearance of inorganic or organic fluoride is not known, but is of obvious interest because of the recent suggestion that tetracycline is associated with methoxyflurane toxic effects and its use in this study in the patient with a nephrotoxic reaction (page 86).

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Nonproprietary and Trade Names of Drug

Methoxyflurane—Penthrane.

References
