Fluoride-Induced Diuresis: Plasma Concentrations in the Rat[1] (35599)

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The administration of fluoride to laboratory animals (1, 2) and to man (3) has been reported to cause polyuria, but no measurements of corresponding plasma fluoride concentrations have been made in these experiments. The latter information would help to evaluate the suggestion that excessive plasma fluoride concentrations may be the cause of the polyuria and nephrotoxicity following the administration of methoxyflurane (4).

This is a report of the urine flow rates and plasma fluoride concentrations in rats given graded levels of fluoride by intravenous infusion.

Methods. The basic experiment was to anesthetize four rats at a time with each receiving fluoride at a different rate: 0, 100, 500, and 1000 nmoles/min. All solutions contained 150 m*M* sodium, but the concentrations of chloride and fluoride were varied. Solutions were infused continuously at 20 μl/min into the left iliac vein. The rats were all females, weighed approximately 200 g and were anesthetized with 40 mg/kg of sodium pentobarbital.

Urine collection was begun 10 min after the start of the infusion and continued for seven 30-min periods. Blood samples were collected for fluoride analysis at about the midpoint of the second and fourth through seventh collection periods. This basic experiment was done 5 times, during afternoon hours. One rat (a normal saline control) was lost from the series because of technical difficulties prior to the start of urine collection.

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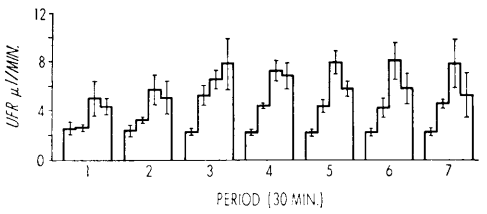

FIG. 1. Time course of the diruesis: mean urine flow rates ± SEM for given collection periods; (first bar in each group) data from controls; (second, third, and fourth bars) from groups receiving 100, 500, and 1000 nmoles of fluoride/min, respectively.

Urine was drawn through indwelling intraurethral PE-50 polyethylene catheters and collected in capillary tubes of known volume and constant inside diameter (Drummond Microcaps). Urine volumes were determined by measuring the length of the urine column in the capillary tube. The accuracy of this method is 0.43% ± 0.19 (SEM) when compared to the weighing method.

Blood from the severed tail tip was collected in heparinized capillary tubes and centrifuged. The capillary tube was scored at the cell–plasma interface and the plasma was expressed into containers to await analysis.

Fluoride was measured by the Orion fluoride electrode after diffusion into 0.20 ml of 0.15 *N* NaOH and the addition of 0.10 ml of 0.60 *N* acetic acid (5).

Student's *t* test (two-tailed) was used for statistical analyses.

Results. Figure 1 shows the time course of the fluoride induced diuresis. Each bar and perpendicular midline represents the mean plus or minus one standard error of the mean for all animals in a given infusion rate group. The control group shows little change

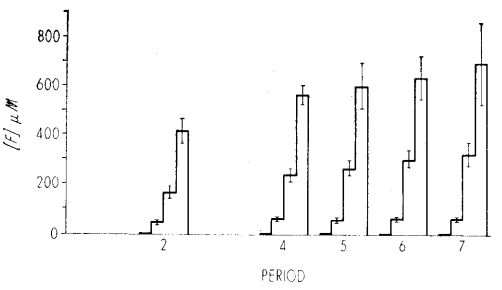

FIG. 2. Time course of plasma fluoride concentrations (mean ± SEM): Blood was taken at the midpoint of the indicated urine collection period. The grouping within each period is as for Fig. 1.

in urine flow with time, as expected with low infusion rates of isotonic saline. All fluoride-infused groups demonstrate a significant increase in urine flow rate by the third 30-min period with little change thereafter except for a progressive decrease in the highest infusion rate group.

Figure 2 shows the plasma fluoride concentrations for 5 of the 7 collection periods. Values for the control group could not be precisely determined because of the low concentrations, but were less than 3 μM. Plasma fluoride concentrations for the 100 nmoles/min group were essentially unchanged after the fourth period, suggesting a steady-state condition. The values for the groups receiving 500 and 1000 nmoles/min continued to

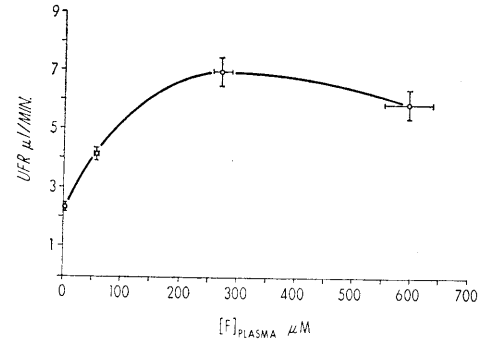

FIG. 3. Mean values ± SEM for urine flow rates and plasma fluoride concentrations for all samples within specified fluoride infusion rate groups: (left to right) 0, 100, 500, 1000 nmoles of fluoride/min. Each group receiving fluoride had an increased urine flow rate compared to controls with $p < .001$.

increase with time, 70 to 90% from the second to the final period.

Figure 3 combines all urine flow rates and all plasma fluoride concentrations within each of the four groups. This summary suggests that the diuresis is directly related to plasma fluoride concentration up to about 300 μM, but at higher concentrations—about 600 μM—there is some loss of effect. A diuresis of 180% of the control value is clearly present at a serum fluoride concentration of 56 μM.

Discussion. The present findings indicate that 50 μM plasma fluoride results in a definite increase in rate of urine flow and are consistent with the estimate (4) made from the experience of Goldemberg (3) in humans. The present findings also agree with the data from 3 patients who had received methoxyflurane anesthesia (4). Two of these patients had inorganic serum fluoride concentrations of 20 to 30 μM and no obvious diuresis; whereas the patient with a concentration of 275 μM had marked polyuria. The agreement lends further weight to the suggestion that metabolism of methoxyflurane to inorganic fluoride is a major factor in the nephrotoxicity noted after anesthesia with methoxyflurane.

Further work is being done to establish the mechanism of the fluoride effect. Preliminary data indicate that the renal sodium gradient (cortex to papilla) is markedly reduced. This would supply an explanation for the diuresis, as well as for the observation that the diuresis in humans after methoxyflurane anesthesia is unresponsive to ADH (6).

Summary. The rates of urine flow and the plasma fluoride concentrations were measured in anesthetized rats receiving continuous infusions of graded levels of fluoride in isotonic solutions. Infusion of 500 nmoles of fluoride/min produced the maximum diuresis, three times the mean control urine flow rate, and a plasma fluoride concentration of 272 μM. The 100 nmoles/min fluoride infusion rate produced an 80% increase in urine flow rate with a plasma fluoride concentration of 56 μM. These findings are consistent with estimates made for man and with the suggestion that the nephrotoxicity following methoxyflurane anesthesia is at least in part

due to metabolism of methoxyflurane to inorganic fluoride.

1. Bond, A. M., and Murray, M. M., Brit. J. Exp. Pathol. **33**, 168 (1952).

2. Gottlieb, L., and Grant, S. B., Proc. Soc. Exp. Biol. Med. **29**, 1293 (1931).

3. Goldemberg, L., Rev. Soc. Med. Int. Soc. Tisiol., **6**, 217 (1931).

4. Taves, D. R., Fry, B. W., Freeman, R. B., and Gillies, A. J., J. Amer. Med. Ass. **214**, 91 (1970).

5. Fry, B. W., and Taves, D. R., J. Lab. Clin. Med. **75**, 1020 (1970).

6. Crandell, W. B., and MacDonald, A., J. Amer. Med. Ass. **205**, 789 (1968).

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