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# *Renal Fluoride Excretion and Plasma Fluoride Levels during and after Enflurane Anesthesia Are Dependent on Urinary pH*

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**To determine the effects of urinary *p*H on fluoride ion excretion and the resulting plasma fluoride concentrations during and after enflurane anesthesia, renal function, plasma inorganic fluoride levels, and fluoride excretion were studied in two groups of patients pretreated with either $NH_4Cl$ or acetazolamide to produce acidic or alkaline urine, respectively. During anesthesia, urinary flow rate, inulin clearance ($C_{In}$) and para-aminohippurate (PAH) clearance ($C_{PAH}$) were 7, 61, and 43 per cent of control values in the acidic-urine group and 22, 74, and 57 per cent of control values in the alkaline-urine group, respectively. Fractional fluoride clearances ($C_F/C_{In}$) during anesthesia and operation were 0.06 ± 0.05 in the acidic-urine group (urinary *p*H 5.08) and 0.68 ± 0.23 in the alkaline-urine group (urinary *p*H 8.16). Values of total fluoride excretion during the same period were 0.06 ± 0.04 mg and 0.87 ± 0.29 mg, respectively. Mean maximal plasma levels of fluoride were 26.3 ± 7.3 μM in the acidic-urine group and 13.5 ± 2.4 μM in the alkaline-urine group. The differences between groups in fluoride clearance, fluoride excretion, and plasma fluoride levels were all statistically significant. The data clearly show that renal fluoride clearance is closely related to urinary *p*H. (Key words: Anesthetics, volatile: enflurane. Biotransformation: fluorometabolites. Ions: fluoride. Kidney: function, nephrotoxicity; urine. Metabolism: metabolites. Pharmacokinetics. Toxicity: metabolites.)**

THE BIOTRANSFORMATION of enflurane during and after anesthesia and the resulting plasma levels of fluoride are well documented.[1–3] Fluoride ions are cleared from plasma by renal excretion and by uptake into calcified tissues.[4,5] In a previous report, we described how fractional fluoride excretion (fluoride clearance/inulin clearance; $C_F/C_{In}$) after enflurane anesthesia varied directly with spontaneous urinary *p*H fluctuations.[6] Fluoride excretion seemed to be related to urinary *p*H. It was postulated that fluoride was reabsorbed in the renal tubules by nonionic diffusion, most likely in the form of hydrogen fluoride, and that this would increase during acidotic urinary conditions. In the present investigation we have examined whether it is possible to influence fluoride excretion during and after enflurane anesthesia by actively manipulating urinary *p*H.

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## Materials and Methods

Ten patients undergoing abdominal hysterectomy were investigated. They were randomly divided into two groups of five each. Patients in the first group (mean age 47 years, range 50–43 years; mean weight 63 kg, range 70–58 kg) received ammonium chloride, 1 g × 4, during the day before operation and 1 g on the morning of operation to acidify the urine. Those in the second group (mean age 45 years, range 50–41 years; mean weight 60 kg, range 65–54 kg) received acetazolamide, 500 mg, iv, 60 min before the clearance determinations were started, to alkalinize the urine. The patients had no known history of renal disease. They were receiving no medication except iron. Preoperative plasma electrolyte and creatinine levels were normal. The Ethical Committee of Karolinska Sjukhuset had given its consent to the study, the scope of which was explained to the patients and their informed consent obtained.

Premedication consisted of morphine sulfate, 0.1 mg/kg, and scopolamine hydrobromide, 0.006 mg/kg, administered im. Thiopental, 4 mg/kg, was used for induction, and endotracheal intubation was facilitated by muscle relaxation with pancuronium bromide, 0.1 mg/kg. Anesthesia was maintained with enflurane, 1.5 per cent, in nitrous oxide and oxygen, 2:1. Ventilation was controlled (Engström 300) and adjusted to maintain a normal $Pa_{CO_2}$ based on blood-gas determinations (Il-413). End-tidal enflurane concentration was measured with a mass spectrometer (Centronic, MGA 200). Stable end-tidal enflurane concentrations were reached after 30 min at 1.25 ± 0.12 per cent (mean ± SEM). Anesthetic times was 150 ± 6 min and 148 ± 7 min in the acidic-urine and alkaline-urine groups, respectively.

Renal function was evaluated employing standard clearance techniques. The details are described elsewhere.[3] Sodium, osmolar, and free water clearances were measured and the corresponding fractional excretions were calculated. After priming the patients with inulin and PAH and allowing 60 min for equilibration, there were two 30-min collection periods prior to induction of anesthesia. When end-tidal enflurane concentration had reached near steady state, renal function was studied at 45-min intervals throughout the remaining peroperative anesthesia, then immediately postoperatively during two consecutive three-hour periods.

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Inorganic fluoride concentrations in plasma and urine were measured with a fluoride ion-sensitive electrode (96-09, Orion Research). Plasma levels were determined before anesthesia and then every 15 min during and every 60 min after anesthesia for six hours. Fluoride concentrations and *p*H were measured in all the urine specimens collected during the different clearance periods.

The patients received 10 $ml \cdot kg^{-1} \cdot hr^{-1}$ of a balanced electrolyte solution containing 25 mg/ml glucose during the equilibration and preoperative measurement periods. All intraoperative fluid losses plus an additional 1,000 ml for insensible fluid losses were replaced with the same solution.

Mean values and standard deviations of the different groups of data were calculated. Student's *t* test for unpaired data was used for statistical comparisons. Differences with a random probability of 5 per cent or less were considered significant.

## Results

Control plasma fluoride concentrations were 0.7 ± 0.2 μM in both groups. After induction of anesthesia, plasma fluoride concentrations increased rapidly in the two groups (fig. 1). After 45 min of anesthesia, the acidic-urine group (urinary *p*H 5.08 ± 0.25) had higher plasma concentrations of fluoride than did the alkaline-urine group (urinary *p*H 8.16 ± 0.26). Plasma fluoride concentrations increased more rapidly in the patients with acidic urines compared with those with alkaline urines, in whom plasma fluoride levels after 75 min of anesthesia remained almost constant. Maximal fluoride concentrations were 26.4 ± 7.9 μM and 13.5 ± 2.4 μM in the acidic-urine and alkaline-urine groups, respectively. These levels were reached two hours after termination of anesthesia.

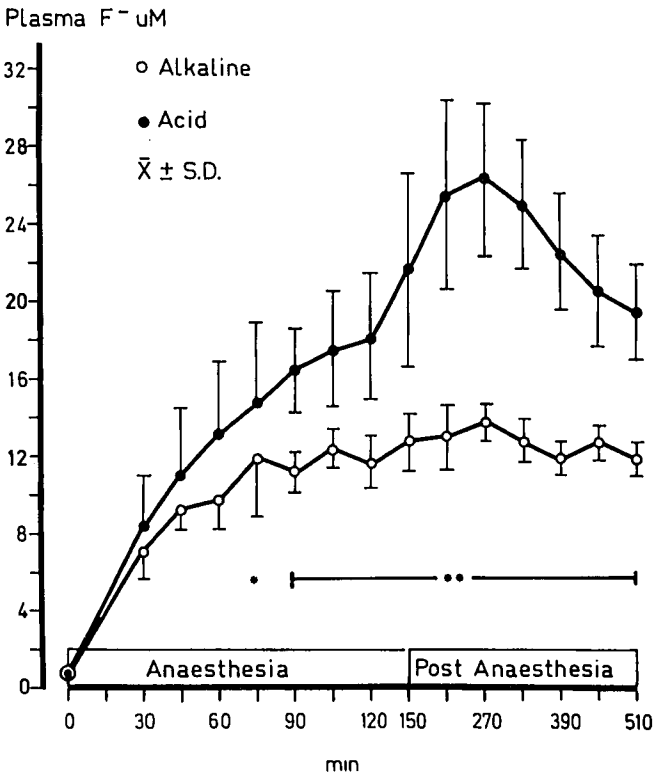


FIG. 1. Plasma fluoride levels before, during, and after enflurane anesthesia in two groups of patients with preoperatively induced alkaline and acidic-urinary conditions (mean ± SD). *$P < 0.05$; **$P < 0.01$.

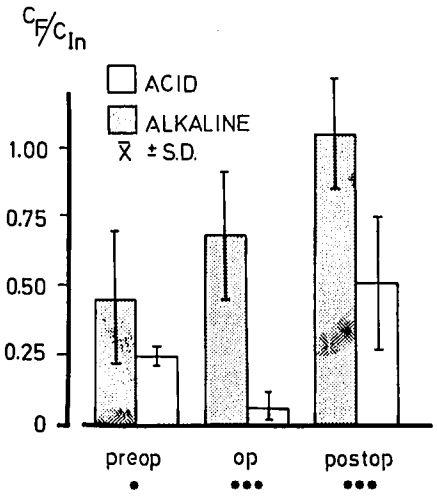


FIG. 2. Fractional fluoride excretion before, during, and after enflurane anesthesia in two groups of patients with preoperatively induced alkaline and acidic-urinary conditions (mean ± SD). *$P < 0.05$; ***$P < 0.001$.

In the acidic-urine group $C_F/C_{In}$ decreased from 0.24 ± 0.03 before induction of anesthesia to 0.06 ± 0.05 during anesthesia and operation. Postoperatively, it rose to 0.51 ± 0.24 (fig. 2). Corresponding values in the alkaline-urine group were 0.45 ± 0.24, 0.68 ± 0.23, and 1.05 ± 0.20, respectively (fig. 2). Total urinary excretion of fluoride during anesthesia was 0.06 ± 0.04 mg in the acidic-urine group, compared with 0.87 ± 0.29 mg in the alkaline-urine group (table 1).

Urinary flow rates (UF) were 5–10 ml/min in both groups before induction of anesthesia, with major reductions during anesthesia and operation (table 2). Postoperatively, UFs were 1.58 ml/min in the acidic-urine group and 2.22 ml/min in the alkaline-urine group (table 2). There was no significant difference between groups concerning renal hemodynamics (table 2).

Preoperatively values for fractional free water excretion ($C_{H_2O}/C_{In}$) were 5.22 in the acidic-urine group and 2.43 in the alkaline-urine group. During

TABLE 1. Fractional Fluoride Excretion ($C_F/C_{In}$), Total Fluoride Excretion ($U_F \times V$), and Urinary *p*H before, during, and after Enflurane Anesthesia in Acidic and Alkaline Urinary Conditions (Mean ± SD)

| | $C_F/C_{In}$ | | | $V_F \times V$ (mg) | | | Urinary *p*H | | |
|---|---|---|---|---|---|---|---|---|---|
| | Preoperative | Operative | Postoperative | Preoperative | Operative | Postoperative | Preoperative | Operative | Postoperative |
| Acidic | 0.24 ± 0.03 | 0.06 ± 0.05 | 0.51 ± 0.24 | 0.02 ± 0.01 | 0.06 ± 0.04 | 7.01 ± 1.74 | 5.73 ± 0.38 | 5.08 ± 0.25 | 5.77 ± 0.83 |
| Alkaline | 0.45 ± 0.24 | 0.68 ± 0.23 | 1.05 ± 0.20 | 0.02 ± 0.01 | 0.87 ± 0.29 | 8.83 ± 1.24 | 8.33 ± 0.39 | 8.16 ± 0.26 | 7.79 ± 0.18 |
| Significance of difference | $P < 0.05$ | $P < 0.001$ | $P < 0.001$ | N.S. | $P < 0.001$ | N.S. | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ |

anesthesia and operation $C_{H_2O}/C_{In}$ turned into free water reabsorption ($T^c_{H_2O}/C_{In}$) in both groups. Postoperatively $T^c_{H_2O}$ increased further in both groups (table 3). Fractional sodium excretion values ($C_{Na}/C_{In}$) in the acidic-urine group were 0.85, 0.47, and 1.28 before, during, and after anesthesia, respectively. Corresponding values in the alkaline-urine group were 6.08, 2.03, and 2.73, respectively (table 3). Fractional osmolar clearances ($C_{Osm}/C_{In}$) had patterns similar to those of $C_{Na}/C_{In}$ in the two groups (table 3). Arterial blood-gas values were measured only during anesthesia. Values of *p*H were 7.36 ± 0.04 and 7.39 ± 0.03 in the acidic-urine and alkaline-urine groups, respectively ($P > 0.05$). Corresponding values for $P_{CO_2}$ in the two groups were 36 ± 3 torr and 35 ± 3 torr, respectively ($P > 0.05$).

## Discussion

The data obtained in the present study clearly show that fluoride excretion in association with enflurane anesthesia is influenced by urinary *p*H, and that this influence results in significant differences between plasma fluoride levels achieved during acidic and alkaline urinary conditions. Plasma fluoride concentrations in both groups were well below the level associated with renal dysfunction.[7]

Normally, 40–60 per cent of ingested fluoride is excreted in the urine and the remainder is accumulated in the calcified tissues.[4,5,8] Renal handling of fluoride is characterized by glomerular filtration followed by varying extents of tubular reabsorption. Stop-flow studies in dogs have shown that the reabsorption mainly occurs in the distal tubules and the collection ducts.[9] Normal renal clearance of fluoride in healthy volunteers ranges from a third to two thirds of the actual glomerular filtration rate (GFR).[4,8] During enflurane anesthesia $C_F$ is decreased to approximately a tenth of the actual GFR.[3,6] In the present study, $C_F/C_{In}$ decreased markedly during anesthesia and operation in the acidic-urine group, while it increased in the alkaline-urine group compared with preoperative control values. This apparent dependency of $C_F$ on urinary *p*H was found earlier in rats[10] and in volunteers[11] receiving sodium fluoride. We also observed this in an earlier study.[6] The probable explanation is that fluoride is reabsorbed by nonionic diffusion, as hydrogen fluoride (HF), from the renal tubules during acidotic urinary conditions. The $pK_a$ of HF is 3.45.[12] Within the physiologic range of urinary *p*H,[13] HF would represent 0.003 per cent to approximately 15 per cent of the fluoride in solution. As soon as even small amounts of hydrogen fluoride are formed in the tubules, a diffusion gradient for HF is created, which will increase rapidly as urinary *p*H decreases. The uncharged HF molecules penetrate the tubular epithelium more easily than do the free

TABLE 2. Urinary Flow Rate (UF), Inulin Clearance ($C_{In}$), and Para-aminohippurate (PAH) Clearance ($C_{PAH}$) before, during, and after Enflurane Anesthesia in Acidic and Alkaline Urinary Conditions (Mean ± SD)

| | UF (ml/min) | | | $C_{In}$ (ml/min) | | | $C_{PAH}$ (ml/min) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Preoperative | Operative | Postoperative | Preoperative | Operative | Postoperative | Preoperative | Operative | Postoperative |
| Acidic | 8.17 ± 1.58 | 0.53 ± 0.18 | 1.58 ± 0.87 | 115 ± 18 | 71 ± 19 | 119 ± 11 | 735 ± 174 | 315 ± 97 | 667 ± 245 |
| Alkaline | 6.29 ± 2.53 | 1.54 ± 1.10 | 2.22 ± 0.79 | 106 ± 26 | 78 ± 19 | 111 ± 21 | 689 ± 242 | 396 ± 107 | 640 ± 175 |
| Significance of difference | N.S. | $P < 0.05$ | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. |

TABLE 3. Fractional Excretions of Sodium ($C_{Na}/C_{In}$), Osmoles ($C_{Osm}/C_{In}$), and Free Water ($C_{H_2O}/C_{In}$) before, during, and after Enflurane Anesthesia in Acidic and Alkaline Urinary Conditions (Mean ± SD)

| | $C_{Na}/C_{In}$ | | | $C_{Osm}/C_{In}$ | | | $C_{H_2O}/C_{In}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Preoperative | Operative | Postoperative | Preoperative | Operative | Postoperative | Preoperative | Operative | Postoperative |
| Acidic | 0.85 ± 0.18 | 0.47 ± 0.40 | 1.28 ± 0.71 | 2.33 ± 0.66 | 1.35 ± 0.10 | 2.80 ± 1.35 | 5.22 ± 1.01 | −0.61 ± 0.13 | −1.43 ± 0.66 |
| Alkaline | 6.08 ± 2.91 | 2.03 ± 1.27 | 2.73 ± 1.49 | 7.30 ± 2.48 | 3.36 ± 1.70 | 4.18 ± 2.01 | 2.43 ± 1.17 | −1.38 ± 0.67 | −1.90 ± 0.86 |
| Significance of difference | $P < 0.001$ | $P < 0.01$ | $P < 0.05$ | $P < 0.001$ | $P < 0.01$ | N.S. | $P < 0.05$ | $P < 0.01$ | N.S. |

charged fluoride ions. In the peritubular fluid, where *p*H is higher and the fluoride concentration lower (relative to the tubular fluid), HF is dissociated and the fluoride ions are returned to the systemic circulation via the peritubular capillaries. This continuous removal of fluoride from the interstitium by the peritubular blood flow assures that the diffusion gradient for HF is maintained. The dependency of fluoride reabsorption on urinary *p*H is similar to the renal handling of other weak acids and bases, such as amphetamine,[14] lidocaine and prilocaine,[15] barbiturates,[16] and ammonia.[17]

Fluoride excretion increases with increasing urinary flow rates.[8,10,18] The reduction in UF during anesthesia and operation, compared with the preoperative period, could thus have contributed to the decrease in $C_F/C_{In}$ observed in the acidic-urine group. During anesthesia there was a rise in $C_F/C_{In}$ in the alkaline-urine group, despite a concomitant reduction in UF. This indicates that urinary *p*H is a relatively more important factor than UF in controlling fluoride excretion. However, the less pronounced decrease in UF in the alkaline-urine group compared with the acidic-urine group, which was due to the use of acetazolamide in the former, might have contributed to the observed difference in $C_F/C_{In}$. The difference in UF is, however, not of sufficient magnitude to account for the difference in values obtained for $C_F/C_{In}$.[8] The differences in UF, fractional sodium, and osmolar and free water excretion observed between the two groups can be explained by the natriuresis caused by acetazolamide.

Intraoperative changes in $C_{In}$ and $C_{PAH}$ were similar in magnitude to those reported to occur with other inhalational anesthetics[19] and with neuroleptanesthesia.[20] Renal hemodynamics were, however, promptly restored postoperatively.

It seems unlikely that the induced urinary *p*H changes would affect the hepatic metabolism of enflurane, causing the difference in plasma fluoride concentrations. Patients in the acidic-urine group had a mean blood *p*H that was slightly lower than that of the alkaline-urine group. Variations in systemic blood *p*H could theoretically influence hepatic drug metabolism by affecting cytochrome P-450 activity and/or by changing hepatic blood flow, thereby influencing the bioavailability of the drug to the hepatic metabolic system. Changes of *p*H in the blood may also have influenced the osseous uptake of fluoride. It has been reported that metabolic acidosis increases the rate of reabsorption by bone and that metabolic alkalosis increases the rate of osseous accretion in rats.[21] This could have contributed to the difference in plasma fluoride concentrations.

In conclusion, by alkalinization of the urine it is possible to increase fluoride excretion and decrease plasma fluoride levels during and after enflurane anesthesia.

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