Urinary Fluoride Excretion in Fluoride Exposed Workers with Diminished Renal Function

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Abstract: Studies were made on the usefulness of measuring the fluoride concentration in the serum and urine as an index for the health care of hydrofluoric acid (HF) workers, particularly for those with diminished renal function. Renal clearance of fluoride (C_F), the amount of fluoride filtered by the glomeruli per minute (F_F) and tubular reabsorption of fluoride (TrF), which were calculated from the serum concentration, as well as the quantity concurrently excreted in the urine and the glomerular filtration rate (GFR), were investigated in patients with chronic renal failure (CRF) and healthy controls after the oral administration of sodium fluoride (as 4 mg F^-) with water loading. After the administration the 24-hour excretion of fluoride in the patients with CRF was significantly lower ($p < 0.001$) than controls. C_F , F_F , and TrF were also lower in the patients. C_F and creatinine clearance (C_{cr}) were well correlated ($r = +0.87$) with C_F averaging 48% of the C_{cr} . Elevated concentrations of fluoride were observed in the serum of patients with CRF and HF workers. Three HF workers who had clinical evidence of renal failure showed a higher level of serum fluoride. However, their urinary level of fluoride showed normal values. The results showed that the urinary excretion of fluoride decreased with the reduction of renal function. Moreover, compared to urinary levels the fluoride concentration in the serum may be a more direct indicator of exposure in patients with kidney hypofunction.

Key words: Fluoride metabolism—Hydrofluoric acid workers—Patients with chronic renal failure—Renal fluoride clearance—Index of fluoride exposure

INTRODUCTION

It is well known that ingested fluoride is mainly excreted via the kidney.^{1,2)} For this reason, urinary fluoride is widely measured as an early indicator of fluoride poisoning among not only fluoride exposed workers but also inhabitants of fluoride-polluted area.³⁻⁶⁾

When the renal function deteriorates, the ability to excrete fluoride markedly decreases, possibly resulting in greater retention of fluoride in the body. In fact, fluoride concentrations in the plasma and bone significantly increases in uremic patients.⁷⁻⁹⁾ Kim *et al.*¹⁰⁾ demonstrated that in patients with advanced renal disease, fluoride content in the bone was strikingly higher than in patients without renal or bone diseases.

At present, fluoride metabolism of the patients with chronic renal failure (CRF), in whom the function of the main pathway of fluoride excretion is impaired, is not completely understood.

In this study, fluoride concentrations were measured in the serum and urine specimens of patients with CRF, hydrofluoric acid (HF) workers and healthy controls. In addition, the renal clearance of fluoride (C_F), the amount of fluoride filtered through the glomeruli per minute (F_F), and the tubular reabsorption of fluoride (TrF) were investigated in the patients with CRF and controls after the oral administration of sodium fluoride solution. Furthermore, some basic findings are discussed on the usefulness of measuring the fluoride concentration in the serum and urine as indicators for the health care of HF workers, especially for persons with diminished renal function.

MATERIALS AND METHODS

In the first part of this study, the fluoride concentration in the serum and urine was determined in three groups of subjects. The first group consisted of 40 male and female patients ranging in age from 30 to 70 years presenting with CRF and shown to have serum creatinine and blood urea nitrogen (BUN) values greater than 5 mg/dl and 50 mg/dl respectively. The second group was composed of 120 male workers aged 20 to 60 years who had been irregularly exposed to a relatively low level (1-3 ppm) of HF in the electronic industry. As a control group, 320 healthy subjects aged 30 to 70 years living in a rural area were included. Water fluoridation is not practiced in Japan and in this community the fluoride level in the drinking water was approximately 0.1 ppm.

Venous blood samples (5 ml) and urine specimens (10 ml) were taken from all subjects at a specific time (between 12:00 and 15:00 hours) for the measurement of fluoride concentrations in the serum and urine.

For the second part of this study, 5 patients with CRF and same number of healthy controls were selected. The subjects were given sodium fluoride (as 4 mg F^-) by a single oral administration with 300 ml water loading after an overnight fasting.

Blood and urine samples (10 ml) were collected before and 0.5, 1, 2, 4, 6, 12, 24, 48, and 96 hours after the fluoride administration.

Renal clearance of fluoride (C_F) after the oral administration was calculated

according to the following formula.

$$C_F (\text{ml/min}) = \text{U-F } (\mu\text{g/ml}) \times V (\text{ml/min}) / \text{S-F } (\mu\text{g/ml}) \\ \times 1.48 (\text{m}^2) / A \text{ m}^2$$

where U-F is the concentration of fluoride in urine at the specific time ($\mu\text{g/ml}$)

S-F is the concentration of fluoride in serum at the same time ($\mu\text{g/ml}$)

V is the urinary flow during 1 minute at the same time (ml/min)

1.48 is the mean body surface of Japanese (m^2)

A is the body surface of the subject (m^2)

The amount of fluoride filtered through the glomeruli per minute (F_F) was calculated by the following equation.

$$F_F (\mu\text{g/min}/1.48 \text{ m}^2) = \text{S-F } (\mu\text{g/ml}) \times \text{GFR } (\text{ml/min}/1.48 \text{ m}^2)$$

where GFR is the glomerular filtration rate, which is the creatinine clearance (Ccr) in this study.

The tubular reabsorption of fluoride (TrF) was determined from the following equation.

$$\text{TrF } (\mu\text{g/min}/1.48 \text{ m}^2) = F_F (\mu\text{g/min}/1.48 \text{ m}^2) - [\text{U-F } (\mu\text{g/ml}) \\ \times V (\text{ml/min})]$$

Fluoride concentrations in the serum and urine were measured by a fluoride electrode method using an Orion Model 901 ion analyzer as detailed by Yoshida *et al.*¹¹⁾

Creatinine concentrations in the serum and urine were measured by the Folin-Wu method using a Hitachi Model 706D auto analyzer.

Differences between means were evaluated by Student's t-test.

RESULTS

The serum and urine concentrations of fluoride in 40 patients with CRF, 120 HF workers, and 320 healthy controls are shown in Table 1. The serum concentrations of fluoride in patients with CRF and HF workers were remarkably higher ($p < 0.001$) than control subjects. Urinary concentration of fluoride in HF workers was also higher ($p < 0.001$) than that in control subjects. Although the serum fluoride concentrations of patients with CRF were markedly higher than controls, their urinary content of fluoride remained normal. Serum concentrations of fluoride in three HF workers, who had clinical evidence of chronic renal disease and undergone treatment at the experiment, were strikingly higher (mean of 3 patients: 172 ppb) than in other patients with CRF and HF workers. Their urinary concentrations of fluoride, however, were within normal limits (mean value: 0.66 ppm).

Table 2 shows the 24-hour urinary fluoride excretion in 5 patients with CRF and 5 healthy controls after the oral administration of sodium fluoride with water loading. Both groups were on a very low intake of fluoride before and during the

Table 1. Serum and urinary concentrations of fluoride in patients with chronic renal failure (CRF), HF workers, and control group

Subject	No	Fluoride concentration (mean $\pm$ SD)	
		Serum (ppb)	Urine (ppm)
CRF	40	61.14 $\pm$ 26.44	0.47 $\pm$ 0.37
HF worker	120	40.10 $\pm$ 23.72	0.98 $\pm$ 0.75
Control	320	24.50 $\pm$ 12.10	0.54 $\pm$ 0.30

* $p < 0.001$ **Table 2. Urinary fluoride excretion (U-F) after oral administration of sodium fluoride with water loading**

Subject	Urinary fluoride excretion (μ g 24-hrs)				
	Base (1)	Total (2)	(2)-(1)	U-F/Dose %	24-hr urine ml
CRF	A 161	431	270	6.8	848
	B 448	672	244	6.1	2490
	C 379	587	208	5.2	1405
	D 73	346	273	6.8	803
	E 259	503	244	6.1	1082
Mean $\pm$ SD	264 $\pm$ 153*	507 $\pm$ 127*	248 $\pm$ 26.2*	6.2 $\pm$ 0.7*	1326 $\pm$ 693
Control	A 997	2913	1916	47.9	1690
	B 782	4047	3264	81.6	1908
	C 392	1581	1189	29.7	1154
	D 751	2383	1632	40.8	1708
	E 645	2409	1764	44.1	2477
Mean $\pm$ SD	714 $\pm$ 220	2667 $\pm$ 907	1953 $\pm$ 781	48.8 $\pm$ 19.5	1789 $\pm$ 476

* mean statistically different from control group at $p < 0.01$

experiments. In this Table, the base line value (1) was calculated from the urinary concentration of fluoride before the experiment and 24-hour urine volume. The total value (2) was calculated from the urinary concentrations of fluoride, at the abovementioned times during the experiments, and urine volumes. The excretion ratio of fluoride in the urine during the 24-hour period was calculated using the formula: $(2)-(1) \mu\text{g}/\text{dose} (4000 \mu\text{g}) \times 100$

As shown in Table 2, in patients with CRF, only 6.2% of the ingested fluoride was excreted in the urine during a 24-hour period. This was markedly lower than in control subjects (48.8%). In patients B and C, the 24-hour urine volumes showed reference range, however, urinary excretion of fluoride was also reduced.

The results of the clearance studies in the same patients with CRF and the control subjects at 2 hours after fluoride administration with water loading are shown in Table 3. Mean serum concentrations of fluoride in both groups were similar after 2 hours. On the other hand, urinary concentrations of fluoride at that time, urinary flow per minute, Ccr, C_F, F_F, and TrF in patients were markedly lower than control subjects.

Table 3. Clearance studies in patients with chronic renal failure (CRF) and control group

Subject	Sex	Age	S-F	U-F	Urine vol.	Ccr	C _F	E _F	TrF	
			($\mu\text{g/ml}$)	(ml/min)	($\text{ml/min}/1.48\text{ m}^2$)	($\mu\text{g/min}/1.48\text{ m}^2$)				
CRF	A	M	78	0.18	0.77	1.0	7.6	4.8	1.37	0.49
	B	F	64	0.13	0.56	0.3	10.0	1.4	1.30	0.18
	C	M	70	0.13	0.40	1.1	6.0	3.3	0.78	0.35
	D	F	40	0.14	0.64	1.2	8.7	6.1	1.22	0.36
	E	M	56	0.06	0.49	1.1	18.8	9.3	1.13	0.54
Mean $\pm$ SD			62 $\pm$ 15	0.1 $\pm$ 0.04	0.6 $\pm$ 0.14*	0.9 $\pm$ 0.4*	10.2 $\pm$ 5.02	5.0 $\pm$ 3.0*	1.2 $\pm$ 0.23*	0.4 $\pm$ 0.1
Control	A	M	34	0.19	4.49	1.9	84.2	40.4	16.00	8.44
	B	M	20	0.08	4.40	1.0	87.2	50.6	6.98	2.83
	C	M	29	0.14	2.09	3.8	77.6	58.2	10.86	2.75
	D	M	58	0.06	0.77	4.4	116.3	55.1	6.98	3.57
	E	M	57	0.17	5.18	1.7	91.2	55.6	15.50	6.06
Mean $\pm$ SD			40 $\pm$ 17	0.1 $\pm$ 0.06	3.4 $\pm$ 1.87	2.6 $\pm$ 1.5	91.3 $\pm$ 14.9	51.9 $\pm$ 7.0	11.3 $\pm$ 4.39	4.7 $\pm$ 2.5

* mean statistically different from control group at $p < 0.01$

Fig. 1. Correlation between creatinine and fluoride clearance

As shown in Figure 1, the clearances of fluoride and creatinine were well correlated ($r = +0.87$), with the fluoride clearance averaging 48% of the creatinine clearance. The fluoride clearance ranged from 20 to 70 $\text{ml/min}/1.48\text{ m}^2$ except when the creatinine clearance was very low.

The relationship between renal fluoride clearance and urinary diuresis is shown in Fig. 2. A high coefficient of correlation ($r = +0.86$) was also obtained in healthy subjects. However, the fluoride clearance did not increase with the elevation

Fig. 2. Relationship between fluoride clearance and urinary flow

of urinary flow in patients with CRF, and the coefficient of correlation was found to be low ($r = +0.28$).

DISCUSSION

The major pathway of fluoride elimination from the human body is via the kidney. Because fluoride has a short biological half-life, 40 to 70% of the ingested fluoride appears in the urine during a 24-hour period.^{1,12,13)} In this investigation, nearly 50% of the ingested fluoride was excreted in the urine during this period.

The findings of fluoride clearance from the serum by the kidney, which in these subjects averaged 48% of the creatinine clearance, is in agreement with the data of Waterhouse *et al.*¹²⁾ When the creatinine clearance fell below 25 ml/min/1.48 m², the fluoride clearance markedly decreased. This finding clearly indicates that the fluoride clearance is dependent on the glomerular filtration rate. There was a direct correlation of fluoride clearance with urinary flow. This relation has also been noted in the study by Ekstrand.²⁾ In present study, a high correlation was obtained between the fluoride clearance and urinary flow in health subjects, but the patients with CRF did not exhibit a proportional increases in fluoride clearance after the water loading. However, our data on this point are too limited to be conclusive.

Once renal function is severely impaired, the excretion of fluoride in the urine decreases and serum fluoride concentrations increases. Juncos and Donadio¹⁴⁾ reported two patients with a combination of renal insufficiency and systemic

fluorosis. The patients ingested a large amount of fluoride from their drinking and cooking water. In this study, a marked increase in serum fluoride but a normal range of urinary fluoride was observed in the patients with CRF. Three patients, who had been exposed to relatively low level of hydrofluoric acid in the work place, showed a clearly elevated level of serum fluoride compared to the other patients. Their urinary fluoride concentrations, however, remained within normal range. These findings indicated increased retention of fluoride in the body of patients with CRF, especially in those exposed to fluoride in a work place.

Fluoride concentration in urine had been recognized as a good index of fluoride exposure,⁶⁾ in the case of HF workers with diminished renal function, however, it is may not be adequate to only measure the urinary fluoride concentration. The frequent monitoring of serum fluoride also appear to be necessary as an indicator of fluoride excess.

Although the fluoridation of drinking water is not practiced in Japan, our results suggest that engagement in fluoride exposed work as well as the excessive intake of tea or marine products, which contain much fluoride, is contraindicated in persons who have clinical evidence of renal failure in order to prevent systemic fluoride poisoning.

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