Exposure to excessive fluoride during hemodialysis

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The safety of fluoridated community water supplies for dialysate and long-term intermittent hemodialysis has been questioned since 1965 [1]. The only significant means of clearing fluoride from body fluids are renal excretion and incorporation into bone [2]. When dialysate is prepared with fluoridated water, fluoride ion moves along a concentration gradient from dialysate to blood [3, 4]. Because renal excretion is defective or absent in such patients, the fluoride administered during dialysis is incorporated into the skeleton. Under these conditions, serum fluoride concentrations increase progressively, and the bone content of fluoride rises above values obtained in persons with normal renal function who drink water that is fluoridated [3–6] (the serum fluoride concentration in normal persons who drink water with a fluoride concentration of 53 μM [1 ppm] is 0.7 ± 0.4 μM [mean ± SD]). Although it has not been established that fluoridated dialysate adversely affects the bone of patients maintained by hemodialysis, this possibility exists, particularly in patients who have been exposed to such a dialysate for many years. This and other problems associated with various substances in tap water have made deionization of water used for dialysate a common practice. Unfortunately, if the deionizer is improperly maintained, the fluoride content of the water may actually increase as the deionizer becomes exhausted.

Methods and Results. To determine whether the excessive use of a deionizer could result in elution of retained fluoride, polystyrene tubing (224 mm long, 8 mm I.D.) was filled with resin taken from an ion exchanger (Illgo-Way) supplied by the Illinois Water Treatment Company, Rochester, Illinois. Tap water

with a fluoride concentration of 41 μM was made to flow by gravity through the resin. The cumulative volume of effluent was measured; the concentration of fluoride was measured by the modified diffusion technique; and fluorescence was determined with the Morin-Thorin reagent [7, 8].

Fluoride was eluted when the deionizer column was exhausted, after which the concentration of fluoride in the effluent became the same as in tap water (Fig. 1).

To determine the point at which elution of fluoride occurred with a commercial deionizer (Culligan) used for dialysis patients, fluoridated tap water was allowed to run through the deionizer until it became exhausted. Electric resistance of the effluent and the total dissolved solids, osmolality, pH and concentrations of calcium, magnesium and fluoride were measured at regular intervals. Results indicate that the concentration of fluoride increased abruptly when the resistance of the effluent was less than 80,000 ohms (Table 1). The concentrations of calcium and magnesium, however, did not exceed the concentrations of these substances in the tap water at any point. The peak concentration of fluoride in the effluent was approximately three times higher than that in the untreated tap water.

The practical consequence of this observation was possibly observed in the following patient: A 46-year-old man with bilateral polycystic renal disease was maintained by long-term intermittent hemodialysis. At first, a commercial water softener (Culligan), which provided fluoridated water, was used (1 ppm, 53 μM). The mean calcium concentration of the dialysate was 7.2 mg/100 ml, and the mean magnesium concentration was 1.6 mg/100 ml. Results of serial determinations of serum and dialysate concentrations of fluoride, calcium and magnesium; serum concentrations of phosphorus and alkaline phosphatase activity; and radioimmunoassays of parathyroid hormone concentrations are shown in Fig. 2.
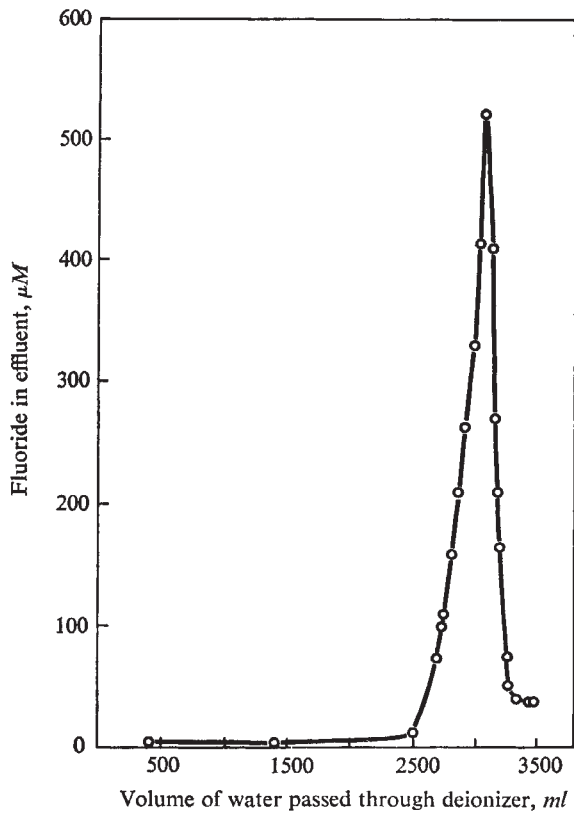
Fig. 1. *Fluoride concentration in the effluent from an ion-exchanger related to the volume of water which was passed through it.*

Fig. 2. *Serum and dialysate fluoride, calcium and magnesium concentrations and serum phosphorus, serum alkaline phosphatase activity, and radioimmunoassay values for serum parathyroid hormone in a patient exposed to fluoridated dialysate who subsequently received a renal allograft.*

Although the initial skeletal survey showed no evidence of bone disease, within a year after starting dialysis the patient complained of chest pain and pain in the feet, and the skeletal radiologic survey showed generalized demineralization and fractures of the fifth through the eighth ribs posteriorly, but no evidence of bone resorption. In spite of a good appetite and a good intake of food, his body weight decreased by 11 kg.
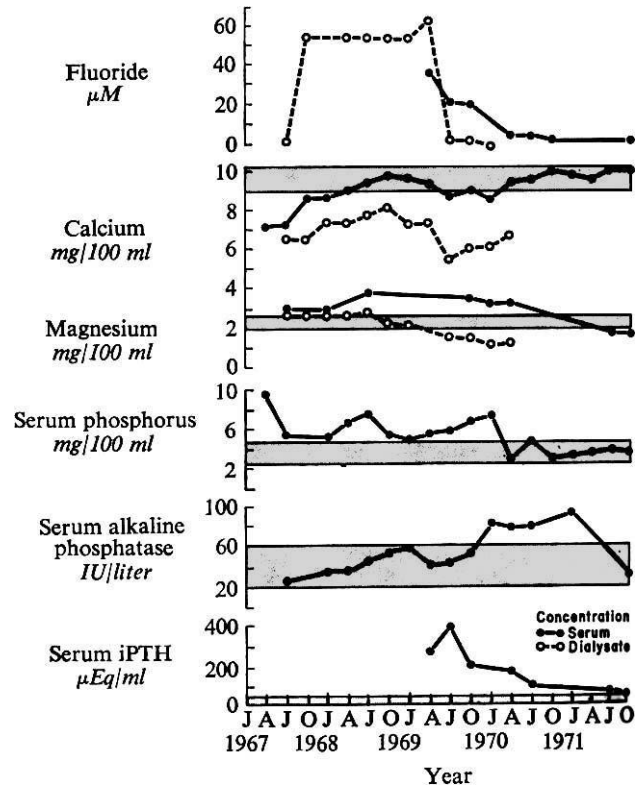
Because we had not seen such severe bone disease in a patient while on relatively high concentrations of dialysate calcium when fluoride-free dialysate had been employed, we recommended in October, 1968, that a commercial mixed-bed (Culligan) deionizer be installed to remove the fluoride. Repeated determinations of fluoride in the dialysate, however, showed

Table 1. Composition of effluent from deionizer

Resistance, ohms	Total dissolved solids, *ppm*	*mOsm/kg*	pH	Calcium, *mg/100 ml*	Magnesium, *mg/100 ml*	Fluoride, μM
1,000,000	0.75	0	7.6	0.01	0	0.1
200,000	2.00	0	8.0	0.02	0.01	1.2
100,000	8.00	1.0	6.1	0.03	0.04	5.4
80,000	10.00	1.0	6.1	0.04	0.05	7.9
40,000	25.00	4.0	5.2	0.08	0.14	22.9
20,000	38.00	—	5.4	0.12	0.21	112.3
10,000	100.00	7.5	6.1	0.20	0.37	230.0
5,000	210.00	10.0	6.7	0.62	0.77	152.0
0	310.00	12.0	7.1	1.56	2.22	113.5
Tap water						
Start	290.00	12.0	6.4	7.65	2.10	68.0
End	310.00	12.0	6.8	7.40	2.08	73.2

variable concentrations, the levels sometimes exceeding the concentration of fluoride in tap water (Fig. 2). Inspection of the apparatus indicated that because the conductivity meter was defective, the patient had been using the water meter to determine when the deionizer required regeneration (after approximately 5,000 gallons of water had been used). Although this practice did not result in dangerous elevations of calcium or magnesium in the dialysate, fluoride appeared to be eluted from the column when the resin was exhausted. In April, 1969, a new conductivity meter was installed, and the resin was regenerated when the conductivity of the water indicated a resistance of 80,000 ohms. Consequently, dialysate and serum fluoride concentrations decreased (Fig. 2).

Bone biopsy specimens of the iliac crest taken in April and three months later were examined by the microradiographic technique [9]. They showed severe osteomalacia, increased bone resorption and decreased bone formation. Bone resorption decreased and osteomalacia improved, coincident with the lowering of dialysate, serum and bone concentrations of fluoride. Bone fluoride decreased from 3.38 to 2.97 fluoride/calcium M% (normal, 0.5 to 1.0 M%).

In spite of this, the patient did not improve clinically. Since it seemed unlikely that sufficient fluoride could be removed by dialysis alone, it was decided to proceed with transplantation. During the interval between the preliminary nephrectomy and splenectomy and subsequent renal transplantation, he experienced a grand mal seizure and suffered additional fractures of the right fifth rib, the fifth lumbar vertebra and the right femoral neck. In February, 1970, renal transplantation was carried out successfully using a kidney from a sibling donor. Bone pain gradually subsided. The patient regained 21 kg of body weight, and serial roentgenograms showed remineralization of the skeleton and healing of the fractures.

Immediately after successful renal transplantation, the patient excreted 319 μmoles of fluoride in the urine per day, though there was no fluoride in his drinking water. After dismissal from the hospital, he returned to his community where the water was fluoridated. Two years later in February, 1972, the serum creatinine concentration was 1.35 mg/100 ml and the endogenous creatinine clearance, 84 ml/min/1.73 m². The serum fluoride concentration remained elevated to 2.6 μM, but urinary excretion of fluoride had decreased into the normal range of 62 μmoles/day.

Discussion. These data indicate that a patient maintained by hemodialysis in a community using fluoridated water may be exposed to a fluoride concentration higher than that present in tap water if the deionizer is allowed to become exhausted while the

patient is being dialyzed. The concentration reached 520 μM in the laboratory deionizer and 230 μM in the patient's model. Since the concentration of fluoride in blood returning from the dialyzer is about one-half to two-thirds that in the dialysate, the concentration could reach 150 μM in human serum. This would probably not be fatal inasmuch as concentrations of 500 to 1,400 μM are necessary to cause death of the rat or rabbit [11, 12]. Repeated exposures to excessive fluoride concentrations, however, could lead to saturation of the skeleton with fluoride and sustained elevation of serum fluoride to concentrations of more than 30 μM. Under these circumstances, loss of weight and disturbance of bone mineralization or other toxic effects could occur. The excessive amounts of osteoid seen in the bone biopsy specimen and the decrease in osteomalacia subsequent to correcting the deionizer operation are consistent with a fluoride effect. However, it is not necessary to prove that our patient was harmed by excessive concentrations of fluoride to make the point that unwarranted risks are taken when fluoride is allowed to accumulate in the deionizer and to elute during dialysis, and to suggest that there be a systematic check to guard against the use of a deionizer beyond its capacity.

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