

## THE EFFECT OF TETRACYCLINES ON THE MOBILIZATION OF FLUORIDE

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The teeth and the bone are the most important sites of fluoride accumulation in the body. The effect of tetracycline and oxytetracycline on the mobilization of fluoride from these sites was examined. Investigations of chronic exposure to fluoride were carried out on rabbits which received 20 mg of fluoride/kg body weight by oral administration daily for 30 days. The results indicate that tetracyclines induce mobilization of deposited fluoride.

Chronic exposure to fluoride causes an accumulation of fluoride in the bones and teeth in the form of fluoroapatite (1). It is readily apparent that fluoride penetration into the crystal structure of the hydroxyapatite lattice is a reversible process; fluoride is partly released from the sites of deposition and can be determined in the urine even after cessation of fluoride administration (2). Fluoride mobilization is thus a spontaneous process which is due to remodelling in mineralized tissues. A study (3) of fluoride uptake and elimination in rats demonstrated constant mobilization 2-3 months after fluoride exposure.

The ability of the skeleton to retain fluoride is of great importance, because it prevents harmful effects of fluorine ion on the organism (4). The presence of fluoride deposits in the body is a permanent source of risk because of possible rapid mobilization, increased concentration in the circulation, and subsequent toxic effects. On the other hand a slower, controlled mobilization could be usefully applied for safer removal or reduction of fluoride deposits.

Our previous experiments *in vitro* into the solubility of fluoroapatite (5) have shown that some substances and drugs have influence on the release of fluoride from its deposition sites. Among the substances that showed a marked effect were tetracyclines. In this study we used these antibiotics *in vivo*.

## MATERIAL AND METHOD

Experimental animals were female rabbits (*Oryctolagus cuniculus* - Belgian hare) seven months old and weighing 2.5-3.0 kg. They were placed into three groups of 8 rabbits each. The animals were fed a normal diet, and had free access to drinking water. They received a daily dose of 20 mg fluoride/kg body weight. Fluoride levels in the diet were low (45  $\mu\text{mol}$  per kg oats and 56  $\mu\text{mol}$  per kg hay). Drinking water contained fluoride in the amount of 5.26  $\mu\text{mol/L}$ . Aqueous solution of sodium fluoride was intubated daily, for 30 days.

The effect of two different tetracyclines on the mobilization of fluoride was examined three months after cessation of fluoride administration. One group of animals was treated with tetracycline and the other with oxytetracycline. Both tetracyclines were intubated as aqueous suspensions, 0.1 g/kg body weight, daily for 30 days. The animals exposed to fluoride but not treated with tetracyclines served as controls.

Fluoride concentration was measured in plasma and in 24-hour urine samples before treatment with antibiotic, and then once weekly during the treatment. The plasma samples were taken 60-90 minutes after tetracycline administration. Urine was collected during 24 hours after intubation of antibiotic in a volume of 50-70 millilitres. Fluoride content in the incisor teeth and femoral bones was determined before tetracycline administration, and at the end of it.

Fluoride analyses in all samples were carried out with an ion-selective electrode (6), in plasma and urine immediately after mixing with the TISAB-buffer in 1:1 ratio, and in the bones and teeth after fluoride separation by microdiffusion (7).

For each group the mean concentrations and the standard deviations were calculated. The significance of the difference between the means was estimated by Student's t-test.

## RESULTS

Results are presented in Tables 1-4. The treatment with tetracyclines did not change the plasma levels of fluoride to any significant extent (Table 1). The same treatment, however, induced increased urinary excretion of fluoride, compared with the controls (Table 2).

Tables 3 and 4 show changes in fluoride content in the teeth and bone which were induced by tetracyclines. Under given conditions of exposure, an accumulation of fluoride was observed in the teeth and in the bones. Tetracycline administration significantly reduced (43%) fluoride level in the teeth, whereas the decrease in the bones (7%), when compared to controls, was not significant.

Table 1.

*The effect of tetracyclines on fluoride levels in the plasma of rabbits pretreated with fluoride*

Days	Fluoride in plasma ( $\mu\text{mol/L}$ )		
	Control	Tetracycline	Oxytetracycline
0	10.00 $\pm$ 0.62*	10.00 $\pm$ 1.45	10.00 $\pm$ 1.56
7	10.00 $\pm$ 0.62	10.20 $\pm$ 1.75	10.52 $\pm$ 1.63
14	10.06 $\pm$ 1.45	10.32 $\pm$ 1.45	11.57 $\pm$ 1.53
22	10.15 $\pm$ 1.01	11.05 $\pm$ 1.82	11.57 $\pm$ 2.78
30	10.20 $\pm$ 1.18	11.05 $\pm$ 1.82	11.05 $\pm$ 2.06

\*Groups of 8 rabbits, mean  $\pm$  SD

Table 2.

*The effect of tetracyclines on urinary excretion of fluoride in rabbits pretreated with fluoride*

Days	Fluoride in urine ( $\mu\text{mol/L}$ )		
	Control	Tetracycline	Oxytetracycline
0	6.85 $\pm$ 0.80*	6.85 $\pm$ 0.80	6.85 $\pm$ 0.80
Weekly during the experiment	6.90 $\pm$ 1.22	11.86 $\pm$ 1.91**	12.04 $\pm$ 2.54**

\*Groups of 8 rabbits, mean  $\pm$  SD  
 \*\* P < 0.001

Table 3.

*The effect of tetracyclines on fluoride deposition in the bone*

Days	Fluoride in femurs (mmol/kg)		
	Control	Tetracycline	Oxytetracycline
0	200.00 $\pm$ 13.25*	200.00 $\pm$ 13.25	200.00 $\pm$ 13.25
30	198.94 $\pm$ 11.86	184.84 $\pm$ 10.48	184.73 $\pm$ 13.52

\*Groups of 8 rabbits, mean  $\pm$  SD



Table 4.

*The effect of tetracyclines on fluoride deposition in the teeth*

Days	Fluoride in plasma ( $\mu\text{mol/l}$ )		
	Control	Tetracycline	Oxytetracycline
0	118.42 $\pm$ 10.14*	118.42 $\pm$ 10.13	200.00 $\pm$ 13.25
30	107.89 $\pm$ 11.34	58.42 $\pm$ 10.56**	61.05 $\pm$ 9.96

\* Groups of 8 rabbits, mean  $\pm$  SD

\*\*  $P < 0.001$

#### DISCUSSION

The teeth and the bone are the most important deposits of fluoride in the body. Our previous experiment *in vitro* (5) showed that some substances, particularly tetracycline antibiotics caused dissolution of fluoroapatite. Further investigations (8) of chronic fluoride exposure carried out on rabbits, demonstrated that vitamin C (acidum ascorbinicum) and aspirin (acidum acetylsalicylicum) induced mobilization of fluoride from skeletal deposits. According to the results of the present study *in vivo* tetracyclines also induce mobilization of fluoride deposited in mineralized tissues. Tetracyclines were given three months after cessation of fluoride administration when, presumably, spontaneous elimination was constant (3). The tetracyclines are well known metal binding agents (9-11). Their binding ability was a most probably cause of fluoride mobilization from the bones and teeth in this investigation. Recent studies with other metal binding agents (12) have shown that these agents have the potential to redistribute metals within the body. In this study the tetracycline treatment significantly increased urinary fluoride excretion, whereas in mineralized tissues fluoride level decreased significantly only in the teeth but not in the bones. Different mechanisms controlling localization and concentration of tetracycline in different calcified tissues (13) could explain the observed difference in the degree of fluoride mobilization between the bones and the teeth. The increase in fluoride concentration in plasma during tetracycline administration was not significant, a fact of considerable importance for the therapy of fluorosis. The fact that both tetracyclines used in this study had the same effect on fluoride redistribution in the body showed the elementary structure of the tetracycline molecule to be responsible for the observed activity of these antibiotics.

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### Sažetak

#### UTICAJ TETRACIKLINA NA MOBILIZACIJU FLUORIDA

Zubi i kosti su najznačajniji depoi fluorida u organizmu. U ovom radu ispitivan je uticaj tetraciklina i oksitetraciklina na mobilizaciju deponovanih fluorida kod kunića hronično izloženih fluoridima. Intoksikacija je ostvarena oralnim unošenjem 20 mg fluorida/kg telesne mase, svakodnevno, tokom 30 dana. Dobijeni rezultati pokazuju da tetraciklini izazivaju mobilizaciju deponovanih fluorida.

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