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PRELIMINARY STUDIES OF THE CARIES INHIBITING POTENTIAL AND ACUTE TOXICITY OF SODIUM MONOFLUOROPHOSPHATE

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LITTLE is known concerning the forms in which fluorine may be administered to be effective against dental decay. All studies to date have dealt with compounds which dissociate to some extent in water to yield the fluoride ion. It was of interest, therefore, to test the ability to inhibit caries activity and the acute toxicity of a complex fluoride, monofluorophosphate, which does not yield fluoride ions in aqueous solution.

The sodium salt of monofluorophosphate used in this study may be characterized as follows:‡ It is soluble to the extent of about 25 Gm. in 100 Gm. of water at room temperature yielding a solution with a pH of 7.0 to 7.5. The salt yields the PO_3F^- ion which is stable at ordinary temperatures in neutral or slightly alkaline solutions. In acid solution the complex slowly hydrolyzes to orthophosphate and fluoride. The PO_3F^- ion does not give the analytical reactions of fluoride or of phosphate ions and gives few insoluble salts. The calcium salt, for example, has a solubility of about 1 Gm. per 100 Gm. of water at 20° C., a value several hundred times greater than the solubilities of calcium fluoride or calcium phosphate.

EFFECT OF SODIUM MONOFLUOROPHOSPHATE ON EXPERIMENTAL DENTAL CARIES IN SYRIAN HAMSTER

Experimental

Sixty Syrian hamsters (*Cricetus auratus*), 29 to 42 days of age from 11 litters, were divided by litter-mate distribution into 3 groups of 10 males and 10 females each. All groups received the same high carbohydrate caries-producing diet¹ ad libitum and were housed in screen bottom cages. The groups differed only in the drinking solutions supplied ad libitum:

Group I received distilled water; Group II received distilled water containing 40 ppm fluoride as sodium fluoride, and Group III received distilled water containing 40 ppm fluoride as sodium monofluorophosphate (303 ppm). In order to preclude the possible decomposition of the dilute solution of sodium monofluorophosphate, a 1.519 per cent stock solution was prepared and stored at 6° C. Every second day a 20 c.c. portion of this solution was diluted to 1,000 c.c. with distilled water and placed into cleaned drinking bottles of Group III. The duration of the experiment was 113 days.

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‡These data kindly supplied by the Research Laboratory of the Ozark-Mahoning Co. of Oklahoma.

Results

The average weights of the animals at the time of sacrifice were as follows:

GROUP	MALES	FEMALES
I (H ₂ O)	92	87
II (NaF)	89	87
III (Na ₂ PO ₃ F)	95	88

Three animals died during the course of the experiment; 2 in the male control group and 1 in the male sodium fluoride group. The cause of death was not ascertained.

No significant difference in gross appearance was noted among the animals of the various groups.

Table I gives in detail the caries experience of each of the animals. The data are summarized in Table II.

TABLE I
CARIES EXPERIENCE OF MALE AND FEMALE SYRIAN HAMSTERS DRINKING:
DISTILLED WATER, 40 PPM F FROM NEF, 40 PPM F FROM Na₂FPO₃

FEMALES					MALES				
NO.	MA*	CN†	AA‡	TS§	NO.	MA*	CN†	AA‡	TS§
<i>Control</i>									
23	11	21	14.0	30.8	2	12	16	29.3	78.5
17	12	20	6.5	13.0	43	12	17	26.0	60.8
6	10	14	6.5	9.5	57	1	1	0.3	0.3
9	12	20	10.3	16.5	22	11	16	37.3	92.8
1	8	8	3.8	8.3	50	8	13	18.8	40.0
49	6	7	4.8	9.8	15	8	9	17.8	47.0
26	12	21	21.8	45.8	37	10	17	31.3	86.0
45	11	16	19.5	44.3	34	11	16	47.5	102.3
55	7	12	8.3	21.3					
12	11	20	16.3	21.5					
Avg.	10.0	15.9	11.2	22.1	Avg.	9.1	13.1	26.0	63.4
<i>NaF</i>									
19	4	6	1.0	1.0	32	1	1	1.5	3.0
11	6	9	2.3	2.3	29	5	5	0.3	0.3
14	5	5	4.8	10.3	46	5	6	2.0	4.8
25	4	4	2.8	5.8	54	3	3	0.5	0.5
33	8	15	4.5	5.0	36	3	3	0.3	0.3
8	7	9	2.3	2.3	21	3	4	1.0	1.0
42	4	4	1.5	2.3	59	2	2	0.3	0.3
48	6	7	2.0	2.0	13	4	5	3.0	8.0
5	8	9	6.5	6.5	40	6	7	1.3	1.8
53	5	5	1.3	2.3					
Avg.	5.7	7.3	2.9	4.0	Avg.	3.5	4.0	1.2	2.2
<i>Na₂FPO₃</i>									
47	8	12	2.3	3.3	52	3	3	0.5	0.5
41	6	7	2.0	3.0	60	2	2	0.3	0.3
4	12	19	5.0	5.0	35	3	3	0.0	0.0
51	6	6	0.5	0.5	58	3	3	0.0	0.0
56	1	1	0.0	0.0	39	3	3	0.3	0.3
28	4	6	2.8	3.3	44	6	10	1.0	1.5
24	7	11	4.0	6.5	3	6	11	0.5	0.8
10	6	7	1.8	2.3	31	8	9	2.5	4.3
18	11	18	4.3	5.8	20	4	4	0.8	1.0
7	7	10	6.0	10.8	27	6	6	2.8	5.8
Avg.	6.8	9.7	2.9	4.0	Avg.	4.4	5.4	0.9	1.4

*Molars affected.

†Number of cavities.

‡Total area of teeth affected.

§Total caries score (area × depth).

TABLE II
AVERAGE CARIES EXPERIENCE OF ANIMALS DRINKING:
DISTILLED WATER, 40 PPM F FROM NaF, 40 PPM F FROM Na₂FPO₃

GROUP	NO. OF ANIMALS	MOLARS AFFECTED	NO. OF CAVITIES	AREA AFFECTED	TOTAL CARIES SCORE
Males					
I (H ₂ O)	8	9	13	26	63
II (NaF)	9	4	4	1	2
III (Na ₂ PO ₃ F)	10	4	5	1	1
Females					
I (H ₂ O)	10	10	16	11	22
II (NaF)	10	6	7	3	4
III (Na ₂ PO ₃ F)	10	7	10	3	4

In the females the number of molars affected and the number of cavities were reduced approximately 30 to 50 per cent by fluoride as sodium monofluorophosphate or sodium fluoride. In the same animals the total area of the teeth affected by caries and the total caries scores were reduced about 70 and 80 per cent, respectively, for both compounds.

The number of molars affected and the number of cavities was reduced in the male hamsters about 55 and 70 per cent, respectively, for both compounds, while the total area of the teeth affected and the total caries scores were reduced approximately 95 per cent.

Discussion

The close agreement of the final body weights and the absence of any obvious differences in appearance of the animals indicate that the materials in the concentration employed had no marked effect on the well-being of the animals.

It appears from the data on caries experience (Tables I and II) that the addition to the drinking water of 40 ppm of fluoride either as F⁻ or FPO₃⁻ will markedly decrease the destruction of tooth substance by caries in the Syrian hamster. The best quantitative expression of this difference in tooth destruction is obtained by contrasting the total caries scores. It will be seen that while the hamsters drinking water containing monofluorophosphate averaged total caries scores of 1.4 for males, 2.2 for females, and the males and females given NaF averaged 4, the control males and females averaged scores of 63 and 22, respectively. It is impossible to say from this work whether fluoride as monofluorophosphate is more effective than fluoride as sodium fluoride because the level of 40 ppm of fluoride employed gave very nearly maximal protection with each compound. By comparing the caries experience at lower fluoride concentrations any differences in potency against dental caries might appear.

A recalculation of the amount of fluoride administered as fluorophosphate based upon more exact data concerning the purity of the compound* indicates that a level of 39 ppm fluoride was obtained in the drinking water of the sodium monofluorophosphate group. Of the total 39 ppm, 7 ppm F were contributed by the 20 per cent of impurities contained in the test sample. How-

*Wayne E. White. Personal communication.

ever, the 7 ppm of fluoride contributed by the impurities would not, if given as NaF, have produced the caries reduction observed in these experiments.³

ACUTE TOXICITY OF SODIUM MONOFLUOROPHOSPHATE

Experimental

Intraperitoneal Injection.—One hundred and five albino rats weighing 200 to 300 grams were divided into 13 groups of from 5 to 15 animals. Graded doses of from 74 mg./kg. to 465 mg./kg. of sodium monofluorophosphate as a 5 per cent aqueous solution were administered intraperitoneally and the number dead in 24 hours noted. From these data the predicted LD50 was calculated by use of the Winthrop logarithmic-probit graph paper.⁴

Oral Administration.—Forty-five fasted albino rats weighing 200 to 300 grams were divided into 9 groups of 5 animals. Single doses of from 263 mg./kg. to 1323 mg./kg. of the 5 per cent aqueous solution were given by stomach tube. The percentage mortality observed in 24 hours was calculated and the predicted LD50 obtained by graphical analysis.

For comparison, the acute oral toxicity of sodium fluoride as a 2.5 per cent solution for 200-300 gram rats was also obtained. 98 rats were used and graded oral doses of from 22 to 288 mg./kg. were given in single injections by stomach tube.

Results

The predicted LD50 of sodium monofluorophosphate by intraperitoneal injection was found to be 220 ± 32 mg./kg.* Compared to the reported⁵ LD50 of 24 mg./kg. for sodium fluoride (as a 2 per cent aqueous solution) in 200 to 300 gram rats, sodium monofluorophosphate is about 8 to 9 times less toxic.

The predicted LD50's of sodium monofluorophosphate and sodium fluoride by oral administration were found to be 570 ± 68 mg./kg. and 80 ± 5 mg./kg., respectively. $\text{Na}_2\text{PO}_3\text{F}$ is one-eighth as toxic as NaF.

The results are summarized in Table III which contrasts the toxicities of sodium monofluorophosphates and sodium fluoride on both the basis of milligrams of compound per kilogram of body weight and milligrams of fluoride per kilogram of body weight.

TABLE III
ACUTE TOXICITY OF $\text{Na}_2\text{PO}_3\text{F}$ AND NaF IN 200 TO 300 GRAM RATS

DOSE	$\text{Na}_2\text{PO}_3\text{F}$ (MG./KG.)	NAF (MG./KG.)
Intraperitoneal LD50	220	24
Oral LD50	570	80
<i>On Basis of Fluoride Content</i>		
DOSE	F AS $\text{Na}_2\text{PO}_3\text{F}$ (MG./KG.)	F AS NAF (MG./KG.)
Intraperitoneal LD50	29	10
Oral LD50	75	32

Discussion

Sodium monofluorophosphate is considerably less toxic to rats than is sodium fluoride. On the basis of fluoride content, which is a more pertinent

*Standard error.

comparison for dental purposes, the complex fluoride apparently is 2.5 to 3 times less toxic than the free ionic form indicating that neither in the tissue fluids (intraperitoneal injection) nor in the gastrointestinal tract (oral dose) is the complex appreciably hydrolyzed.

CONCLUSIONS

When administered at a level of 40 ppm of fluoride in the drinking water of Syrian hamsters, sodium monofluorophosphate and sodium fluoride caused comparable and nearly maximal reductions in the destruction of tooth substance by dental decay.

Sodium monofluorophosphate was found to be 7 to 8 times less toxic in 200 to 300 gram rats than was sodium fluoride. Calculated on the basis of fluoride content the complex fluoride is 2.5 to 3 times less toxic than the free ionic form.

In view of the fact that the monofluorophosphate complex was apparently not appreciably hydrolyzed in the animal body, one may infer that fluorine does not have to be in a free ionic form to inhibit dental decay in the Syrian hamster.

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