Intra-oral Effects on Acid-softened Enamel of NaF Lozenges Administered in Divided Daily Doses

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The purpose of this investigation was to study the intra-oral effects of multiple daily applications of NaF lozenges upon acid-softened enamel. Bovine enamel slabs were softened with 0.1 mol/L lactate buffer at pH 4.0 for 14 hrs and subsequently mounted in a mandibular removable Hawley appliance. Control slabs were worn for seven days by eight adult male subjects who brushed their natural dentition daily with a fluoride-free dentifrice. Test slabs were exposed to one 0.55-mg NaF lozenge (0.25 mg F) 4x/day for seven days and the natural dentition brushed with a fluoride-free dentifrice. The efficacy of 0.25-mg F lozenges used 4x/day over that of a 1-mg F lozenge administered 1x/day was established by a pilot study with two subjects. Microhardness testing was performed after intra-oral exposure (IOE) and following immersion in 0.01 mol/L lactate buffer containing Ca and PO_4 for 24 hrs at a pH of 4.0. Fluoride uptake was measured on separate control and test slabs after KOH wash and after acid-resistance-testing (ART). Recovery of microhardness following IOE was 40.9% for controls and 53.9% for treated slabs, while control slabs retained 1.3% resistance to ART, compared with 25.6% for test slabs. The F content of the control slabs was significantly less than that of lozenge-treated and lozenge-treated-ART slabs throughout the depth of the lesion. The F content of the lozenge-treated-ART slabs was significantly less than that of the lozenge-treated slabs only at the 0-5-μm depth. The NaF lozenge-treated enamel lesions demonstrated both significantly greater rehardening and F uptake than did the untreated control enamel lesions.

J Dent Res 66(5):1020–1024, May, 1987

Introduction.

Dietary fluoride supplements have caused significant anticaries effects in young children living in fluoride-deficient areas (Margolis *et al.*, 1975; Marthaler, 1969; Aasenden and Peebles, 1974). Such supplements are marketed commercially as chewable tablets, lozenges, and swish-and-swallow mouthrinses, which are consumed daily in dosages adjusted to existing suboptimal fluoride levels in the drinking water. The use of fluoride supplements causes prolonged elevation of salivary F levels (Parkins, 1971), an elevation which provides not only a topical effect to erupted teeth by direct contact with enamel (Lemke *et al.*, 1970) but also, upon ingestion, incorporation into the enamel of unerupted teeth (Ahrens, 1976).

As the benefits of fluorides have been more extensively investigated, it has become increasingly clear that the resultant reduction in caries is due, in part, to the remineralization of incipient caries (Koulourides *et al.*, 1974; Grøn, 1977; Mellberg and Ripa, 1983). The process of remineralization appears to be facilitated by the frequent repetitive use of fluoride agents of low concentration for prolonged periods (Arends and Gelhard, 1983; Ostrom *et al.*, 1984; Featherstone *et al.*, 1982; Silverstone, 1985), conditions fulfilled by the use of fluoride lozenges, especially when administered in divided daily doses. Clark *et al.* (1986a) demonstrated significant *in vivo* rehardening of demineralized enamel following the use of 0.5-mg F lozenges administered four times daily, but that total dosage was in excess of the total daily dose recommended for young children.

It was our purpose to study the intra-oral rehardening of demineralized bovine enamel with a 0.25-mg F lozenge used four times daily, which represents the total daily dose recommended by the Council on Dental Therapeutics of the American Dental Association (Accepted Dental Therapeutics, 1984) for children three years of age or older and living in fluoride-free areas.

Materials and methods.

Enamel slabs (3 × 3 × 2 mm) were cut from the labial surfaces of bovine permanent incisors and mounted on acrylic disks by means of sticky wax. Using a paralleling device, we removed approximately 50 to 100 μm of the surface enamel by polishing to a smooth flat surface with wet emery paper (240-, 400-, and 600-mesh) (Koulourides *et al.*, 1976).

Following exposure to 1% ethylene oxide vapor for eight hrs, each slab was demineralized by exposure to 20 mL of 0.1 mol/L lactic acid for 14 hrs at 37°C. The acid solution contained 1% sodium carboxymethylcellulose with 3 mmol/L calcium and 1.8 mmol/L phosphate and the pH adjusted to 4.0.

Removable mandibular acrylic appliances were fabricated for eight healthy male subjects, ages from 25 to 55 yrs (Zimmermann *et al.*, 1985). Recesses large enough to accommodate up to 16 slabs each were cut into the right and left sides of each appliance. Sixteen pre-softened slabs were mounted lingually on each side of the appliance, with sticky wax used to seal the lateral borders of the slabs and create a smooth contour for comfort while the appliance was being worn. Thirty-two control slabs were worn for seven days by each subject, 16 of which were used for microhardness-testing and 16 for fluoride analysis. Thirty-two slabs were used initially for the experimental phase with NaF lozenges (16 for microhardness, 16 for fluoride uptake). An additional 16 slabs were treated with the same NaF lozenge regimen, and those slabs were subsequently subjected to *in vitro* acid exposure prior to analysis for F content. The location of individual slabs in the appliance was recorded for each subject in all phases of the experiment so that we could determine site-to-site variations. The appliance was worn continuously by each test subject except at mealtimes. All subjects gently cleansed the enamel slabs with moistened cotton swabs and brushed the natural dentition with a fluoride-free dentifrice (Pepsodent, Lever Brothers Co., NY) 4x/day during both control and experimental periods.

Each subject ingested a single 0.55-mg NaF (0.25 mg F) lozenge (Luride Lozi Tabs, Hoyt Laboratories, Needham, MA) 4x/day during the seven-day experimental phase. The lozenge was placed on the tongue and dissolved slowly in the saliva which was swished and ultimately swallowed. The ingestion of each lozenge followed the four daily brushings (*i.e.*, following regular meals and at bedtime) for seven consecutive

Received for publication June 27, 1986
Accepted for publication November 4, 1986
This investigation was supported in part by USPHS Grant DE-02371 from the National Institute of Dental Research.

days. All slabs were worn for approximately eight hrs after the last lozenge was administered.

A Tukon Microhardness Tester (Wilson Instrument Division, Bridgeport, CT) with a pyramidal diamond indenter and a 500-g load was used to determine microhardness values of all slabs at four different times: (1) prior to acid-softening, (2) following acid-softening, (3) following intra-oral exposure (IOE), and (4) following acid-resistance-testing (ART). Each prior set of measurements was re-measured for assurance that no changes in lengths of previous indentations had occurred.

Acid-resistance-testing was performed by immersion of each slab in 20 mL of 0.01 mol/L lactic acid-sodium hydroxide buffer (pH 4.0), containing 1% sodium carboxymethylcellulose with 3 mmol/L calcium and 1.8 mmol/L phosphate, at 37°C for 24 hrs. The percentage changes in microhardness following both IOE and ART were calculated by the method described by Gelhard *et al.* (1979). Paired *t* tests were performed so that we could test differences in IOE and ART values between control and test slabs.

Prior to the initiation of the present study, we performed a pilot study to compare the effects of a 1-mg F lozenge used 1x/day with those of the same total amount (1 mg F) applied in four equally divided doses (0.25 mg F) for a period of seven consecutive days. Two subjects (A and B), who demonstrated in previous studies their consistent ability for intra-oral rehardening of demineralized bovine enamel (Corpron *et al.*, 1986a; Clark *et al.*, 1986a; Clark *et al.*, 1986b), wore 16 acid-softened bovine enamel slabs for each period for controls, 1-mg F lozenges used 1x/day, and 0.25-mg F lozenges used 4x/day for seven consecutive days, as described in previous paragraphs. Microhardness-testing was performed and IOE% and ART% calculated for determination of the more effective experimental regimen to be subsequently utilized in the expanded study using the eight subjects.

Those slabs to be analyzed for fluoride content following intra-oral exposure were removed from the appliance, cleansed with a cotton swab and distilled water, and glued on the end of a plastic rod (0.64 cm in diameter). The lateral borders were sealed with blue inlay wax, and the slabs were immersed in 0.5 mL of 1.0 mol/L KOH for 24 hrs at room temperature so that the alkali-soluble fluoride would be removed from the surface (Caslavska *et al.*, 1975). These vials were retained for fluoride analysis of the KOH wash, to which 0.5 mL of 1 mol/L HNO_3 and 0.5 mL of modified TISAB II were added prior to fluoride analysis (deBruyn *et al.*, 1985). Sixteen additional experimental slabs were immersed for 24 hrs in KOH following IOE and subsequently exposed to *in vitro* acid-resistance-testing prior to fluoride analysis.

Five layers were removed from the 3 × 3 mm enamel surface by being immersed in separate vials containing 1.0 mL of 0.5 mol/L perchloric acid for 15, 30, 30, 60, and 60 sec. The specimens were rotated at 100 rpm for a standard agitation. The slabs were rinsed with 1 mL of total ionic strength adjusted buffer (modified TISAB II), and dried with a cotton pellet which was added to the vial after each etch. The modified TISAB II (CDTA, Orion Research, Inc., Cambridge, MA) was prepared by combining 100 mL of TISAB II with 15 mL of 1 mol/L NaOH at pH of 5.6. The fluoride concentration was determined directly by means of an Orion Ion Analyzer 901 (Orion Research, Inc., Cambridge, MA) equipped with a fluoride-ion specific electrode (Orion 96-09). The 901 Analyzer was first calibrated with standard fluoride solutions diluted with TISAB II to the same dilution factor as that of the unknown samples. Phosphate concentrations were determined by spectrophotometry by means of the method of Gee *et al.* (1954).

The depth of enamel removed by each etch was calculated from the etched area of enamel (3 × 3 mm) and the amount of phosphate in the aliquots. The phosphate content of bovine enamel was assumed to be 51.2% and the mineral density 2.88 g/cm (Davidson *et al.*, 1976). This density value, and therefore the calculations, were approximations, since the density after partial intra-oral remineralization was not known. However, this procedure provided a convenient means of presenting the F levels in enamel, assuming that the error in enamel density was similar in both regimens.

In order to describe the overall relationship between the depth (μm) and the fluoride content (ppm) for control, F-lozenge-treated, and F-lozenge-ART-treated slabs, we calculated the $\overline{X}$ ± SEM for F content and recorded it in ppm for the approximate midpoint of 5-μm intervals from 0-50 μm and of 10-μm intervals from 50-100 μm from the enamel surface. In order to describe the relationship of the F uptake to depth (μm) of enamel for controls and each set of test slabs, we used the analysis of variance for differences in mean F content among the three sets of slabs for each depth. Modified *t* tests incorporating Bonferroni's correction were used to compare each pair of means when the overall analysis of variance proved significant. Pearson's product-moment correlation coefficient was used to examine relationships between IOE and ART values and between control and treated specimens.

Results.

Microhardness.—Values for $\overline{X}$ ± SD for the two subjects (A and B) involved in the pilot study for the IOE% and ART% were 52.52 ± 4.18 and 28.28 ± 4.74, respectively, for the 1-mg F lozenge ingested 1x/day, as compared with 62.35 ± 0.26 and 33.82 ± 2.78 for the respective IOE% and ART% values when the 0.25-mg F lozenges were used 4x/day. The values for the regimen utilizing the divided dosages were significantly higher ($p < 0.05$) than respective values for the single 1-mg F lozenge. Such differences provided the basis for using the divided doses for the expanded study using the eight subjects.

Values for $\overline{X}$ ± SD for the eight subjects (A-H) for depth of penetration (μm) of the microhardness indenter are shown for control (Table 1) and F-treated slabs (Table 2). These values include the microhardness measurements following: (a) abrasion and polishing, (b) acid-softening, (c) post-IOE, and (d) post-ART. The percentage changes in microhardness appear in Table 3.

The measurement of prior indentations revealed no changes in length of indentation, indicating that the integrity of the surface layer was maintained throughout acid-softening, IOE, and ART procedures.

TABLE 1
MICROHARDNESS VALUES FOR CONTROL GROUP
(depth of indenter penetration in μm)

Subject	Sound Enamel	Post-softened	Post-IOE	Post-ART
A	5.56	17.31	11.55	15.80
B	5.48	14.46	10.02	14.16
C	5.51	16.47	11.15	15.71
D	5.50	13.35	10.67	14.22
E	5.48	14.01	11.25	14.10
F	5.50	17.85	12.43	15.86
G	5.47	18.35	13.71	20.12
H	5.58	14.70	11.62	14.95
$\overline{X}$	5.51	15.81	11.55	15.62
(± SD)	(±0.04)	(±1.79)	(±1.05)	(±1.84)

TABLE 2
MICROHARDNESS VALUES FOR EXPERIMENTAL GROUP
(depth of indenter penetration in μm)

Subject	Sound Enamel	Post-softened	Post-IOE	Post-ART
A	5.52	17.35	10.01	13.02
B	5.50	18.08	11.29	14.11
C	5.50	15.26	9.15	12.23
D	5.54	15.32	8.98	12.38
E	5.50	17.67	10.27	14.20
F	5.46	17.62	11.70	14.74
G	5.56	17.39	13.57	15.79
H	5.49	15.33	10.80	14.41
$\overline{X}$	5.51	16.75	10.72	13.86
(± SD)	(±0.03)	(±1.14)	(±1.40)	(+1.15)

TABLE 3
REHARDENING VALUES (PERCENTAGE RECOVERY)
(listed by descending Lozenge-ART values)

Subject	Seven-day Lozenge		Seven-day Control	
(N=8)	Post-IOE	Post-ART	Post-IOE	Post-ART
A	62.09	36.60	49.00	12.84
B	53.99	31.58	49.44	3.34
C	62.60	31.04	48.54	6.93
D	64.79	30.08	34.10	−11.12
E	60.81	28.51	32.36	−1.06
F	48.69	23.68	43.89	16.11
G	32.28	13.55	36.08	−13.76
H	46.05	9.38	33.73	−2.72
$\overline{X}$	53.91*	25.55*	40.89	1.32
(± SD)	(±11.12)	(±9.46)	(±7.56)	(±10.63)

*Significant difference from controls ($p<0.05$).
└┘ Significant difference between IOE and ART ($p<0.05$).

The lozenge-treated slabs developed a significantly higher rehardening (53.9%) following IOE, compared with controls (40.9%, $p<0.05$). More significantly, the lozenge-treated slabs retained approximately one-half of their rehardening (25.6%) following ART compared with controls, which lost virtually all of their rehardening (1.3%) following ART ($p<0.05$).

A direct correlation was found between the mean values for %IOE and %ART for lozenge-treated slabs ($r = 0.72$) and between control %IOE and %ART values ($r = 0.82$). Conversely, there was no significant correlation between the control and treatment ART values, nor between control and treatment IOE values.

There was no consistent site-to-site variation of microhardness of slabs in any of the subjects.

Fluoride uptake. — The mean values and standard error of the means (SEM) for F content of control and lozenge-treated slabs are shown in the Fig.

There was a significant difference ($p<0.05$ using Bonferroni's correction) in fluoride content between control and both test groups when the three groups were compared by analysis of variance at each depth. Pairwise Student's t tests demonstrated that a significant difference ($p<0.05$ using Bonferroni's correction) in fluoride content existed at all depths of enamel when the control slabs were compared separately with each of the experimentally treated slabs.

In comparing the two groups of experimentally treated slabs, we found that there was no consistent difference ($p>0.05$ using Bonferroni's correction) in fluoride content between the slabs exposed to acid and KOH and those exposed only to KOH,

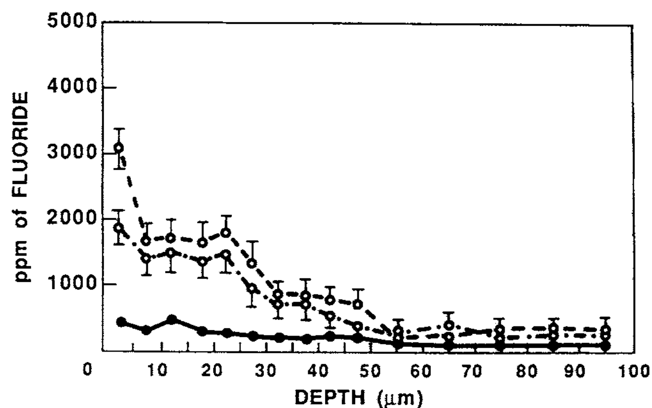

Fig. — Fluoride concentration (ppm) *vs.* depth (μm) from the enamel surface. Control (o——o); Lozenge - KOH (o - - - - o); Lozenge KOH-ART (o · · · · · o). SEM (Φ)

except at the most superficial depth considered (*i.e.*, from 0 to 5 μm).

Similar to the absence of site-to-site variation in the microhardness values, there was no consistent site-to-site variation in fluoride uptake.

The mean values for the alkali-soluble F content of the KOH washes were 0.31 ± 0.18 μg/cm for the control slabs and 0.83 ± 0.54 μg/cm for the treated slabs.

Discussion.

There exists considerable clinical evidence of anticaries effects following the consumption of dietary F supplements (Bibby *et al.*, 1955; Arnold *et al.*, 1960; DePaola and Lax, 1968; Marthaler, 1969; Hennon *et al.*, 1967; Aasenden and Peebles, 1974; Driscoll *et al.*, 1977; Margolis *et al.*, 1975), but the cariostatic mechanisms involved are not completely understood. There is general agreement that the ingestion of fluoride supplements leads to incorporation of fluoride ions into developing enamel (Ahrens, 1976), and supplements such as fluoride lozenges, designed to dissolve slowly in the oral cavity, cause elevated salivary F levels (Parkins, 1971; Graf and Mühlemann, 1969; McCall *et al.*, 1981), providing a topical effect upon the enamel surfaces of erupted teeth (Torell, 1965; Lemke *et al.*, 1970). This effect by topical fluoride agents during the post-eruptive period has led investigators to conclude that the resultant reduction in decay was due, in part, to the remineralization of existing incipient enamel caries (Koulourides *et al.*, 1976; Grøn, 1977; Mellberg and Ripa, 1983).

Enamel remineralization is considered to be a natural phenomenon which depends upon the degree of saturation of saliva with respect to fluorapatite (FAP) and/or hydroxyapatite (HAP) (Ericsson, 1949; McCann, 1968). The degree of saturation depends upon the pH and the concentration of calcium, phosphate, and fluoride ions in the saliva, and it appears that low levels of fluoride in saliva can effectively stimulate remineralization (Arends and Gelhard, 1983; Featherstone, 1983). On the other hand, high fluoride levels (*i.e.*, 1.23% APF) cause formation of CaF_2 on the surface of the enamel (Larsen *et al.*, 1981), which can initially block or retard remineralization (Bodde and Arends, 1980). Remineralization, therefore, appears to be promoted by the frequent, repetitive use of topical agents containing low levels of fluoride used for prolonged periods, the concept which influenced the design of the current study.

Since it is desirable for children who live in fluoride-deficient areas to be provided with the same cariostatic benefits

attained by those living in fluoridated areas (Arnold *et al.*, 1960; Aasenden and Peebles, 1974; Margolis *et al.*, 1975), dietary F supplements in the form of lozenges offer the potential of both protection for developing teeth and remineralization of incipient enamel lesions in erupted teeth. It was previously demonstrated that F lozenges (0.50 mg F administered 4x/day) could cause significant rehardening in demineralized enamel in adults (Clark *et al.*, 1986a), but the total dose of 2 mg F/day is excessive in children. In this study, the use of 1 mg F/day in four equally divided doses provided repetitive, frequent, low doses which could be effective in both children and adults without exceeding the maximum daily dose for children. Additionally, the slow dissolution of the lozenge should prolong the direct exposure of the enamel surface to the elevated salivary F levels (McCall *et al.*, 1981; Graf and Mühlemann, 1969). The results of rehardening due to the use of a single 1-mg lozenge 1x/day, compared with the same amount administered in four equally divided daily doses (0.25 mg F), obtained in the pilot portion of this study supported the concept of the greater efficacy of frequent divided daily doses, compared with that of the same total dose applied at one time, in the remineralization of demineralized enamel.

The results of this study provide additional information regarding the mechanisms of rehardening of demineralized enamel by means of F lozenges, but the results obtained on pre-softened bovine enamel in a removable appliance cannot be directly equated with those benefits which would be received by natural white-spot lesions in human teeth.

Following intra-oral exposure to the F lozenge, KOH washes were used to ensure the removal of alkali-soluble F (*i.e.*, CaF_2) which might have formed on the surface of the enamel (Caslavska *et al.*, 1975). When the KOH washes from test slabs were analyzed for F, no appreciable amount was found, demonstrating that deposition of CaF_2 was not a factor in the rehardening following the dissolution of the F lozenge. The significantly greater microhardness and increased F content in the treated enamel slabs after IOE, as compared with those of controls, illustrate that the differences were caused by increased deposition of stable F compounds, such as FAP and/or FHAP (Hercules and Craig, 1968). These mineral compounds provided significant protection to the enamel from the *in vitro* acid exposure (Table 3). It appears that only the outermost portion of the surface layer (from 0 to 5 μm) experienced significant loss of F following ART, demonstrating that the outer F-rich surface layer protected the deeper areas of the lesion from acid attack. Conversely, the control slabs re-softened after ART to almost the original post-softening values (Table 3), due to the uniformly low levels of F throughout the depth of the lesion (Fig.).

The variability of rehardening of enamel lesions in our subjects (Table 3) supports similar observations by Featherstone *et al.* (1982) and the findings of our previous studies using other topical F agents (Corpron *et al.*, 1986a; Clark *et al.*, 1986a). However, there appeared to be some consistency for each individual's ability to reharden enamel lesions and the ability of the newly rehardened lesions to resist subsequent acid attack (ART).

Weatherell *et al.* (1984) studied the migration of fluoride in the oral cavity following the dissolution of a 1-mg F tablet placed asymmetrically in the mandibular buccal sulcus. Their analyses indicated that relatively little transfer from the site of dissolution occurred to the opposite side of the mouth. In an additional study using a F mouthrinse, Weatherell *et al.* (1986) observed a rapid clearance of F from beneath the tongue following the use of the mouthrinse. In the present study, we observed no consistent site-to-site variation in rehardening, suggesting that the slow dissolution of the lozenge on the dorsal or ventral surface of the tongue allowed for prolonged contact of the salivary F with the sublingually placed enamel slabs, especially since the subjects were encouraged to recirculate the saliva instead of swallowing immediately during dissolution of the lozenge.

Although currently not widely advocated, the use of divided doses of dietary F lozenges appears to fulfill the requirements for remineralizing action of the lozenges. Dividing the daily dose into four lozenges each containing 0.25 mg F means more frequent application of a smaller dose than the normal application of the individual 1.0-mg F lozenge once per day. Compliance of the divided doses could easily become a problem over extended periods, possibly limiting the use of divided doses to the periods of peak caries activity or for special patients.

Acknowledgments.

The authors gratefully acknowledge the technical assistance of Patricia Landry, and Betty Christopherson's help in preparation of the manuscript.

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