



## Enamel uptake and patient exposure to fluoride: comparison of APF gel and foam

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### Abstract

*This crossover study with 46 child dental patients compared two topical APF products, a gel and a foam, with respect to the amounts of product and fluoride (F) applied, salivary F concentrations, and enamel F uptake. Half the subjects were treated for 4 min with the gel first and the other half with the foam. After approximately 16 days, each patient received a second treatment using the other product. An acid-etch enamel biopsy was performed and whole saliva samples were collected before and after each treatment. Significantly less F was applied to the teeth and retained by the subjects when the APF foam was used. Salivary F concentrations after treatment with the gel were higher than after treatment with the foam. The differences in enamel F uptake at both 15 min and 16 days after the APF applications, however, were not significant. We concluded that: 1) the two products are equivalent with respect to enamel F uptake; 2) only about one-fifth as much of the foam product is required for adequate coverage of the teeth, which significantly reduces F exposure and retention by the patient. (Pediatr Dent 17:199–203, 1995)*

**A**cidulated phosphate fluoride (APF) solutions and gels have been shown to be effective cariostatic agents.<sup>1,2</sup> These products contain sodium fluoride and phosphoric acid. The concentration of F in most APF products is 1.23% (12,300 ppm) and the pH is typically in the range of 3–4, which is close to the  $pK_a$  of hydrofluoric acid (HF). Thus, approximately one-half of the F is ionic and the remainder is HF which — as will be discussed later — is a potent gastric irritant.

Several studies have shown that substantial amounts of F are ingested following APF gel treatments and that high plasma and urinary F concentrations may ensue.<sup>3–5</sup> One study reported plasma levels that are known to interfere transiently with the ability of the kidney to concentrate the urine.<sup>3</sup> Other reports have indicated that unwanted effects, chiefly nausea and vomiting, are not uncommon during or after APF gel treatment.<sup>6–8</sup>

Concerns about safety and patient acceptance have led to recommendations designed to minimize systemic F exposure either by lowering the F concentration<sup>9</sup> or by refining the application technique.<sup>10,11</sup> Another approach is represented by a new APF product dispensed as a foam. The product has the same F concentration and pH as conventional gels but, because it is a foam, smaller amounts of the product are required to adequately fill the trays, thus exposing the patient to less F.<sup>12</sup> The results of an in vitro study<sup>13</sup> that compared APF foam with APF gel indicated that there was little difference in the amounts of F deposited on the enamel but there are no published data from clinical studies on this subject. This study was done to partially fill this gap in our knowledge and to provide additional information concerning the relative amounts of F retained by the patients.

### Methods and materials

The test materials were Topical Fluoride Foam® (Lot No. 921201, Laclede Research Laboratories, Gardena, CA) and NuPro® APF Gel (Lot No. 1J1156P, Johnson & Johnson Co, New Brunswick, NJ). The F concentrations of the products were stated to be 1.23% (12,300 ppm). The criterion for use of the products was that the F concentrations be within 5% of the stated values, i.e., 1.17 to 1.29%.

Forty-six healthy participants, ranging in age from 8 to 12 years, were recruited from the patient population of the Department of Pediatric Dentistry at the Medical College of Georgia (MCG), Augusta, Georgia, where the clinical procedures were done. The mean ( $\pm$ SE) age of the female subjects ( $N = 18$ ) and was  $9.89 \pm 0.36$  years and male subjects ( $N = 28$ ) was  $9.86 \pm 0.28$  years. Each subject and a parent or guardian signed the informed consent form, which had been approved by the MCG Human Assurance Committee.

The criteria for inclusion of a subject in the study were: 1) the maxillary central incisors must be fully erupted and free of clinically detectable caries; 2) the

normal number of teeth must be present according to the child's age; and 3) an APF gel or foam treatment must not have been done within the preceding 14 days.

The teeth were cleaned using a nonfluoride prophylaxis paste applied with a rubber cup mounted on a slow-speed handpiece. The absence of F in the paste was confirmed by chemical analysis. A control whole saliva sample (ca 1–2 mL) was collected in a 50-mL plastic vessel while the subject chewed a small piece of wax (Parafilm®, American Can Co, Greenwich, CT). A control acid-etch enamel biopsy then was performed as described below.

An amount of the APF gel or foam product sufficient to fill hinged, maxillary, and mandibular foam stock trays (Centwins, medium [Oral-B Laboratories, Redwood City, CA]) to approximately one-third of their capacity was placed in the trays. The net weights of the products placed in the trays were recorded to the nearest 0.01 g. The trays then were placed over the teeth and the subject was instructed to close the jaws with the trays in contact for 4 min. During this time, the child was seated in an upright position with the head inclined forward and downward to minimize swallowing. The child was instructed not to swallow but to allow the saliva to drool into a 400-mL plastic beaker held directly under the mouth. At the end of the topical treatment, the trays were removed from the mouth and placed in the same beaker. The child then expectorated once into a separate 50-mL plastic vessel and then continued expectorating the remaining mixture of saliva and APF product into the 400-mL beaker for 30 sec. Ten minutes after removing the trays from the mouth, a third whole saliva sample was collected in a separate, preweighed 50-mL vessel for 2 min while the subject chewed Parafilm. Fifteen minutes after removing the trays from the mouth, a second acid-etch enamel biopsy was performed. The child then was dismissed from the clinic.

Each child received two topical APF treatments, once with the Laclede foam and once with the NuPro gel. The treatments were separated by an average ( $\pm$  SE) of  $16.28 \pm 0.58$  days. Half the subjects were treated with the foam product first and the others with the gel product first. The order in which the products were used was determined by coin toss at the beginning of the first visit.

The maxillary central incisor to be biopsied at the first clinic visit was selected randomly by coin toss. The contralateral central incisor was biopsied at the second clinic visit. While the child was lying in the supine position, the tooth was dried with a sterile gauze sponge and an air stream. A strip of nonwetable adhesive tape (3M Co, #471) with a hole (2.2 mm diameter) punched in its center was burnished onto the tooth. For the control acid-etch biopsy, the hole was located in the middle third of the longitudinal aspect of the tooth to the right of the tooth midline. For the post-treatment biopsy, the hole was located in the middle third of the longitudinal aspect of the same tooth to the left of the midline.

The enamel biopsy was done by placing 5.0  $\mu$ L of 0.5 N perchloric acid on the enamel demarcated by the hole in the tape. The acid was dispensed using a fixed volume pipettor (5.00  $\mu$ L) and nonwetable plastic tips. As the tape and enamel surface were not wettable, the acid drop was a hemisphere. After 15 sec, the acid was removed by drawing it back into the plastic tip and was placed in a plastic microbeaker containing 50  $\mu$ L of Total Ionic Strength Adjustment Buffer (TISAB). Two separate rinses of the biopsy site, each using 5.0  $\mu$ L of 0.25 N NaOH, then were done to neutralize and permit collection of any remaining acid. The NaOH rinses were added to the same microbeaker.

The biopsy solution was analyzed for F and calcium. The mass of enamel biopsied was calculated based on the assumption that enamel is 37% calcium by weight. The depth of the biopsy was calculated based on the assumptions that the density of enamel is 2.95 and that the geometry of the biopsied site was a cylinder.<sup>14</sup> The equations used were:

$$\text{Mass of enamel biopsied} = \frac{\text{Mass of Ca biopsied}}{0.37}$$

$$\text{Depth of biopsy} = \frac{\text{Mass of enamel biopsied}}{(\text{Density of enamel}) (\text{Biopsy surface area})}$$

The weight of F applied for each topical treatment was calculated by multiplying the F concentration of the foam or gel by its weight. After 50  $\mu$ L of the saliva-and-APF foam or gel mixture (collected immediately after the 4-min treatment) were removed for F analysis, the remaining mixture was transferred with multiple distilled water rinses to the 400-mL beaker containing the drool and stock trays. Any APF foam or gel adhering to the trays was collected in the beaker using a forceful stream of distilled water. The total volume was then adjusted to 400 mL with distilled water. The solution was swirled using a spin bar and magnetic stirrer until no traces of the foam or gel were visible. The solution then was analyzed for F. The total amount of F recovered from the mouth was calculated as the product of the concentration and volume. The weight of F retained was calculated by subtracting the weight recovered from the weight applied.

The chemical analyses were done in a "blind" manner, i.e., the analyst was unaware of the subject's identity and whether the samples were associated with the foam or gel. F was analyzed using the ion-specific electrode (Model 9409, Orion Research) and a miniature calomel reference electrode coupled to a potentiometer. The F concentrations of the test products were determined after making a 1:1000 dilution with distilled water. Prior to analysis, all standards and samples were buffered by the addition of an appropriate volume of TISAB to adjust the pH (5.0) and ionic strength of the standards and samples to the same values. Calcium in the acid-etch biopsy solution was determined using flame atomic absorption spectroscopy (Varian Spectra 20, Varian Sugarland, TX).

**TABLE 1. WEIGHTS OF THE APF PRODUCTS AND FLUORIDE APPLIED AND OF FLUORIDE RETAINED BY THE SUBJECTS**

	<i>Product Applied (g)</i>	<i>F Applied (mg)</i>	<i>F Retained (mg)</i>
Laclede Foam	0.89 ± 0.02 (46)	10.72 ± 0.20 (46)	1.24 ± 0.10 (40)
NuPro Gel	3.86 ± 0.06 (46)	48.18 ± 0.75 (46)	6.95 ± 0.77 (40)
<i>P value</i>	0.0001	0.0001	0.0001

Data expressed as mean ± SE (N).

**TABLE 2. SURFACE ENAMEL FLUORIDE CONCENTRATIONS BEFORE AND 15 MIN AFTER TOPICAL APF TREATMENTS AND NET CONCENTRATION INCREASES**

	<i>Enamel [F] Before APF Treatment</i>	<i>Enamel [F] After APF Treatment</i>	<i>Net Increase in Enamel [F]</i>
Laclede Foam	2909* ± 179 (46)	6834 ± 315 (46)	3925 ± 290 (46)
NuPro Gel	2615 ± 134 (46)	6520 ± 407 (46)	3905 ± 413 (46)
<i>P Value</i>	0.107	0.397	0.959

\* Unit: ppm. Data expressed as mean ± SE (N).

The data are expressed as mean ± SE (N). The standard error (SE) is related to the standard deviation by the square root of the sample size (N) and was selected as the means to express the data, because it is the value directly used to determine statistically significant differences among groups. An alpha of 0.05 was selected a priori as the indicator for statistical significance. The data were analyzed for statistically significant differences using repeated measures analysis of variance (ANOVA) and *t*-tests where appropriate.

## Results

The F concentrations of the Laclede Topical Fluoride Foam and the NuPro APF Gel were 12,047 ppm and 12,469 ppm, respectively. These concentrations were within the required, specified range of 12,300 ± 615 ppm.

The weights of the products and F applied to the subjects' teeth are shown in Table 1. Also shown are the weights of F that were retained (not recovered from the mouth) by the subjects. All these variables were significantly smaller when the foam product was used.

Table 2 shows the F concentrations in the surface enamel immediately before and 15 min after the APF treatments and the net increases in the F concentrations. The data were tested for statistically significant differences using repeated measures ANOVA. The enamel F concentrations of the two groups, both before and after the APF treatments, did not differ with statistical significance. The average concentration after the use of the each product, however, was significantly higher than the control concentration ( $P < 0.0001$ ). The av-

erage net increases in enamel F concentration after the use of the foam and gel were 3925 ppm and 3905 ppm, respectively. The difference between these values was not statistically significant. The ANOVA also included a test for the order in which the products were used in this crossover study. The order effect was not significant ( $P > 0.6$ ).

Table 3 shows the depths of the enamel acid-etch biopsy sites. Neither the depths of the control biopsy sites nor the after-treatment biopsy sites differed with statistical significance. It was noteworthy, however, that the depth of the after-treatment site was significantly less than that of the control site for each product. The alpha value for the foam was 0.030 and for the gel product was 0.041.

Table 4 shows the F concentrations of the whole saliva samples. The "control saliva" samples were taken a few minutes before the first acid-etch enamel biopsy; the "saliva/APF" samples were taken immediately after the 4-min APF treatment; the "post-treatment saliva" samples were taken 10 min after the APF treatment. The difference between the F concentrations of the control saliva samples was not statistically significant, but the differences between the mean values of the samples collected immediately after and 10 min after the APF treatments were significant. The F concentration of the saliva/APF sample after using the gel was 2.5 times that observed after using the foam.

**TABLE 3. DEPTHS OF ENAMEL ACID-ETCH BIOPSY SITES BEFORE AND 15 MIN AFTER TOPICAL APF TREATMENTS**

	<i>Depth of Etch Before APF Treatment</i>	<i>Depth of Etch After APF Treatment</i>
Laclede Foam	2.86* ± 0.13 (46)	2.47 ± 0.13 (46)
NuPro Gel	2.92 ± 0.10 (46)	2.63 ± 0.11 (46)
<i>P Value</i>	0.712	0.280

\* Unit: μm. Data expressed as mean ± SE (N).

**TABLE 4. WHOLE SALIVA FLUORIDE CONCENTRATIONS BEFORE, IMMEDIATELY AFTER, AND 10 MIN AFTER THE TOPICAL APF TREATMENTS**

	<i>Control Saliva</i>	<i>Saliva/APF</i>	<i>Post-treatment Saliva</i>
Laclede Foam	0.116* ± 0.013 (46)	1469 ± 152 (45)	22.4 ± 2.3 (44)
NuPro Gel	0.137 ± 0.019 (46)	3646 ± 258 (45)	31.0 ± 3.4 (44)
<i>P value</i>	0.372	0.0001	0.005

\* Unit: ppm. Data expressed as mean ± SE (N).

## Discussion

This comparative clinical study with Laclede's foam and NuPro APF gel was designed to determine:

1. The amounts of product and F used when the trays were filled sufficiently to provide adequate coverage of the teeth
2. The amounts of F retained (not recovered from the mouth) after the APF treatments
3. The F concentrations in whole saliva
4. The uptake of F by enamel.

The first three purposes were of interest because of the long-standing concern about the potentially excessive exposure to F associated with 1.23% (12,300 ppm) APF gel treatments.<sup>3, 10, 12, 15</sup> Each gram of such a gel contains 12.3 mg of F. When stock trays are used, between 2 and 4 g of product are typically placed in each tray, which introduces between 49 and 98 mg of F into the patient's mouth.<sup>16</sup> The pH of the APF products is approximately 3.4, which is the  $pK_a$  of hydrofluoric acid, HF. Thus, one-half of the F in the products exists as HF, the chemical form of F, which has been shown to cause structural and functional damage to the gastric mucosa of laboratory animals.<sup>17-21</sup> HF also is believed to be the chemical form responsible for the nausea and vomiting experienced by some dental patients during or shortly after treatment with 1.23% APF gels.<sup>6-8</sup> The fourth purpose was of interest because, even if the patient were exposed to less F by using the foam product, this benefit could be offset if less F were deposited on the enamel.

Visual inspection after positioning the trays over the teeth revealed that trays filled to about one-third of their depth allowed the foam or gel product to cover the teeth without flowing into the vestibules. This loading procedure was used consistently throughout the study and resulted in the use of  $0.89 \pm 0.02$  g of the foam product ( $10.72 \pm 0.20$  mg of F) and  $3.86 \pm 0.06$  g of the gel product ( $48.18 \pm 0.75$  mg of F; Table 1). The amounts of F not recovered from the mouth were  $1.24 \pm 0.10$  mg for the foam and  $6.95 \pm 0.77$  mg for the gel. Compared with the gel, the foam product required only 23% as much material by weight and exposed the patients to only 22% as much F. In terms of reducing patient exposure to F, therefore, the foam product was found to offer a significant advantage. Wei and Chik<sup>12</sup> also compared F retention by child dental patients treated with the same APF foam and gel and reached the same conclusion.

The F concentrations of whole saliva were determined and used as an additional indicator of the amount of F potentially available for ingestion. The data in Table 4 are consistent with the facts that more F was introduced into the mouth with the gel product and that more was retained subsequently. The weights of saliva expectorated during the timed, 2.0-min collections starting 10 min after the use of the foam and gel were  $2.73 \pm 0.19$  and  $2.83 \pm 0.25$  g, respectively. Therefore, the significant difference between the F concentrations of the post-

treatment samples was not explained by a difference in salivary flow but, instead, was due to more F remaining in the mouth after using the gel product.

As shown in Table 2, the average enamel F concentrations after using the foam was 6834 ppm and after the gel was 6520 ppm. The average net increases in enamel fluoride concentrations were 3925 and 3905 ppm, respectively. These data indicate that the two APF products were equivalent in terms of their abilities to deposit F on the enamel surface.

The enamel F concentrations determined before and after the APF treatments in this study were similar to those reported by Wei and Hattab<sup>13</sup> who determined F uptake by human premolars in vitro after 4-min treatments with the same products that were used in our study. After the treatments, the teeth were washed for 1.5 min with water and then biopsied using 0.5 M perchloric acid for 15 sec, as was done in our study. They reported control and post-treatment F concentrations very similar to those contained in this report. They reported net F uptake values of 3446 ppm after treatment with foam and 4565 ppm after treatment with gel, values also similar to those shown in Table 2.

One additional point about our study should be made. The depth-of-etch data were determined because enamel F concentrations decline sharply from the surface to approximately 100  $\mu$ m beneath the surface. When comparing enamel F concentrations as a result of different treatments, therefore, it is important to know that the depths of the acid-etch biopsy sites were similar. As shown in Table 3, the difference between the depth values was not statistically significant either before or after the APF treatments. This indicates that the enamel F concentrations and the net F uptake data were not influenced by this variable.

## Conclusions

Based on the results of this study, two major conclusions can be drawn:

1. Compared with the gel product, exposure to and retention of F by the patient are significantly less when the foam product is used.
2. The two products are equivalent in terms of their abilities to deposit F on the enamel. Thus, the use of the APF foam can be expected to provide a greater margin of safety and increased patient acceptance.

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