



Assessment of the Influence of Meal Type on Fluoride Absorption due to Ingestion of professionally Applied Gels

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ABSTRACT

Aims: The aim of this study is to assess the influence of eating, prior to application of professionally used gels, on the rate of fluoride absorption due to the ingestion of 1.23% acidulated phosphate fluoride (APF).

Materials and methods: After fasting for 12 hours, 16 adult volunteers (>65 kg) ingested two types of meal: Breakfast (n=8) and Lunch (n=8). Accidental ingestion of fluoride gel used in molding trays was simulated (12,300 ppm; 61.5 mg F; pH=4.65) 15 minutes after eating. After ingestion of the fluoride solution, 3 mL of venous blood were collected at the following times: Zero (before ingestion) and 15, 30, 45 minutes, 1, 2, and 3 hours. Fluoride concentrations in blood plasma were determined using an ion selective electrode.

Results: With the exception of time 0 ($p > 0.05$), the average blood plasma concentration of the breakfast group (BG) (0.34 ± 0.04 mg/L) was higher than that of the lunch group (LG) (0.24 ± 0.03 mg/L), with the moment of peak concentration being 2 hours after ingestion for both groups (BG=0.4 mg/L; LG=0.28 mg/L).

Conclusion: Results reinforce the idea that eating before undergoing professional application of fluoride is a factor of extreme importance regarding its safety, and that the time following a patient's heaviest meal should be the time of choice for planning clinical care.

Clinical significance: Our results should be considered when planning collective action that involves the application of the

gel on children in a school environment, thus ensuring the procedure's safety.

Keywords: Children, Clinical trial, Fluoride, Safety, Topical fluoride gel.

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INTRODUCTION

Fluoride gel is one of the most widely used professional dental products in clinical practice, having been endorsed for use on individual and collective levels by the National Oral Health Policy and by international associations, such as the American Dental Association and the American Academy of Pediatric Dentistry, and its clinical efficiency has been demonstrated in controlled studies.¹⁻⁶

Its clinical use is important for treating tooth decay; however, it may pose risks when accidentally ingested due to the high concentration of fluoride in products used professionally.^{5,7} In this regard, knowledge of the ion's mechanism of action and its toxic levels on the human body is essential for the safe handling of these compounds.^{6,8}

High-concentration products can be safely used with the following recommendations, such as using the minimum amount needed to cover the teeth, vertical position during application, using a suction system throughout the procedure, and expectoration for 30 seconds afterwards.⁹ There is little or no danger of systemic toxicity when products containing fluoride are used as recommended; however, these products are sometimes ingested in excessive quantities.^{9,10}

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An acute dose of fluoride that may cause systemic toxicity is 5 mg/kg.^{9,11,12} Reports of acute intoxication due to ingestion of dental products are more common in young children and in children less than 6 years old. A potentially toxic dose may be attained due to their low average body weight, taking into account the concentration of the product used and the amount ingested, among other factors that influence absorption, such as stomach contents.^{7,9,10,13-18}

The influence of eating before the use of fluorinated compounds has been assessed in previous studies, which evaluated the use of products with low fluoride concentrations, such as toothpastes and fluoride tablets, and have indicated that eating beforehand reduces fluoride absorption by 19% when the compounds are ingested after breakfast and by around 33% after lunch.^{11,18-20}

No studies were found in the literatures that assess the effects of stomach contents on the absorption of fluoride arising from the ingestion of professionally used products with high fluoride concentrations. The ingestion of fluoride gel after application, assuming removal or nonremoval of any excess with gauze, was assessed in just one study in which volunteers had fasted, and showed that this clinical precaution significantly reduced patients' chances of nephrotoxicity, as the peak blood plasma concentrations of fluoride ions varied between 330 and 2,180 ng/mL when the excess was not removed.²¹

Cases of severe systemic toxicity and death due to acute exposure are rare nowadays; however, the occurrence of toxic signs and symptoms are more frequent, with gastric symptoms, such as nausea, vomiting, and diarrhea being reported.⁹ In this sense, knowledge of the influence of meal type on fluoride absorption when high-concentration products are used may contribute to forming a basis for safety recommendations regarding the use of professional fluoride products.

MATERIALS AND METHODS

The study was approved by the Research Ethics Committee at the São Leopoldo Mandic School of Dentistry, Campinas, São Paulo, under opinion no. 542.807/2013.

Sample Selection

All participants, residents of the same town (Balsas, Maranhão, Brazil; which does not add fluoride to its public water supply) and weighing at least 65 kg, received information regarding the nature and details of the study and gave written informed consent. The size of the sample was based on previous studies that used similar methodology.^{18,20,22}

Composition: Cellulose gum, glycerin, Malva sylvestris extract, silica, sodium benzoate, sodium lauroyl sarcosinate, sorbitol, sucralose, xylitol, aroma, CI 54530, and water

Sixteen (n=16) adult volunteers (between 18 and 42 years of age, 4 females and 12 males) participated in this study, which was analyzed and approved by the Research Ethics Committee at the São Leopoldo Mandic School of Dentistry.

Volunteers underwent medical examinations and reported in their medical histories that they did not have heart, liver, or kidney problems and were not using any medication.

Stage of Preparation of the Participants

The volunteers were instructed not to use fluoride solutions in the 7 days prior to the commencement of the study, and to use the nonfluoride toothpastes provided by the researcher (Malvatrikids Baby*; Laboratório Daudt Oliveira Ltda.).

All the stages of the study were carried out in clinical laboratories, with volunteers being assured supervision by the researcher and medical assistance if necessary. During the experimental phase (3 hours), volunteers could not eat or ingest any kind of liquid.

Initial Procedures

Drawn at random, the volunteers were split into two study groups according to the two different meal types: Breakfast Group (BG; n=8) and Lunch Group (LG; n=8).

After fasting for 12 hours, the volunteers simultaneously received meals based on those normally consumed in Brazil,¹⁸ in accordance with the study group into which they were sorted:

- BG: French bread with 10 gm of margarine and 200 mL of coffee with milk (1:3);
- LG: Rice (170 gm), meat and potatoes (160 gm), and a lettuce, cucumber, and tomato salad (60 gm).

Fifteen minutes after the meals, a solution containing 5 mL of acidulated phosphate fluoride (APF) gel (12,300 ppm; pH=4.65; 61.5 mgF) diluted in 10 mL of distilled water was ingested by all the volunteers, simulating the accidental ingestion of the suggested amount for professional application of fluoride gel with molding trays.²³

Collection and Analysis of Fluoride in the Volunteers' Blood Plasma

After ingesting the solution containing fluoride, 3 mL of venous blood were collected from each volunteer at the following times: 0 (before ingestion of the solution containing fluoride), 15, 30, 45 minutes, 1, 2, and 3 hours. Samples were then centrifuged at 16,000 rpm for 10 minutes. The plasma was separated and kept refrigerated (between 2 and 8°C) awaiting analysis.^{18,20}

Fluoride concentrations in blood plasma were blindly and simultaneously determined for each volunteer and each measurement, 3 hours after the last blood sample collection, using an ion selective electrode.^{11,21,24}

For potentiometric determination of the ions, calibration curves were drawn, using standard samples of sodium fluoride solution with concentrations varying from 0.05 to 0.5 ppm F, using a NaF solution at 1,000 ppm F as the initial baseline. One milliliter of plasma was then added to one milliliter of buffer solution and the samples were then divided.²⁵

At the end of the study, bottles of Simeco plus (Laboratórios Supera Farma), containing aluminum hydroxide (120 mg/mL), magnesium hydroxide (60 mg/mL), and simethicone (7 mg/mL) were given to the volunteers to alleviate potential gastric symptoms. Of the 16 volunteers, seven reported of having used them.

Statistical and Pharmacokinetic Analysis

Computer software (PK Solutions, Summit Research Services, Montrose, CO, USA) was used to obtain the following parameters: C_{max} : maximum concentration observed during the 3-hour study period; T_{max} : the time at which C_{max} occurred; and AUC0-3: the area beneath the blood plasma concentration time curve from 0 to 3 hours.

Inferential methods were applied after the assessment of the data regarding fluoride concentration over time, maximum fluoride concentration, time of maximum fluoride concentration, and area beneath the curve, to check if they satisfied the assumptions of normality and homogeneity of variance. For data regarding fluoride concentration over time, the two-factor repeated measures, analysis of variance (ANOVA) and a Tukey test, were carried out to separate the interaction. For the response variables, such as maximum concentration and area under the curve, unpaired Student's t-test was used. For data regarding maximum concentration time, the nonparametric Mann-Whitney U test was used, due to heterogeneity of variance. Statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) version 20 software, at a 5% significance level.

RESULTS

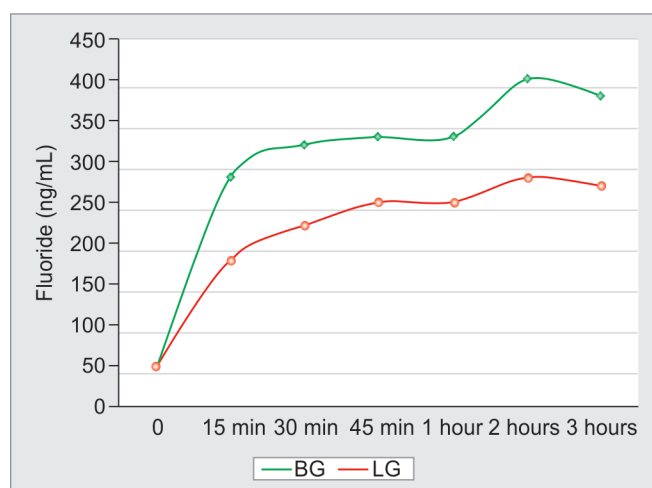
Table 1 shows, for both groups, the relationship between the quantity of fluoride ion ingested (61.5 mg) by volunteers' body weight.

Concentration of Fluoride in the Blood and Peak Absorption Time

One of the two-factor repeated measures, ANOVA, applied to the data on fluoride concentration over time, indicated significant interaction between the type of meal

Table 1: Relationship between volunteers' body weight and proportion of fluoride ion ingested

Volunteer	BG		Volunteer	LG	
	Body weight (kg)	F/kg		Body weight (kg)	F/kg
1	75.0	1.22	6	75.4	1.23
2	74.8	1.22	7	73.9	1.20
3	89.0	1.45	8	72.0	1.17
4	74.0	1.20	9	74.0	1.20
5	71.0	1.15	10	70.4	1.14
11	65.5	1.07	12	68.0	1.11
13	75.8	1.23	15	76.9	1.25
14	82.6	1.34	16	79.3	1.29
BG average	76.0	1.24	LG average	73.7	1.20



Graph 1: Concentrations of fluoride in blood plasma, measured in ng/mL, at the times of observation, for each study group

and the time elapsed after ingesting the gel ($p < 0.001$), with a statistical power of 0.997. Using the Tukey test, it was found that, with the exception of time 0, at which point there was no significant difference between the fluoride concentrations measured in the volunteers' blood plasma, fluoride concentration was, at all times, significantly higher in the BG, and was remaining so even after 3 hours ingestion (Graph 1).

Note that the time of maximum fluoride concentration in blood plasma (peak concentration) was not influenced by stomach content, as for both groups peak concentration was observed 2 hours after eating (Mann-Whitney U-test: $p = 0.674$).

Area Beneath the Blood–Time Concentration Curve

The areas beneath the plasma concentration curves were calculated for each volunteer, taking into account the initial observation up until the final observation (last quantifiable concentration). The difference found in the

area beneath the curve (BG = 61.69 ± 0.42 $\mu\text{g}\cdot\text{min}/\text{mL}$; LG = 44.25 ± 0.73 $\mu\text{g}\cdot\text{min}/\text{mL}$) was significantly higher for the BG (Student's *t*-test, $p < 0.001$). The reduction in fluoride absorption as a function of meal type was approximately 28.3%.

DISCUSSION

The application of fluoride gel is a simple, practical method that is well accepted and is of low cost, with strong evidence of its inhibitory effects on tooth decay.^{4,26,27} It is considered a safe method with regard to acute toxicity, and the currently recommended procedure for professional application of APF gel minimizes the amount likely to be swallowed, minimizing the risk of even temporary stomach irritation.^{4,23,28}

Professional application of fluoride gel is rarely performed on 1-year olds, but it is recommended for 2-year olds (average weight of 12.4 kg). In these situations, if the molding trays are filled with the recommended limit of 5 mL, then the potentially toxic dose in the eventuality of ingesting all the gel may be exceeded, causing at worst an upset stomach.⁹

In this study, the inclusion of healthy people with a minimum weight of 65 kg ensures complete safety for the volunteers, as the doses ingested were five times less than the potentially toxic dose. On the other hand, studies show that young animals are more resistant to the toxic effects of fluoride than adult animals, due to the higher rate of fluoride incorporation in the bones of the former, whose loosely organized and uncompressed bone crystals provide a much larger surface area for quick absorption of the ion.⁹ In this sense, the volunteers were under medical supervision throughout the study period and, although they reported nausea and abdominal discomfort, these symptoms were similar to those reported by participants in studies where the ingestion of toothpastes and residue of 1.3% acidulated fluoride gel was assessed.^{21,26,29} No volunteers abandoned the experiment or needed medical assistance during the study.

The assessment of fluoride absorption via blood plasma analysis enabled this study to indicate more sensitive results, as the pharmacokinetic curve of fluoride in saliva and in blood plasma has a ratio of 0.63:1.^{25,30-32}

Dental surgeons must possess an adequate knowledge of the safety limits when performing high-concentration professional fluorotherapy.^{4,26} Its effects depend on stomach contents, and thus being important to monitor the period of time in order to reduce risks in case of accidental ingestion during professional fluoride application.

The means used in similar studies include a solution of fluoridated toothpaste containing 550 and 1,100 ppm of

fluoride and 1.3% acidulated fluoride gel, with regard to parameters related to nephrotoxicity.^{18,21} No experiments were found in the literature that have determined fluoride absorption as a function of stomach contents, assuming the occurrence of accidental ingestion of gel during professional application.

A previous study involving the ingestion of residual fluoride gel after application, asking volunteers either to spit out or not to spit out the excess gel, showed higher blood plasma concentration values than those found in the present study. This is because the amount applied was 60% higher and, unlike the present study, volunteers were still fasting when the gel was applied.²¹ Eating prior to fully ingesting the gel ensured that, at no time during the study did blood levels indicate subclinical toxicity (> 950 ng/mL).³³ Only at the 2-hour mark did the BG show a value slightly higher (400 ng/mL) than that related to nephrotoxicity (380 ng/mL), which was offset by the fact that these values, which would have been adverse if maintained for more than 18 hours, were maintained for a short period of time.³⁴

The type of meal did not influence the time of maximum fluoride concentration in blood plasma, which was 2 hours after eating, for both groups. This is probably due to the fact that the time of complete gastric emptying for liquids with low osmotic pressure is 2 hours.^{21,35,36} The difference was that, in the present study, peak concentration occurred after 2 hours, whereas in similar studies that involved APF gel and fasting volunteers, peak concentration occurred between 30 to 60 minutes.²¹

At time 0, there was no difference in blood plasma fluoride concentration between volunteers from either group, which indicates that the volunteers' preparation was effective and the groups were homogenous regarding the parameters assessed. At the other times of observation, fluoride absorption was always higher in the BG, as can be observed in the literature concerning toothpaste ingestion.¹⁸

The reduction of fluoride absorption as a function of meal type was approximately 28.3% for the "lunch" meal type. Similar results were observed when comparing the bioavailability of ingested fluoride, in humans, in the form of NaF tablets (2.21 mg) taken together with milk.¹⁹

Note that between 30 to 60 minutes after ingestion of the gel, blood plasma concentration in both groups remained constant and increased at the next point of observation. For the LG, at no time during the analysis was blood plasma concentration higher than that of the BG, suggesting that topical application of fluoride should be carried out up to 2 hours after heavy meals, because of the fact that the increase in concentration is related to gastric emptying.

It is worth noting that the meals offered to the volunteers, although typically consumed in Brazil, are

not equivalent to meals eaten by a young child. Thus, the application of high-concentration products should follow all the recommendations already pointed out in the present study.

Therefore, this study reinforces the recommendation that high-concentration fluoride application should be performed only on individuals who have recently eaten, and its results should be considered when planning collective action that involves the application of the gel on children in a school environment, thus ensuring the procedure's safety.

CONCLUSION

Eating prior to the professional application of fluoride does influence fluoride absorption rates, thus being a factor of extreme importance, as it ensures the safety of the procedure even in cases of accidental ingestion. The period following the heaviest meal should be chosen when planning clinical care.

CLINICAL SIGNIFICANCE

Results reinforce the idea that eating before undergoing professional application of fluoride is a factor of extreme importance regarding its safety, and that the time following a patient's heaviest meal should be the time of choice for planning clinical care. Our results should always be considered when planning collective action that involves the application of the gel on children in a school environment; thus ensuring the procedure's safety.

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