International Journal of Paediatric Dentistry 2006; **16:** 174–180

Erosive effect of an antihistamine-containing syrup on primary enamel and its reduction by fluoride dentifrice

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Summary. *Aim.* This study evaluated the action of an antihistamine-containing syrup (Claritin D) on enamel that was subsequently submitted or not to applications of fluoride dentifrice.

Methods. Two hundred sixty-four slices ($n = 44$ per subgroup) prepared from exfoliated primary molars were evaluated in hardness tests. Six subgroups were submitted to different treatments for 10 days. The controls underwent pH cycling with (positive control) or without (negative control) three daily immersions in fluoride dentifrice/distilled water slurry. The test subgroups related to daytime use of the antihistamine syrup underwent pH cycling and two 5-min applications of Claritin D, coupled or not to the three daily immersions in the fluoride slurry. The subgroups related to nocturnal use of the syrup were submitted to the same procedures of daytime subgroups, respectively, but with one of the applications of Claritin D lasting for 8 h.

Results. The median hardness values obtained after use of the syrup were significantly lower than the initial ones. Equivalent values for subgroups submitted to fluoride applications in addition to treatment with the syrup were significantly higher.

Conclusion. It was concluded that the antihistamine-containing syrup reduced the hardness of primary enamel and that, in this experiment, the use of fluoride dentifrice was able to diminish this erosive effect.

Introduction

Dental caries is the most prevalent disease of the oral cavity and may affect individuals at any stage of their lives. Nevertheless, tooth dissolution can also be caused by erosion, which is the mineral loss of dental tissue when its surface is exposed to acids or chelates, in a systematic manner and without bacterial involvement [1].

According to Linnett and Seow [2], the prevalence of dental erosion has increased especially among children and adolescents. The aetiology has been related to the regular use of products with low endogenous pH, high acidity, and absence or low concentrations of ions including those of calcium, fluoride, and phosphate in their composition. Among these products are medications that may be erosive because they possess these characteristics, and which may be of a particular risk when used for treatment of chronic diseases. Antihistamine-containing medicines may be an example of a potentially erosive agent.

Besides the acid components found in such medications, other factors such as high frequency of ingestion (two or more times a day), bedtime consumption, high viscosity, and the collateral effect of a reduction in salivary flow may contribute to the risk for dental erosion [2,3].

Many recommendations have been made in order to minimize tooth damage caused by the regular use of liquid medications. Among these is the use of the medication at meal times in order to avoid ingestion between them [4]. Oral hygiene or mouth rinsing with water or chewing sugar-free gum after taking the medication have also been recommended [3], as have the addition of calcium, fluoride, or phosphate to formulations [3] and the use of topical fluoride agents [4].

Although the efficacy of fluoride in preventing dental caries is widely accepted, the same is not evident in relation to erosion, as the ability of treatments with fluoride to prevent the loss of dental tissue through erosion is still questioned [1,5].

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Unlike what occurs during the caries process, in erosion the acid challenge is much stronger, and after erosive mineral loss only a thin, partly demineralized and softened surface layer is left to provide a structure for remineralization. In addition, the stability of the calcium fluoride under erosive conditions is still unknown, but it may be speculated that this compound provides additional mineral to be dissolved during an acid attack before the underlying enamel is affected. Thus it may be hypothesized that, in a similar way to its anticariogenic properties, fluoride may assist in strengthening hard tooth tissue against acids and re-harden an eroded enamel surface [6].

The aim of this *in vitro* research was to evaluate, through hardness tests, the action of Claritin D syrup (Schering-Plough; São Paulo, SP, Brazil) on the enamel of primary molars and the effect, if any, of concomitant applications of fluoride dentifrice.

Methods

This experimental study evaluated, *in vitro*, the hardness of 264 samples of primary enamel. The samples were exposed to pH cycling, antihistamine-containing syrup, and fluoride dentifrice. The pH cycling simulated a low acid challenge in relation to feeding [7], and the antihistamine-containing syrup was applied to sound primary enamel in situations set up to represent its use during the day and at bedtime in order to investigate the action of fluoride dentifrice on different usage patterns.

Medication selection

Claritin D syrup (Schering-Plough) was selected for this study because it is frequently used for chronic conditions and has the characteristics of low endogenous pH (pH 3·84 ± 0·04) and high acidity (30·69 mL ± 1·98 mL of NaOH 0·1 N solution to neutralize 100 mL of the diluted medication). Preliminary chemical analysis of the product was made in triplicate using samples from three different batches. The pH was measured with a digital pH meter (MP 220 – Mettler Toledo; São Paulo, SP, Brazil) and the titrable acidity by the method AOAC 22·058, which determines the quantity of NaOH 0·1 N solution necessary for the product to reach neutral pH or pH above it (pH ≥ 7·0) [8].

Chemical parameters considered important in Claritin D syrup, such as quantities of fluoride, citric acid, calcium, and phosphate, were also determined. Tests demonstrated that the medication did not contain fluoride or phosphate; the percentage of citric acid was 0·0147% and of calcium, 0·00034%.

Preparation of dental samples

Samples were obtained from 88 exfoliated primary molars cut longitudinally, in a mesio-distal direction, in slices 2 mm thick. The dental sections were invested in polyester resin (FiberGlass Ind. & Com. Ltda; Florianópolis, SC, Brazil) and, after polymerization, were smoothed (abrasive papers of sizes 800, 1000, 1200, 1500 and 2000; 3M Ind. & Com. Ltda; St Paul, MN, USA) and polished (Arotec Ind. & Com. Ltda; São Paulo, SP, Brazil felt discs and 1 and 0·3 μm oxide aluminium suspension, South Bay Technology Inc.; San Clemente, CA, USA) in a water-cooled grinding machine (Panambra DP-10, Struers; São Paulo, SP, Brazil). After the polishing procedure, samples were viewed under an optical microscope (Aus Jena, model 444181, with a 40× objective; Astro Optics Division, Montpelier, MD, USA) in order to check that surfaces were flat, polished, and without irregularities that could interfere with hardness testing.

Initial hardness determination

In order to make the indentations, the hardness tester (Shimadzu, model HMV – 2000; Nakagyou, Kyoto, Japan) was calibrated with a Knoop tip and load of 50 g was applied for 5 s. The initial indentation was located in a standard position 1·5 mm below the cusp tip and 0·1 mm from the enamel external surface. Three indentations, at the same height, toward the dentin, spaced 100 μm from each other, were made and their average value was taken as equivalent to the hardness value of the specimen (Fig. 1).

Following the initial hardness test, 264 dental sections with an enamel hardness value between 272 and 440 Knoop hardness number (KHN) were selected, as these were considered compatible with sound dental human enamel [9].

Group allocation

Sections were next allocated into control and experimental groups and into six subgroups. Two

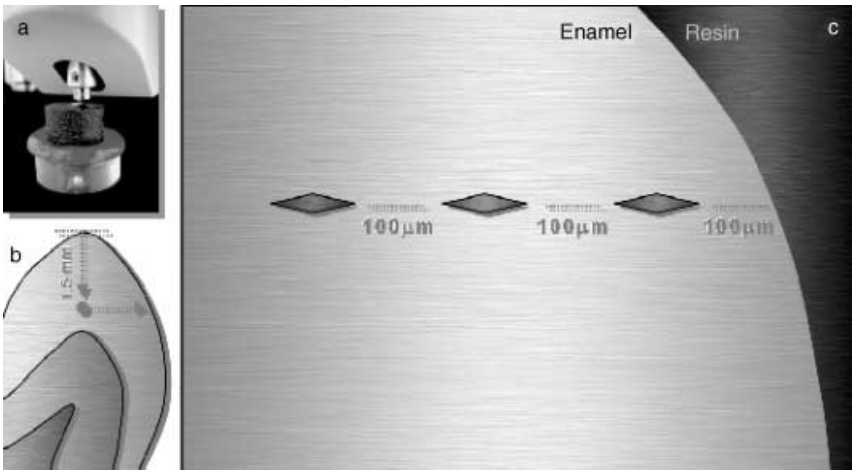

Fig. 1. (a) Hardness tester with Knoop tip. (b) Drawing of the dental slice: initial position of the hardness tester tip and dislocation direction. (c) Enlargement of drawing b: from the external limit (in contact with the resin) there is a space of 100 μm among the indentations.

formed control groups (positive and negative) and four were experimental groups representing daytime medication, daytime medication + fluoride dentifrice, nighttime medication, and nighttime medication + fluoride dentifrice.

Cycles of demineralization and remineralization were based on the pH cycling proposed by Ten Cate and Duijsters [7] and modified by Featherstone *et al.* [10]. This cycling includes 10 cycles in which the samples are immersed daily, at 37 °C, for 3 h in the demineralizing solution followed by 21 h in the remineralizing solution.

Thus, each 1 mm^2 of dental tissue was immersed in 6·24 mL of demineralizing solution (acetate buffer 75 mM containing 2·0 mM of Ca and P at pH 4·3) and in 3·12 mL of remineralizing solution (Tris buffer 0·1 M containing 1·5 mM Ca, 0·9 mM P, and 150 mM KCl at pH 7·0). Because this cycling was carried out for 14 days and involved 10 cycles of pH, after the fifth day the samples were stored in remineralizing solution for 48 h, after which both solutions were changed for a new cycle of 5 days [7,10].

The samples from the control group were submitted only to pH cycling (negative control – C1) or to pH cycling added to immersion in slurry of fluoride dentifrice (Tandy, Kolynos-Brazil, silex-based gel with 1·1 mg/g F in NaF form) and distilled water (proportion 1 : 3) that presented 0·948 mg/g of fluoride and pH of 7·2 (positive control – C2). The specimens were immersed in the slurry of fluoride dentifrice and distilled water, 0·625 mL/mm^2, for 1 min on three occasions, in order to simulate the topical action exerted by the fluoride during tooth brushings after main meals [11].

Two subgroups belonging to the experimental group were submitted to pH cycling and to antihistamine syrup application, representing daily and daytime use for 10 days (E1) or daily and nighttime use for the same period of time (E3). The amount of syrup used for each sample was the equivalent of 0·25 mL two times a day. In subgroup E1, the applications lasted for 5 min each and in subgroup E3, one of them lasted for 5 min and the other for 8 h.

To evaluate the topical effect of daily use of fluoride dentifrice on the primary enamel that received antihistamine syrup application, two subgroups were included in the experimental group. Each specimen from subgroup E2 had the same treatment as subgroup E1 added to the utilization of fluoride dentifrice/distilled water slurry (1 min immersion in fluoride dentifrice/distilled water slurry three times a day). The samples from subgroup E4 underwent the same procedures as subgroup E3 plus use of the dentifrice.

Strategies of treatment for each subgroup, over a period of 24 h, are summarized below.

C1 (negative control subgroup): demineralizing solution for 1 h + remineralizing solution for 4 h + demineralizing solution for 1 h + remineralizing solution for 6 h + demineralizing solution for 1 h + remineralizing solution for 11 h.

C2 (positive control subgroup): demineralizing solution for 1 h + fluoride dentifrice/distilled water slurry for 1 min + remineralizing solution for 4 h + demineralizing solution for 1 h + fluoride dentifrice/distilled water slurry for 1 min + remineralizing solution for 6 h + demineralizing solution for 1 h + fluoride dentifrice/distilled water slurry for 1 min + remineralizing solution for 11 h.

E1 (experimental subgroup simulating daily and daytime use of medication): demineralizing solution for 1 h + remineralizing solution for 2 h + application of medication for 5 min + remineralizing solution for 2 h + demineralizing solution for 1 h + remineralizing solution for 6 h + demineralizing solution for 1 h + remineralizing solution for 2 h + application of medication for 5 min + remineralizing solution for 9 h.

E2 (experimental subgroup simulating daily and daytime use of medication and of fluoride dentifrice): demineralizing solution for 1 h + fluoride dentifrice/distilled water slurry for 1 min + remineralizing solution for 2 h + application of medication for 5 min + remineralizing solution for 2 h + demineralizing solution for 1 h + fluoride dentifrice/distilled water slurry for 1 min + remineralizing solution for 6 h + demineralizing solution for 1 h + remineralizing solution for 2 h + application of medication for 5 min + fluoride dentifrice/distilled water slurry for 1 min + remineralizing solution for 9 h.

E3 (experimental subgroup simulating daily and nighttime use of medication): demineralizing solution for 1 h + remineralizing solution for 2 h + application of medication for 5 min + remineralizing solution for 2 h + demineralizing solution for 1 h + remineralizing solution for 6 h + demineralizing solution for 1 h + remineralizing solution for 2 h + application of medication for 8 h + remineralizing solution for 1 h.

E4 (experimental subgroup simulating daily and nighttime use of medication and of fluoride dentifrice): demineralizing solution for 1 h + fluoride dentifrice/distilled water slurry for 1 min + remineralizing solution for 2 h + application of medication for 5 min + remineralizing solution for 2 h + demineralizing solution for 1 h + fluoride dentifrice/distilled water slurry for 1 min + remineralizing solution for 6 h + demineralizing solution for 1 h + fluoride dentifrice/distilled water slurry for 1 min + remineralizing solution for 2 h + application of medication for 8 h + remineralizing solution for 1 h.

Final hardness determination

Identifications marks on the samples were covered with adhesives and were mixed for blind estimations of final hardness.

The final hardness analysis was performed by the same examiner in exactly the same way as the initial assessment, using the same instrument, number of indentations, load, and application time. The initial indentations were firstly located in carry out the final ones 100 μm below them.

Statistical analysis

The software SAS system 8·02 for Windows (SAS Institute Inc. – Cary, NC, USA) was used for the statistical analysis, using analysis of variance with mixed models. To analyse hardness before and after the specific treatments, two mixed models were made in which the dependent variable was initial and final hardness, respectively, and the fixed effects (explanatory variables) were subgroup and indentation number (which represent enamel depth), whereas the random effect was the sample number. After the treatments, the initial hardness was used as a co-variable in the final hardness model to increase statistical power and to better adjust the model. A third mixed model was made, keeping the same fixed and random effects, but considering the percentual reduction in hardness as the dependent variable.

The covariance structure used was the variance components, and the method to estimate the differences among subgroups and indentations was the Tukey–Kramer with significance level of 1% ($P < 0{\cdot}01$).

Results

Pre-treatment hardness values among the six subgroups did not show a statistically significant difference ($P = 0{\cdot}3687$). All mean values were greater than 330 KHN (Table 1).

The mean hardness values obtained for the six subgroups after the different treatments were all significantly lower than equivalent pretreatment values ($P < 0{\cdot}001$) (Table 1 and Fig. 2), demonstrating that there had been loss of hardness in all subgroups.

In subgroup C1 (pH cycling), there was a decrease in hardness of 20·28% and the mean of post-treatment values was 266·16 KHN. In subgroup C2 (pH cycling and fluoride application), the decrease in hardness was only 5·31% and the mean hardness after treatment was still compatible with sound human enamel (322·61 KHN).

Subgroup E1 (pH cycling and daytime medication use) showed a decrease of 46·83% in enamel hardness and mean hardness after treatment (179·29 KHN) was considered representative of demineralized human enamel. In subgroup E2 (same treatment as E1 added to fluoride application), the decrease in

Table 1. Mean values in KHN and hardness variation after treatments in the six subgroups.

Subgroup	Pre-treatment hardness mean	Post-treatment hardness mean	Hardness reduction percentual mean
C1	334·87[a] (328·56–341·18)	266·16[b] (261·32–271·00)	20·28% (18·89–21·68%)
C2	341·90[a] (335·59–348·21)	322·61[c] (317·76–327·45)	5·31% (3·91–6·71%)
E1	336·42[a] (330·11–342·74)	179·29[d] (174·45–184·13)	46·83% (45·44–48·23%)
E2	335·08[a] (328·77–341·39)	286·05[e] (281·20–290·89)	14·59% (13·19–15·98%)
E3	341·61[a] (335·29–347·92)	36·32[f] (31·48–41·16)	89·14% (87·75–90·54%)
E4	340·83[a] (334·51–347·14)	51·75[g] (46·91–56·59)	84·49% (83·09–85·88%)

Equal superscripts indicated statistical equivalence ($P > 0{\cdot}36$).
Different superscripts indicated statistical difference ($P < 0{\cdot}0001$).
The values in parentheses indicated the confidence intervals of 95% of the means estimated by the three mixed models.

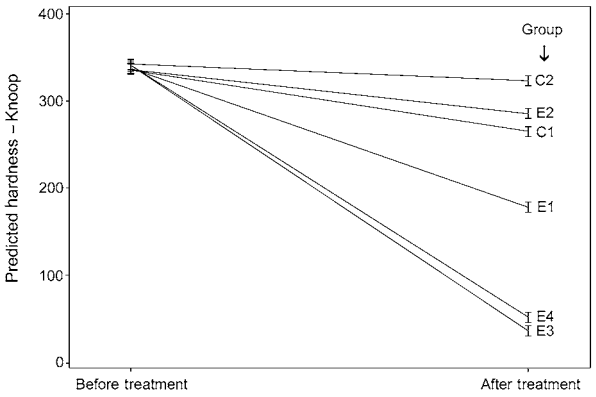

Fig. 2. Mean Knoop hardness values for the six subgroups before and after the treatments.

hardness was lower, at 14·59%, and the post-treatment value was 286·05 KHN.

The subgroup E3 (pH cycling and nighttime medication use) showed the greatest decrease in enamel hardness, at 89·14%, and the final hardness value was only 36·32 KHN. In subgroup E4 (same treatment as E3 added to fluoride application), the hardness decrease was also high, 84·49%, and final hardness value was 51·75 KHN (Table 1 and Fig. 2).

Among the mean values for hardness obtained after the different treatments, statistically significant differences ($P < 0{\cdot}001$) were detected among the six subgroups (Table 1). Values for subgroups submitted to fluoride application were significantly greater than were values for subgroups that did not have contact with fluoride (C2 > C1, E2 > E1, and E4 > E3).

Discussion

Claritin D syrup (Schering-Plough) presents characteristics that may well provide erosive potential. Among these properties are: low endogenous pH [12], high titrable acidity [12], presence of citric acid [13], absence of fluoride and phosphate, and minimal quantity of calcium in its composition [14].

It is common knowledge that the chemistry of enamel changes from its surface to interior and this was evident in the present study, because the internal indentations had lower hardness values than did the external ones. As the mixed model statistic incorporated the coverable indentation depth and there was no interaction with the different treatments, showing that enamel reaction was uniform despite its depth and suggesting that it was unlikely to have acted as a confounder. Thus, investigations using surface tissue may be directly compared to this research.

Subgroup C1 had a substantial loss of mineral, indicating that the immersion of enamel in a remineralizing solution, with a composition similar to human saliva, for 21 h daily, was not enough to prevent the demineralization caused by three acid attacks. These findings corroborated the study of Eisenburger *et al*. [15] in which artificial saliva was not able to restore the superficial hardness or morphology of the eroded dental samples. The results of subgroup C2 supported the findings of studies [16,17] in which the enamel specimens treated with dentifrice containing sodium fluoride showed an increase in hardness, indicating remineralization.

All subgroups where treatment utilized antihistamine-containing syrup showed statistically significant decreases in hardness values when compared to control subgroups. This was irrespective of pattern of treatment.

Considering subgroup E1, it can be suggested that five daily acid challenges were able to cause considerable enamel demineralization. In subgroup E3, it was demonstrated that prolonged exposure

of primary enamel to an acid medication caused an extremely aggressive demineralization that resulted in a reduction of the final hardness mean almost five times greater than did shorter exposure to the same product. The increase in exposure time to acid products that worsened the occurrence of erosion has also been described by Hunter *et al*. [18].

Results for the subgroups submitted to medication and fluoride applications (E2 and E4) showed that fluoride is capable of reducing the erosive effect of an acid product, because it provides enamel protection in relation to its hardness. Similar findings were demonstrated in the studies with dentifrice [19], varnish [4], gel, and fluoride solution [20], which have led to the conclusion that different forms of fluoridation are able to minimize enamel and dentin erosion.

The results of subgroup E4 showed that the presence of fluoride was not enough to prevent an accentuated demineralization because of prolonged acid challenge and that, perhaps, the application of additional fluoride in solutions, gels, or varnishes, as suggested by some authors [20], may be employed in order to protect dental tissues in an extreme situation.

Many researches have indicated that the action of topical fluoride in dental erosion prevention is questionable [5,21] or that this ion only provides a preventive effect when applied in high concentrations [4,20]. Results of this study are contrary to these findings, since the fluoride dentifrice/distilled water slurry was able to reduce the erosive process.

In considering results, the difficulty in reproducing the clinical situation in *in vitro* studies must be borne in mind. This is due to the complexity of the oral environment. Because of that, this research may have overestimated the occurrence of erosive demineralization because of the absence of salivary pellicle, which may be protective, the absence of buffering by saliva, and to its direct contact with the teeth [22,23]. Salivary pellicle is important for protection of enamel because some kinds of pellicle proteins are tenacious even at low pH and may function as a barrier to acid attack [22]. Similar situations may occur in the oral cavity with respect to saliva, since use of medications, such as antihistamines, may reduce salivary flow. This is also the case during nocturnal administration, when salivary flow is naturally reduced. Because of this, use of fluoride is especially important to reduce damage caused by the erosive process. If the fluoride dentifrice is able to diminish erosion *in vitro*, it seems likely to do the same *in vivo*. In addition, if more concentrated fluoride agents could be used simultaneously, even better protection of dental tissues would be assured and, possibly, erosion would be attenuated.

It was possible to conclude that the final hardness values for subgroups that received application of Claritin D syrup (E1 and E3) were significantly lower than values in the control subgroup (C1). This difference was reduced by the fluoride dentifrice/distilled water slurry, because the subgroups submitted to topical fluoride treatment (C2, E2, and E4) presented final hardness values that were significantly greater than those of homologue subgroups without fluoride treatment (C1, E1, and E3).

What this paper adds

- This paper adds information that an acid medication can reduce deciduous enamel hardness, especially when in contact with this tissue for a prolonged period of time and without the presence of fluoride in the environment.

Why this paper is important for paediatric dentists

- Paediatric dentists must be aware of the potential demineralization an acid medication can bring to deciduous enamel and also should have in mind that a fluoride toothpaste can attenuate this harmful effect.

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