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Evaluation of the Erosive Effect of Pediatric Liquid Medicinal Syrups on Primary and Permanent Enamel

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ABSTRACT

Purpose: To evaluate the erosive effect of pediatric liquid medicinal syrups on primary and permanent enamel. **Materials and methods**: Eighty primary and permanent teeth were equally divided into eight subgroups (n=10), according to the immersion solutions: Depakine, Ventolin, Sansovit, and Artificial saliva. The immersion cycles of the drugs were conducted under a 1-min agitation three times daily for 28 days. Enamel microhardness measurements were taken place at 0,7,14,21, and 28 days. The pH, titratable acidity, buffering capacity, and viscosity of the solutions were evaluated. A Scanning electron microscopy and statistical analysis of enamel microhardness measurements were assessed. **Results:** All the tested groups of the drugs had proven to produce significant demineralization of enamel after 28 days of exposure. At baseline, the permanent enamel showed higher mean enamel microhardness values than primary teeth. Generally with all the tested drugs, the primary teeth showed more decrease in enamel microhardness than permanent but without significance. The primary group (0-28days)**,** the highest decrease of enamel microhardness was recorded in Sansovit group, then Ventolin, followed by Depakine group without significant change between the tested drugs, while in the permanent group, the highest decrease of enamel microhardness was recorded in Sansovit, then Depakine, followed by Ventolin group without significant change between the tested drugs. Kruskall Wallis test revealed a significant difference between tested drugs and control groups in both substrates. **Conclusion:** This study revealed that medicines used in the study could erode teeth even though the pH was above critical pH if it had high sugar content and viscosity. Sugar-free formulations have the ability to produce an erosive effect if they have low pH, high titratable acidity, high buffering capacity, and viscosity. This study showed that permanent teeth had higher mean enamel microhardness values than primary teeth, however no significant difference in the erosive potential of both types of teeth.

KEYWORDS

Pediatric syrups,
dental erosion,
primary enamel,
permanent enamel,
enamel microhardness.

- Paper extracted from Master thesis titled "Evaluation of the Erosive Effect of Pediatric Liquid Medicinal Syrups on Primary and Permanent Enamel"

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INTRODUCTION

Dental erosion is outlined as a continuing loss of the hard tissues of the teeth by chemical dissolution in the absence of microorganisms. It is a complex multifactorial permanent process that may be affected by intrinsic, extrinsic, or idiopathic causes. Contact of tooth tissues with stomach acids (i.e., regurgitation and reflux disorders) is the chief intrinsic etiological factor. The main extrinsic etiological factor is due to increased acidic food and drink utilization[1,2].

The tastiness of pediatric liquid medicaments is thanks to sweetened preparations of the previous. Sucrose is the most popular adjoined sweetener to such medications since it is cheap and simply handled. It is the chief factor for dental caries. Thus, it has a role in dental caries with the consumption of such preparations which thereby acts as a supplementary risk factor in the caries process. For drug distribution and chemical stability of the drugs, acidic formulations are used. In addition, it enhances physiological compatibility and flavor. Other factors like recurrent intakes (i.e., two or more times daily), sleep times, and after meals. Also, the reduced salivary flow may also promote increasing the risk of dental erosion[3,4].

Primary enamel is completely different histologically from permanent enamel. Prism arrangements in primary resemble that of permanent enamel. However, prisms in permanent enamel are larger with less defined boundaries and are more narrowly spread than those in primary enamel. However, the prisms in permanent enamel are less smoothly curved, it is more marked, so it is essential to investigate the effect of different pediatric medications on primary and permanent teeth[5]. Thus, this study was intended for assessing the erosive potential of common pediatric liquid medication on primary and permanent enamel.

MATERIAL AND METHODS

Medications selection

This invitro study consisted of three medications: Depakine syrup (Global Napi pharmaceuticals Ltda, Sanovi Aventis, France), Ventolin syrup (Glaxosmithklin Egypt, El-Salam City, Cairo), Sansovit (AuG pharma, 6th of October, Giza, Egypt) and Artificial saliva as control (prepared at Faculty of Science, Al-Azhar University). These medications were selected as they are commonly consumed by pediatric patients for an extended time. Depakine syrup is an antiepileptic, Ventolin is an expectorant and Sansovit is a multivitamin.

PH, titratable acidity, buffering capacity, and viscosity measurements of the solutions

The pH value and titratable acidity of the solutions were measured with a pH meter (Model: pH-MV-temp meter-pH-206., Ltd. China). Titratable acidity is the amount of base needed to elevate the pH to 7.0. To be measured 20ml of the drug in a glass beaker was put in a thermostatically controlled water bath at 37° C. Next, 0.1 M sodium hydroxide solution was gradually added to the beaker until the pH became neutral and the samples were agitated. The amount of sodium hydroxide that was added until pH reached 7 was registered. Buffering Capacity (β) was computed from the equation: $\beta = \Delta C / \Delta$ pH in which ΔC is the amount sodium hydroxide used and Δ pH is the change in pH affected by the addition of sodium hydroxide[6].

The viscosity of the drugs was determined by a digital viscometer (Model: commerce BLVD-508. Middle moro -USA) The speed control was set at 60 rpm and the appropriate spindle for measuring the viscosity of syrups was selected. The spindle of the viscometer was released into the syrup sample and the readings were registered on the viscometer gauge as torque reading in centi Poise (cP). All the procedures were repeated 3 times for all samples to obtain average measurements[6].

Sample selection

The study was carried out in Pediatric Dentistry Department of Al-Azhar University. Research ethics committee approval for the use of extracted human teeth was obtained from the Faculty of Dental medicine for girls, Al-Azhar University (REC17-042). A sum of eighty extracted teeth was collected for the study. Equal samples were taken from primary and permanent teeth with (n=10) for each subgroup. All teeth were sound with no apparent wear or white spot lesions on the enamel surface. The primary teeth were gathered at the patient out clinic of Al-Azhar University_ Pediatric Dentistry Department for this study, and the permanent teeth were collected from the patient out clinic of Orthodontic Department_ Al-Azhar University.

Before sample preparation, the teeth were cleaned with water, then 5% sodium hypochlorite solution was applied for 5 seconds to remove the stain. Rinsing by distilled water was done to eliminate any remaining hypochlorite, and then teeth were kept in saline solution at room temperature (37°C) till the experiment was performed to prevent dehydration. The teeth were cleaned and hand scaled before use to get rid of any calculus or debris on the surface of the teeth[2,7].

Sample preparation

The teeth were cut from the CEJ and roots and were separated from the crowns with a diamond saw (Model: Brown Alumina Oxoid, Henan Tianze Imp). Each crown was then secured in a cold cure acrylic resin mould. The buccal surface was faced upwards. The samples were polished with 0.3-μm alumina paste a water-cooled low-speed polishing machine. Prior to immersion cycles, they were maintained in artificial saliva and transferred to the laboratory for microhardness testing[8].

Evaluation of the enamel microhardness was established using Digital Display Vickers Microhardness Tester (Model: HVS-50, Laizhou Huayin Testing Instrument Co., Ltd. China). A load of 100 g was applied for 10 seconds to the enamel surface. 3 indentations were made on the enamel with even location over a circle with 0.5 mm at least to the next indentations. Microhardness was calculated from the equation: $\mathbf{HV=1.854\ p/d^2}$ where **HV** is Vickers hardness in Kgf/mm^2, **P** is the load in Kgf and **d** is the diagonal length in mm[9].

Grouping of samples for drug immersion

Samples were grouped equally into 2 main groups. **Group A:** represented 40 primary teeth and **Group B**: represented 40 permanent teeth. Each group was subdivided into 4 subgroups. **Group A** was subdivided into **Group A1, Group A2, Group A3** and **Group A4 (**10 primary teeth each) were immersed with Depakine, Ventolin, Sansovit ,and artificial saliva respectively. **Group B was subdivided into Group B1, Group B2, Group B3** and **Group B4 (**10 permanent teeth each) were immersed with Depakine, Ventolin, Sansovit ,and artificial saliva respectively.

Immersion cycles

The immersion cycling protocol was implemented to mimic the habitual number of consumptions. The samples were exposed to 10ml of each drug for 1 min. The cycles were carried out under agitation (30 rpm) by a magnetic stirrer (Model: 78Hw-1, Zenith Lab (Jiangsu) Co, LTD, China), 3 times on a daily basis with 6-h separations between them, then distilled water was used to wash the samples. The teeth were preserved in 10 mL of artificial saliva at 37°C until the following cycle. The medicines were replaced before each immersion. All the solutions were refreshed daily during the whole period of the experiment. Enamel microhardness was estimated at 0, 7, 14, 21, and 28 days[2].

Statistical analysis

Values were expressed by the mean and standard deviation (SD). The comparison between the groups was done through (ANOVA) test. When the ANOVA test revealed a significant difference, Turkey's post

hoc test was used for pairwise comparison. For non-parametric data, Kruskall Wallis test was used for comparing all groups, followed by Mann Whitney U test for pairwise comparison when a significant difference was revealed by Kruskall Wallis test. The Level of significance was determined at $P \leq 0.05$.

Scanning electron microscopy analysis

It was done after completion of immersion cycles in two teeth from each group (n=10) and the most two representative images were taken. The samples were fixed on stubs, sputter-coated with gold, and analyzed in a scanning electron microscope (Model: JSM-5500 LV; JEOL Ltd -Japan) at 15kV. The buccal surface of each tooth was scanned, and the images were taken at 1200x and 1500× magnifications.

RESULTS

A. The pH, titratable acidity, buffering capacity, and viscosity results of the syrup

The pH, titratable acidity, buffering capacity, and viscosity of the syrups were measured to evaluate their effects on enamel microhardness as shown in table (1).

Table (1): pH, titratable acidity buffering capacity and viscosity results of the syrups

Solutions	pH	Titratable acidity	Buffering capacity	Viscosity
Depakine	6.8	0.4ml	2ml	147.4cp
Ventolin	4.5	3.90ml	1.56ml	64.7cp
Sansovit	4.2	6.9 ml	2.46ml	409.9cp
Artificial saliva	7	0	0	16.3cp

B- Statistical analysis results of enamel surface microhardness

All the tested groups of the drugs had proven to produce significant demineralization of enamel after 28 days of exposure. At baseline, the permanent enamel showed a higher mean enamel microhardness values than primary teeth. The mean enamel microhardness values of the Depakine group were (229.70±10.98) (265.30±14.84) for primary and permanent teeth respectively. The mean enamel microhardness values of the Ventolin group were (246.90±15.93) (266.20±31.71) for primary and permanent teeth respectively. The mean enamel microhardness values of the Sansovit group were (233.12±9.52) (261.98±16.80) for primary and permanent teeth respectively. The mean enamel microhardness values of the Artificial saliva group were (227.76±21.37) (264.90±13.45) for primary and permanent teeth respectively. This difference was significant except for Ventolin group.

Generally with all the tested drugs, the primary teeth showed more decrease in enamel microhardness than permanent but without significance. The primary group (From baseline to stage 4) (0-28days), the highest decrease of enamel microhardness was recorded in Sansovit group (-30.83±28.24), then Ventolin (-27.92±28.16), followed by Depakine group (-25.27±24.18) without significant change between the tested drugs. Artificial saliva was significantly different and showed a percentage increase (3.49±14.44). Kruskall Wallis test revealed a significant difference between tested drugs and control groups.

In the permanent group (From baseline to stage 4) (0-28days), the highest decrease of enamel microhardness was recorded in Sansovit(-23.55±7.17), then Depakine (-22.48±6.19), with the least decrease recorded in Ventolin group(-21.18±11.03) without significant change between the tested drugs. Artificial saliva was significantly different and showed a percentage increase (1.98±3.95). Kruskall Wallis test revealed a significant difference between tested drugs and control groups.

C. Scanning electron microscopy analysis results

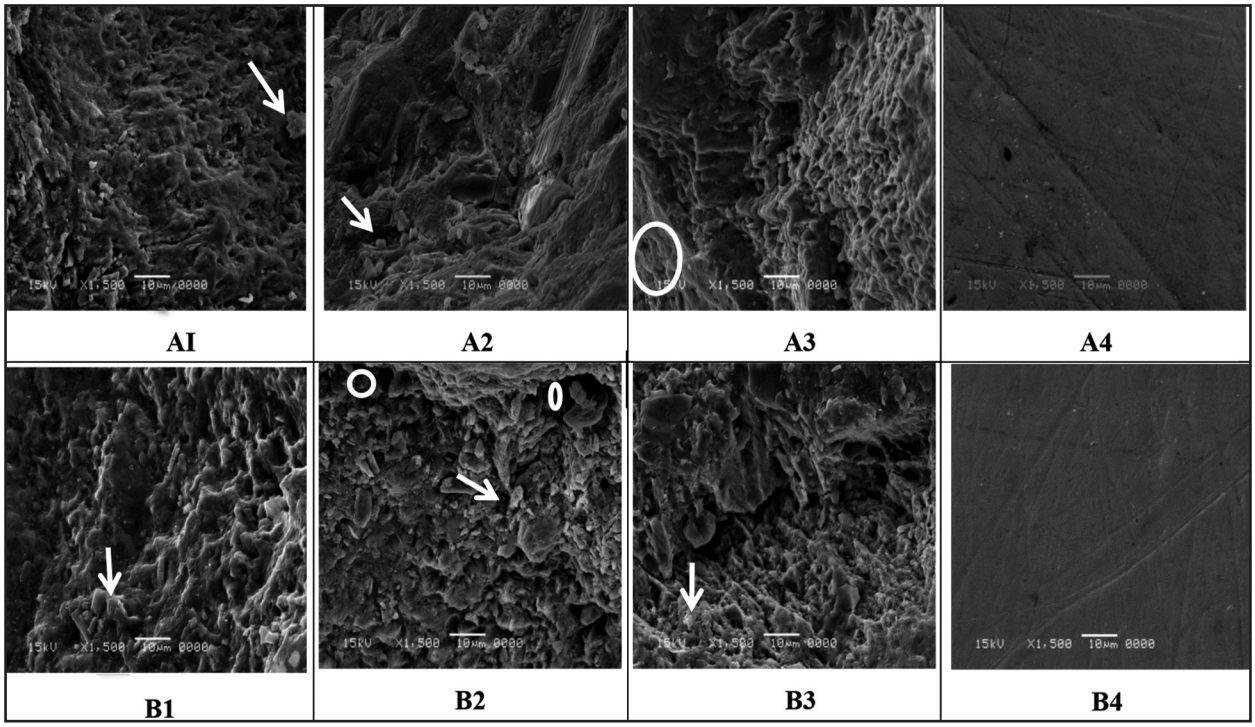

Figure (1): SEM changes of primary and permanent enamel

The surface morphology of the eroded enamel sections as shown in Figure (1). The Depakine group of both primary and permanent teeth showed etched prism patterns and areas of sporadic formation (arrow shape) (Fig.1.A1.B1). In the Ventolin group, the primary subgroup showed a rough irregular surface, crack formation, and area of structural loss (oval shape) (Fig.1.A2), also the permanent subgroup showed an abnormal enamel surface with a rough irregular surface and little sporadic formation (arrow shape). Also, void areas were present (oval shape) (Fig.1.B2).In the Sansovit group, the primary subgroup showed a rough irradiated and irregular ablated pattern. The demineralization resembles a type II pattern where prisms core were demineralized more deeply than prisms peripheries, and multiple circular pits (oval shape) (Fig.1.A3). The permanent subgroup showed a loss of a normal enamel appearance with a rough and irregular surface with little sporadic formation (arrow shape) (Fig.1. B3). The control groups of primary and permanent teeth appeared smoother with no apparent surface changes (Fig.1.A4.B4). The figures revealed significant changes between tested drugs and control groups.

DISCUSSION

The selection of the drugs in this study relied on their usual use in treating familiar childhood illnesses for a long duration, like epilepsy, anemia, asthma, bronchitis, and cough. As the erosive potential of the medicine is affected by exposure time, it was more important to investigate the erosive effects of drugs that are used for a longer duration. Whereas other studies used pediatric medications like analgesics, antipyretics, antibiotics that are used for short durations[10].

The utilization of artificial saliva as immersion media between cycles was because it is proved

to produce a remineralizing effect comparable to human saliva besides it is protective roles, so it is considered the chief biological factor in the erosive process. The selective membrane that is formed of salivary protein-based pellicle on enamel surfaces inhibits close interaction between acids and enamel surface, thus inhibiting the dental erosion, so artificial saliva was used as a media and control to simulate the oral environment which was in accordance with other studies[2,8,11]. In another previous study, distilled water was set as the control group and immersion media between cycles[12].

In our recent study, the handled protocol was established on the usual frequency of syrup ingestion: 10mL undertaken three times a day, under agitation during the immersion cycles. According to previous studies, when a substance is swallowed, an agitation takes place, which stimulates the syrup's ability to produce erosion. As the erosive potential of these liquid oral medications might have relied on the rate, time of acid exposure, and the whole volume of syrups ingested for that reason, 28 days was chosen as the experimental period to mimic what would occur over a prolonged time of medication intake. It is expected that the prolonged time of medication intake prompted more destruction to tooth structures[2].

The benefit of choosing an order of frequent exposures is that it has the advantage of obtaining dependable findings. As, alterations can be significantly observed after several challenges more than a single exposure, so frequent exposures were favored to be implemented during the experimental period[8]. While in another study, the erosive cycle consisted of a single exposure to display the effects of dental erosion[13].

According to previous studies, microhardness is the most suitable way to evaluate enamel erosion, so Vickers microhardness tester was used in this study to measure microhardness[14]. Whereas another study used the profilometer for characterization of the enamel surface changes[15].

In this current study, exfoliated primary teeth and premolar removed for orthodontic reasons were utilized. Primary and permanent teeth were selected to investigate the possible differences in susceptibility of primary and permanent enamel to dental erosion which were in accordance with other study[16]. Whereas other study used primary substrates[17]. Another study used only permanent substrates[18].

This present study revealed that the tested medicated syrups could erode both primary and permanent enamel after successive immersion cycles. Although the Depakine group is less acidic than Ventolin and Sansovit, and the titratable acidity of Sansovit and Ventolin is higher than Depakine, however, the buffering capacity of Depakine is higher than Ventolin and had erosive potential similar to Ventolin and Sansovit. That may be due to the presence of glycerol and sucrose in it is formula.

Sucrose containing drugs as a sweetener (Depakine), have a high viscosity. Increased viscosity of the drug causes the drug to retain in the tooth surfaces for a longer time and subsequent slow salivary clearance and higher buffering capacity which will lead to the greater dissolution of enamel. Sucrose is the most commonly used, as it acts as a preservative, antioxidant, solvent, and thickening agent. Besides, it is a cheap, non-hygroscopic, easily processed substance, as well as a clinician's helper in pediatric therapeutics, given that its satisfying sweet taste encourages medicine approval[19].

The Ventolin group contains a mixture of lactic acid and citric acid. In a previous study, it has been stated that lactic acid at low pH was more erosive than both citric and maleic acids. That results in lower pH and higher titratable acidity than Depakine, however, the viscosity of Depakine is higher than Ventolin which explains why Depakine has a higher buffering capacity[20].

The Sansovit groups, although it is a sugar-free formulation group had a decreasing microhardness similar to the sugar-containing formulation.

This was reinforced by another study assessing the differences in the erosive potential between sugar-free and sugar-containing medicine. Sugar-free medications were observed that they have a similar erosive potential as the sugar-containing medications. That may be due to the addition of "sugar-free" excipients, i.e. calcium saccharate, sorbitol, and xanthan gum, that are found to be acidic under acidic environment and also thickening agents that contribute to increased viscosity of the drug[21].

A significant correlation was observed between enamel demineralization and viscosity. As the viscosity causes the drug to adhere to the tooth surface for a longer duration, so greater viscosities cause more dissolution. That means increased contact of acidic substance, and subsequent increasing contact time with the enamel surface causing higher buffering capacity and subsequent dental erosion[21].

The main ingredients of the drug are malt juice cone, grapefruit juice, and orange juice which are highly acidic. In another study, it had been reported that grape juice has acidity below critical pH 5.5 and was the only beverage tested in which the pH of oral fluids stayed close to pH 4 for a prolonged time. That was related to that grapefruit juice had the highest level of titratable acid and strong buffering capacities[22].

Besides the presence of citric acid which has been associated with dental erosion. Citric acid has a high ability to soften the hydroxyapatite of enamel, and dentine. Besides, it has a high affinity for binding to hydroxyapatite minerals, it also causes a reduction in the supersaturation of saliva, and accelerates the demineralization rate of hydroxyapatite's crystals[23]. This may explain the fact that Sansovit has the lowest pH, the highest titratable acidity, and buffering capacity among the tested drugs.

In conclusion, it is born in our minds when we see drug free sugar formulations label's in a drug prescribed for the strengthening of teeth, bone, and for anemia treatment due to its formula that contains calcium and minerals like iron, calcium gluconate, calcium phospholactate, and multivitamins like A, B, C, D, E, that they are safe for teeth, however, it resulted in a marked decreasing of enamel microhardness after 28 days. However, nothing was published about the erosive potential of these formulations. Moreover, it causes yellowish discoloration of teeth with time.

In this study primary teeth exhibited significantly lower baseline microhardness values than permanent teeth, this is reasonable[24]. Since permanent teeth were harder than primary teeth, it was expected that they would be more resistant to dental erosion however, we noticed that primary teeth had a greater percent decrease of microhardness but without significance after 28 days of incubation in the different medications. That was in agreement with other studies that observed no statistically significant differences between the rate of erosion progress in primary and permanent teeth[15,25]. Whereas other studies observed that dental erosion proceeds more rapidly in primary than in permanent enamel[16,24].

Exfoliated primary teeth used in the study may have been subjected to the oral environment for a much prolonged time than premolars that extracted for orthodontic reasons, adding more acid-resistant fluoridated crystals to its enamel. Another justification is that primary enamel has a prismatic layer on its external surface, which erodes irregularly, and is not predisposed to the dissolution process as the prismatic enamel.

For that an older tooth that has been subjected to the oral environment for much prolonged time leading to more contact with acids and fluoride during it is life cycle than a newly erupted young tooth, making it more mineralized, and acid-resistant[26,27]. That's may explain the insignificance in dissolution rate between deciduous and permanent enamel despite that permanent teeth have initial higher microhardness than deciduous teeth.

CONCLUSION

This study revealed that medicine could erode the teeth even though the pH was above critical pH if it had high sugar content and high viscosity. Sugar-free formulations have the ability to produce erosive effect if it has low pH, high titratable acidity, high buffering capacity, and high viscosity. The buffering capacity of the drug is affected by viscosity than pH and titratable acidity as it needs more amount of saliva to break through the bond between particles then neutralize acidity so drugs with low pH and a high viscosity have the highest erosive potential. The standard concept that 5.5 is the most critical pH can be changed as the demineralization of enamel can occur at a higher pH. This invitro study showed that permanent teeth are harder than primary teeth however, no significant difference in erosive potential in both substrates.

CONFLICT OF INTEREST

None declared

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