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Are paediatric medicines risk factors for dental caries and dental erosion?

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The objective: To assess in vitro the cariogenic and erosive potentials of Brazilian liquid oral paediatric medicines. ***Setting:*** Twenty-three paediatric medicines available on the Brazilian market were evaluated. The sample consisted of antihistamines, antitussives, bronchodilators and mucolytics. ***Main outcome measures:*** Duplicates of each bottle were analyzed for sugar concentration using normal-phase- high-performance liquid chromatography (HPLC). Quantification of sugars and sorbitol was calculated using the peak heights of commercial standards as references. pH measurements were determined using a digital pH meter. Titratable acidity was assessed by diluting three aliquots of each medicine, and increments of 0.1N NaOH were titrated until neutrality was reached. Viscosity was determined using a viscosemeter. ***Results****:* Sugars were detected in 56.5% of the medicines. Sucrose was identified in 10 medicines, with concentrations ranging from 11.36 g% to 85.99 g%. Glucose was detected in five medicines, with concentrations varying from 4.64 g% to 40.19 g%; fructose in six medicines, with concentrations ranging from 5.09 g% to 46.71 g%. Twelve medicines exhibited sorbitol, with values ranging from 5.39 g% to 46.09 g%. Most tested medicines were acidic, with pH values ranging between 2.6 and 5.7. Only two medicines (Fluimucil and Polaramine) presented pH 6.4 and 6.0, respectively. Titratable acidity mean values ranged between 0.28 and 16.33 mL. Viscosity values varied between 2.8 cP and 412.3 cP. ***Conclusions****:* Many paediatric medicines showed high sugar concentration, pH values below the critical value and high titratable acidity values, all of which increase the medicines' cariogenic and erosive potentials.

Key words: Acidity, dental caries, pharmaceutical preparations, sweetening agents, tooth erosion, viscosity,

Introduction

The ideal drug for children should be effective, economical, well tolerated, and palatable (Pawar and Kumar, 2002). Because of the bitter taste of most drugs, sugar is combined with other ingredients to provide palatable dosages forms, thus ensuring patient compliance, especially for paediatric use. In addition to sweetness, sugar provides desirable functional properties, such as acting indirectly as antioxidant, solvent, demulcent and bulking agent (Bigeard, 2000).

The long-term use of liquid oral medicines may contribute to dental caries, as shown by clinical studies (Roberts and Roberts, 1979; Sahgal *et al*., 2002) and plaque pH studies (Mentes, 2001; Rekola, 1989)**.** Acids are also commonly used in medicines as buffering agents to maintain chemical stability, improve flavor and to control tonicity (Maguire *et al*., 2007). The regular and frequent use of acidic medicines coming in direct contact with teeth has been identified as an etiological factor in dental erosion (Costa *et al*., 2006; Hellwig and Lussi, 2006; Linnet and Seow, 2001).

Other factors related to paediatric medicines might also contribute to the risk of dental caries and erosion, for example, high frequency of ingestion, bedtime consumption, reduced salivary flow caused by the use of some drugs and high viscosity (implying longer contact time with tooth surface) (Linnet and Seow, 2001; Lussi *et al*., 2004; Maguire *et al*., 2007). This problem especially concerns chronically sick children, who require long-term medication (Costa *et al.*, 2006; Roberts and Roberts, 1979), and children who receive medications frequently because of various recurrent benign pathologies, such as coughs and colds (Bigeard, 2000).

Although a public-health policy to limit sugar in medicines has been implemented in several developed countries such as Great Britain, the United States, Canada and Australia (Bigeard, 2000; Maguire and Rugg-Gunn, 1997), some developing countries (e.g., Brazil) do not have a policy for the use of paediatric medicines especially because of the lack of information on their sugar content and acidity (Neiva *et al*., 2001). Therefore, the aim of this study was to assess the cariogenic and erosive potentials of Brazilian oral liquid paediatric medicines by determining their sugar content, pH, titratable acidity and viscosity.

Method

Twenty-three samples of liquid paediatric medicines from different brands available on the Brazilian market were selected from the list of the "reference medicines" of the

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Brazilian Health Surveillance Agency, which are products registered at the federal body in charge of the country's sanitary surveillance and commerce. Their efficacy and safety had been scientifically verified by the relevant federal body, at the time of registration (BRASIL, 2003). This list is constantly updated; this study was based on the list available online at 12/22/05 (BRASIL, 2005).

The sample consisted of antihistamines, antitussives, bronchodilators and mucolytics (Table 1), including all liquid paediatric medicines available in these therapeutic classes. These medications are sold both over-the-counter and by prescription. The labels of each medicine were examined to gather information on their sugar and organic-acid content.

Analyses of sugars (sucrose, glucose, fructose) and sorbitol were performed using high-performance liquid chromatography (HPLC), according to Trugo *et al*. (1995).

Samples were prepared in duplicate. One gram of each medicine was diluted to 50 mL in a volumetric flask with Milliq water (Milipore, USA). The mixture was vigorously shaken. Then one aliquot of the supernatant of this solution (500 µL each) was diluted with pure acetonitrile in the proportion 1:1 (vol/vol). The mixture was then centrifuged for 2 min (Beckman Microfuge E™, USA) and the supernatant was used directly for chromatography.

The HPLC system comprised a pump (Isco, USA) and an HP 3395 integrator (Hewlett Packard, USA), with a Rheodyne injection valve (20µL loop) and a refractive index detector (Waters 410, USA). The column was a Lichrospher-5-NH2 (250 x 4 mm i.d.; Merck, Germany), and the mobile phase was acetonitrile:water 85:15 (vol/vol) at 1.0 mL/min.

The concentrations were calculated by peak-height comparison with commercial standards of sucrose, fructose, glucose (Sigma Aldrich, USA) and sorbitol (Vetec Química, Brazil). Results are average of duplicates, being presented as medians of the values of sugars and sorbitol concentrations (g/100g - %).

The pH measurements were determined using a digital pH meter (Analion-PM 600, Brazil). Titratable acidity was measured in three aliquots of each medicine by using a pH meter (Digimed DM 20, USA). Ten mL of each medicine solution was mixed with 50 mL of distilled water in a glass beaker. The titratable acidity of each sample was determined following gradual addition of 0.1N sodium hydroxide (NaOH), previously standardized, to the samples. The analyses were repeated three times for each medicine. The end point for each analysis was reached close to a neutral pH of 7. The total volume of NaOH solution required to reach the end point was recorded, and this corresponded to the titratable acidity value.

Viscosity measurements were carried out on a HAAKE RheoStress 600 viscosimeter (Thermo Electron GmbH, Karlsruhe, Germany) using cone-plate geometry (C60/1°), at a shear rate range of 0.1 to 100 s^{-1} and temperature of 35°C. The values for viscosity shown in the Results were obtained at $20s^{-1}$, the shear rate from which all medicines presented a constant value of viscosity (Table 4).

Results

Concentrations of nonsugared and sugared sweeteners in all investigated medicines are presented in Tables 2 and 3, respectively. All sweetening agents identified in this study were in accordance with medicine labels. It must be noted that only three drug labels mentioned the sugar content and only one medicine did not list the inactive ingredients in the product. Most labels (83.3%) of sugar-based medicines warned that the product should not be consumed by diabetic patients; however, none of them mentioned its cariogenic potential, especially when taken for long periods of time.

Sugars (sucrose, glucose, fructose) were detected in thirteen (56.5%) medicines. Sucrose was detected in 10 of the 23 medicines investigated, with concentrations ranging from 11.36 g% to 85.99 g%. Glucose was detected in five medicines, with concentrations varying from 4.64 g% to 40.19 g%, and fructose in six medicines from 5.09 g% to 46.71g%. Total sugar content varied considerably among the medicines evaluated— from 21.0 g% to 85.9 g% (Table 3). Twelve medicines presented sorbitol as a sweetening agent, with values ranging from 5.39 g% to 46.09 g% (Tables 2 and 3).

Most tested medicines were acidic, with pH values ranging between 2.6 and 5.7. Only two medicines (Fluimucil and Polaramine) presented a pH as high as 6.4 and 6.0, respectively. The majority of them (86.9%) showed a pH below the critical value of 5.5 for enamel dissolution. Titratable acidic mean values ranged from 0.28 mL to 16.63 mL (Table 4).

Viscosity values ranged between 4.7 and 412.3 cP (Table 4). Viscosity values were much greater for Vick and Vick Mel than for any other medicines.

Discussion

Although the prevalence of dental caries in children has decreased significantly in the past decades in many developed countries such as United States, Canada and European countries, it continues to be a major public health problem, especially in poor and disadvantaged groups of several developing economies (Petersen *et al*., 2005). In addition, the prevalence of dental erosion has increased worldwide, especially among children and young adults (Linnet and Seow, 2001).

Most of the medicines (56.5%) analyzed contained fermentable carbohydrates (sucrose, glucose, fructose), sucrose being the most prevalent among the sugars identified, as well as the most cariogenic, although it has been shown that glucose and fructose have acidogenicity and cariogenic potentials similar to sucrose (Duward and Thou, 1997; Rekola, 1989). Studies have demonstrated that when sugar-rich medicines are consumed, there is an *in vivo* drop in pH of the dental plaque (Mentes, 2001; Rekola, 1989). The low toxicity, low cost, high purity and diverse physicochemical properties of sugar account for its popularity in pharmaceutical applications (Bigeard, 2000). In view of all these advantages, Brazilian studies have verified that sucrose was the main sweeteneter used for the majority of paediatric medicines analyzed (Lima *et al*., 2000; Neiva *et al*., 2001), which is confirmed in this study.

Table 1. Brand names, active principles and groups of medications analyzed in the study

Theraupetic purpose	*Brand names*	*Active principles*
Antihistamines	Claritin D®	Loratadine, pseudoephedrine sulfate
	Claritin®	Loratadine
	Desalex®	Desloratadine
	Dimetapp elixir®	Pseudoephedrine chloridrate, guaifenesin
	Muricalm®	Pimethixene
	Polaramine expectorante®	Dexchlorpheniramine maleate, pseudoephedrine sulfate, guaifesin
	Polaramine®	Dexchlorpheniramine maleate
	Zyrtec®	Cetyrize hydrochloride
Antitussives	Silomat Plus®	Clobutimol hydrochloride, doxylamine succinate
	Silomat®	Clobutimol hydrochloride
	Vibral®	Dropropizine
Bronchodilators	Aeroflux®	Salbutamol sulfate, guaifenesin
	Aerolin®	Salbutamol sulfate
	Berotec®	Fenoterol hydrobromide
	Bricanyl broncodilatador®	Terbutaline sulfate
	Bricanyl expectorante®	Terbutaline sulfate, guaifesin
	Brondilat®	Acebrophylin
Mucolytics	Bisolvon®	Bromhexine hydrochloride
	Fluimucil®	Acethylcystein
	Mucolitic®	Carbocystein
	Mucosolvan®	Ambroxol chloridrate
	Vick Mel®	Guaifenesin
	Vick®	Guaifenesin

Table 2. Liquid paediatric medicines with nonsugared sweetener (Sorbitol). Sugars were not detected in any of these.

Brand names	*Label content (sweeteners)*	*Sorbitol**
Aeroflux®	Sodium saccharin, sodium cyclamate	ND
Aerolin®	Sodium saccharin	ND
Berotec®	Sorbitol	38.81 ± 0.47
Bisolvon®	Sodium cyclamate, sorbitol	43.74 ± 0.19
Brondilat®	Sodium cyclamate, sorbitol	46.09 ± 0.21
Fluimucil®	Sodium saccharin	ND
Mucosolvan®	Sorbitol	37.72 ± 0.05
Silomat Plus®	Sodium saccharin, sorbitol	40.78 ± 0.87
Silomat®	Sodium saccharin, sorbitol	37.49 ± 0.00
Zyrtec®	Unspecified	36.31 ± 0.92

* Concentrations are expressed in g% (g/100g) (median ± standard deviation).

Alternative sweeteners have negligible cariogenicity compared with sugars (Rekola, 1989). Although many noncariogenic sweeteners are available, it has been reported that sugar-free medicines are expensive; thus a combination of bulk and intense sweeteners and other flavoring agents must be used to provide the same degree of sweetening. In addition, the low viscosity provided by sweeteners must be compensated with thickening agents (Mentes, 2001). Despite these disadvantages, a tendency for the use of noncariogenic sweeteners such as sorbitol, aspartame and saccharin was observed in the present study, since 10 of 23 analyzed syrups were sugar-free, according to their labels and HPLC analysis. However, it must be emphasized that five medicines contained nonsugared sweeteners combined with sugared sweeteners (Table3). Rekola (1989) verified that syrups sweetened with a combination of fructose and sorbitol produced a marked and long-term drop in plaque pH.

About 83% of the investigated sugar-containing medicines had labels suggesting precautions be taken by diabetic patients. Nevertheless, nothing was mentioned about the cariogenic potential of these preparations. Besides, the majority of the sugar-based medicines did not specify their sugar concentration, since quantifying "inactive" ingredients is not required by Brazilian legislation (BRASIL, 2003).

The acidic pH values presented by most of the medicines investigated in this research may also contribute to

Table 3. Liquid paediatric medicines with sugared sweeteners*

Brand names	*Label content (sweeteners)*	*Sucrose*	*Glucose*	*Fructose*	*Total sugars*	*Sorbitol*
Bricanyl broncodilatador®	Sugar	16.78 ± 0.15	11.93 ± 0.46	14.66 ± 0.46	43.37	ND
Bricanyl expectorante®	Sugar, sodium saccharin	11.36 ± 0.20	4.64 ± 0.08	5.09 ± 0.06	21.09	ND
Claritin D®	Sorbitol, sugar	57.00 ± 0.8	ND†	ND	57.00	5.39 ± 0.06
Claritin®	Sucrose	ND	40.19 ± 0.53	46.71 ± 0.40	86.90	ND
Desalex®	Sorbitol, sucrose	62.60 ± 1.80	ND	ND	62.60	12.51 ± 0.12
Dimetapp elixir®	Sorbitol, fructose syrup, sodium saccharin	ND	ND	43.72 ± 0.30	75.93	32.21 ± 0.39
Mucolitc®	Sucrose	63.08 ± 2.03	ND	ND	63.08	ND
Muricalm®	Sucrose	34.69 ± 0.48	22.05 ± 0.03	26.30 ± 0.03	83.04	ND
Polaramine expectorante®	Sorbitol, sucrose	57.05 ± 1.05	ND	ND	57.05	8.45 ± 0.07
Polaramine®	Sorbitol, sucrose	56.84 ± 0.68	ND	ND	56.84	17.35 ± 0.26
Vibral®	Sucrose, sodium cyclamate	85.99 ± 2.40	ND	ND	85.99	ND
Vick Mel®	Sugar, aspartame, acesulfame K	ND	23.18 ± 0.55	32.89 ± 0.88	56.07	ND
Vick®	Sugar, sodium saccharin	49.55±0.20	ND	ND	49.55	ND

* Concentrations are expressed in g% (g/100g) (median ± standard deviation).
† ND = not detected.

Table 4. Organic acid content, pH, titratable acidity and viscosity values of the evaluated medicines

Brand names	*Acid content according to labels**	*pH*	*Vol NaOH (mL)†*	*Viscosity‡*
Aeroflux®	Citric acid	4.2	16.63 ± 0.28	30.2
Aerolin®	Citric acid	3.6	7.37 ± 0.10	10.9
Berotec®	Citric acid	3.5	3.08 ± 0.09	10.7
Bisolvon®	Tartaric acid	4.1	2.18 ± 0.05	36.6
Bricanyl broncodilatador®	Citric acid	3.8	4.92 ± 0.18	4.3
Bricanyl expectorante®	Citric acid	3.9	4.85 ± 0.29	2.8
Brondilat®	Citric acid	4.9	0.28 ± 0.00	4.9
Claritin D®	Citric acid	3.7	2.39 ± 0.10	40.9
Claritin®	Citric acid	2.8	14.59 ± 0.32	19.7
Desalex®	Citric acid	5.7	0.59 ± 0.05	13.7
Dimetapp elixir®	Citric acid	2.7	11.96 ± 0.05	13.3
Fluimucil®	---	6.4	0.83 ± 0.03	4.7
Mucolitic®	---	5.4	0.26 ± 0.02	6.1
Mucosolvan®	Benzoid acid, tartaric acid	2.6	3.65 ± 0.02	18.3
Muricalm®	Acetic acid	3.8	1.20 ± 0.02	6.7
Polaramine expectorante®	---	5.6	0.36 ± 0.01	7.9
Polaramine®	---	6.0	0.54 ± 0.05	9.7
Silomat Plus®	Chloridric acid	3.3	2.09 ± 0.02	21.3
Silomat®	Chloridric acid	3.3	1.05 ± 0.02	13.9
Vibral®	Citric acid	5.0	0.65 ± 0.00	14.2
Vick Mel®	Citric acid	4.7	7.36 ± 0.12	146.6
Vick®	Citric acid	4.9	4.17 ± 0.14	412.3
Zyrtec®	---	5.0	1.40 ± 0.09	5.1

* (---) not mentioned in labels.
† Volume of NaOH solution required to achieve neutral pH or indicator change.
‡ Viscosity values are presented at shear rate of $20s^{-1}$ (unit of viscosity: cP – centi-Poise = millipascal second, mPa·s).

the development of dental caries and dental erosion. It has been traditionally understood that pH is an accurate indicator and an important variable involved in the erosive potential of food and drink. However, it is not just the pH that is important, but rather the titratable acidity. The greater the buffering capacity of a drink, the longer it will take for saliva to neutralize the acid (Lussi and Jaeggi, 2006). Therefore, it can be presumed that those medicines with lower pH and higher neutralizable acidity values (Table 4) are the ones that might cause dental erosion (Hellwig and Lussi, 2006).

Paediatric medicines may contain several types of acids that contribute to low pH values. According to the labels, citric acid was the main acid used in most medicines evaluated. It should be noted that it is a weak acid, dissociates in solutions of higher pH and is able to act as a buffer over a range of pHs. However, it is a potent erosive agent because of its ability to chelate

calcium in hydroxyapatite, thus increasing enamel's dissolution on exposure to the acid. The chelating properties of citric acid can enhance the erosive process in vivo by interacting with saliva as well as directly softening and dissolving tooth minerals (Lussi and Jaeggi, 2006). But other acids such as acetic acid, tartaric acid and benzoic acid may also be present in paediatric medicines. Again, as occurred with the sweeteners, the actual amounts present in these products were not stated on the labels.

A limitation of the present study is the absence of quantification of the calcium, phosphate and fluoride content of the liquid medicines, because these seem to be important factors for the prediction of the erosive potential (Lussi *et al*., 2004). However, our objective was to identify some other aspects that could increase the risk of dental caries and erosion, such as sugar content, acidity and viscosity. In later studies we intend to assess other chemical aspects (such as the presence of ions) involved in the erosion process. Additionally, the exact contribution of the various acidic components of medicines in eroding enamel is unclear, especially *in vivo*. In these cases, behavioral and biological aspects must also be considered, as proposed by Maguire *et al* (2007). It must be pointed out that this study did not aim to define the degree to which each medicine might damage teeth, but rather observe if they present characteristics that could influence dental erosion.

It seems that adhesiveness and displacement of liquid are also factors to be considered in both the erosion process (Lussi and Jaeggi, 2006) and the caries process (Duward and Thou, 1997). The greater the adherence of an acidic substance, the longer will be the contact time with the tooth surface and the higher the likelihood of erosion (Lussi *et al*., 2004). Therefore, medicines with prolonged oral clearance can constitute a risk to dental health (Maguire *et al*., 2007). Two medicines (Table 4) presented critical viscosity values compared with the others. However, information in the literature about the relation between viscosity and dissolution of dental hard tissues is rare.

Additionally, some medicines, such as antihistamines, may contribute to the danger of erosion and dental caries when reducing salivary flow (Costa *et al*., 2006). Eight of the paediatric syrups analyzed in this study are antihistamines. In addition, four of them had pH values below the critical value and six of them contained fermentable carbohydrates.

Although erosion and caries are different, the two conditions occurring concurrently could be deleterious to dental hard tissues. Therefore, many preventive measures have been suggested to minimize tooth damage caused by acidic medicines, such as avoiding bedtime intake, avoiding toothbrushing immediately after an erosive challenge and emphasizing the consumption of medication at mealtimes (Lussi *et al*., 2004).

Measures to counteract both erosion and caries would be rinsing with fluoride solutions to enhance remineralization and chewing sugarless gum to stimulate the secretion of saliva (Lussi *et al*., 2004). There is no evidence that measures such as toothbrushing or rinsing with water after taking a sugar-based medicine are effective, because paediatric medicines are usually viscous syrups that lodge in fissures and interproximal areas, inaccessible to the toothbrush. A practical and effective way of preventing dental caries caused by medicines is to use a sugar-free preparation (Bigeard, 2000).

Therefore, it is a matter of urgency to promote and organize campaigns and strategies to address this problem. Awareness of the danger posed by these medications should be promoted among practitioners, pharmacists, manufacturers, regulatory authorities and the public to bring about increased availability and use of sugar-free medicines (Duward and Thou, 1997). There is a need for increased education for health professionals to persuade them to put in practice oral health instructions for their patients (Neves *et al*., 2008).

Efforts should be made by the pharmaceutical industry to modify the composition of some medicines, thus reducing their potentially harmful effects on teeth, and reformulate them to be sugar-free with low acid levels and low viscosity. Moreover; it is known in pediatrics that the use of certain dose forms, particularly effervescent and chewable tablets, is increasing (Maguire and Rugg-Gunn, 1997). However, with these changes in dose form and formulation, the potential for widespread dental effects, including tooth wear, has increased (Maguire *et al*., 2007). Further research is needed to quantify the impact of these factors on teeth and to determine the extent of the problem, the strength of association of etiological factors and which factors protect or reduce the cariogenic and erosive potential of liquid paediatric medicines.

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