

***In vitro* analysis of the cariogenic and erosive potential of paediatric antitussive liquid oral medications**

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Abstract: We evaluated *in vitro* the cariogenic and erosive potential of antitussive liquid oral medications for paediatric use. Fifteen paediatric liquid antitussives were sampled. The endogenous pH was evaluated by potentiometry, titratable acidity was measured according to the method adopted by the Association of Official Analytical Chemists, total soluble solids content (TSSC) readings were performed by Brix refractometry using the Abbé refractometer, and the total sugar content was determined according to the Fehling methodology. The experiments were performed in triplicate and the obtained data were entered in the Excel software, analyzed and presented by descriptive statistics (means and standard deviations). Endogenous pH values ranged from 2.49 ± 0.09 (Iodetox[®]) to 6.75 ± 0.005 (Carbocysteine[®]) and twelve medications showed pHs below the critical value of 5.5 for enamel demineralization. Iodetox[®] (0.021 ± 0.01) presented the lowest titratable acidity and Aerofrin[®] (1.171 ± 0.01) presented the highest titratable acidity. Celergin[®] presented the highest TSSC (62.26 ± 0.40) and Acetylcysteine[®] (100 mg granules bags) presented the lowest TSSC (3.25 ± 0.43). Only 5 medications contained sugar, with total sugar content ranging from $35.93\% \pm 6.65$ (Iodetox[®]) to $59.60\% \text{ DP} \pm 6.66$ (Celergin[®]). The paediatric antitussive medications showed low endogenous pH, some of them even below the critical value for enamel dissolution ($\text{pH} < 5.5$). These antitussives are potentially cariogenic and erosive to dental structures if used frequently because of the high titratable acidity and high sugar concentration, especially when adequate oral clearance is not performed after administration of each dose.

Keywords: dental caries, antitussives, hydrogen-ion concentration, Brazil

Introduction

Oral health is essential for children's general health, growth and development. Dental caries is the most common oral disease and the most prevalent infectious disease in the oral cavity (CDC, 2000). Among the theories that explain caries onset, the most widely accepted refers to the action of acids produced by bacterial fermentation of carbohydrates (sugars) from the diet (Wilkinson & Moore, 1990). However, some diseases or medications may increase the risk or severity of caries (Marquezan *et al.*, 2007).

Several liquid medications can be part of the daily routine of children with chronic diseases (Peres *et al.*, 2005) such as asthma, cardiopathies, epilepsy and chronic renal failure (Durward & Thou, 1997; Kenny & Somaya, 1989; Steinbacher & Glick, 2001) as well as those with recurrent benign pathologies such as flu, cold, tonsillitis, otitis, allergic rhinitis and

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sinusitis (Maguire & Rugg-Gunn, 1997; Marquezan *et al.*, 2007). Antibiotics and antitussives are the most common sugar-containing medications regularly used by young children (Cavalcanti *et al.*, 2008).

A previous study found an increasing prevalence in the prescription of drug therapy for the treatment of children with chronic conditions in the United States (Cox *et al.*, 2008). This tendency is also observed in Asia and in some Latin-American countries (Passos *et al.*, 2010). In general, pharmaceutical companies add some type of sugar to different paediatric medicine formulations, usually sucrose, in order to mask the unpleasant taste of some of their active ingredients (Bigéard, 2000; Bradley & Kinirons, 1998; Passos *et al.*, 2010). However, regular use of liquid medications sweetened with sucrose increases the risk of development of carious lesions and enamel dissolution due to erosion (Linnett & Seow, 2001; Lussi *et al.*, 2004; Lussi & Jaeggi, 2008; Nunn *et al.*, 2003; Sahgal *et al.*, 2002).

Paediatric medications may present a high erosive potential to dental tissues due to the existence of acid components in their formulations, low endogenous pH, high titratable acidity and absence or little amount of calcium, fluoride and phosphate ions (Costa *et al.*, 2006). Although erosion and caries have different processes, both conditions may occur simultaneously and be deleterious to the dental tissues (Tahmassebi *et al.*, 2006).

It is important to highlight that in such countries as Brazil (Santos & Coelho, 2006) and Sri Lanka (Mendis *et al.*, 2007) people have easy access to several types of medications and that there is an even higher risk for caries disease when the use of sweetened medications is not associated with effective oral hygiene measures to eliminate residues of the medication after ingestion of each dose (Bigéard, 2000). The objective of this study was therefore to evaluate *in vitro* the cariogenic and erosive potential of antitussive liquid oral medications for paediatric use in Brazil.

Material and Methods

Study area and design

The determination of endogenous pH, titratable acidity, total soluble solids content (TSSC - %Brix) and total sugar content was carried out on the 15 most frequently prescribed paediatric antitussive liquid medications in the city of Campina Grande, PB, Brazil. Fourteen of these medications were in the form of syrups and one in the form of 100mg granules bags (Table 1). The samples were randomly selected into 3 groups for each medication, these were tested and the mean values were recorded. Data were collected by a single calibrated examiner (Kappa = 0.83) and were recorded in study-specific charts.

pH Measurement

The endogenous pH of each medication was determined at room temperature (20°C) using a pH meter (Hanna Instruments Brazil, São Paulo, SP, Brazil) placed directly into each solution. The pH meter accurate to 0.1 was first calibrated according to the manufacturer's instructions, using buffer standards of pH 7 and pH 4. As much as 10 mL of each medication was placed in a beaker, the pH meter was immersed into the syrup and the value was recorded (Cavalcanti *et al.*, 2008).

Titratable Acidity

Titratable acidity was measured according to the method adopted by the Association of Official Analytical Chemists (AOAC, 1984), that is, the amount of 0.1 N KOH solution

needed for the product to reach a neutral pH or a pH value above it. A 10 mL aliquot of the diluted product was titrated (10% solution of the sample) with the 0.1 N KOH solution until the substance reached a pH value between 8.2-8.4, corresponding to the end-point of the phenolphthalein. Readings were done with a pH meter (Hanna Instruments Brazil, São Paulo, SP, Brazil) (Cavalcanti *et al.*, 2008). When this value was reached, the spent KOH volume was recorded and the acid percentage of the substance was calculated using the following equation, with the result being expressed as percentage of citric acid.

$$\text{Acidity (\%citric acid)} = (V \times \text{Nap} \times F \times \text{meq-g (citric acid)} \times 100) / \text{Sample}$$

Where: V = KOH volume; Nap = Normal concentration of the KOH base; F = Normality correction factor; meq-g = miliequivalent per gram of citric acid; Sample= volume of the medication.

Table 1: Commercial brand, active principle and manufacturers of the tested medications

| Commercial Brand | Active Principle | Manufacturer |
|---|--|---|
| Acebrophylline | Acebrophylline | Medley S.A. Ind. Farm., Campinas, SP, Brazil |
| Acetylcysteine | Acetylcysteine | EMS S/A, Hortolândia, SP, Brazil |
| Acetylcysteine* | Acetylcysteine | Medley S.A. Ind. Farm., Campinas, SP, Brazil |
| Aerofrin | Salbutamol sulfate | Pharmascience Laboratórios Ltda, Betim, MG, Brazil |
| Ambroxmel | Ambroxol hydrochloride | Cimed Ind. Med. Ltda., São Paulo, SP, Brazil |
| Bispect | Bromhexine hydrochloride | Uni-Farma Ind. Farm., São Bernardo, SP, Brazil |
| Bronquitós | Theophylline + pyridoxine hydrochloride + diphenhydramine hydrochloride + guaiphenesin | EMS S/A, Hortolândia, SP, Brazil |
| Carbocysteine | Carbocysteine | Cimed Ind. Med. Ltda., São Paulo, SP, Brazil |
| Celergin | Betametasona + Dexchlorpheniramine maleate | EMS S/A, Hortolândia, SP, Brazil |
| Clobutinol hydrochloride | Clobutinol hydrochloride | Medley S.A. Ind. Farm., Campinas, SP, Brazil |
| Clobutinol hydrochloride + Doxylamine succinate | Clobutinol hydrochloride + Doxylamine succinate | Medley S.A. Ind. Farm., Campinas, SP, Brazil |
| Detoss | Potassium iodine + guaiphenesin + mentol | MDCPharma Prod. Farm., Ltda., Tubarão, SC, Brazil |
| Expectovic | Guaiphenesin | MDCPharma Prod. Farm., Ltda., Tubarão, SC |
| Hytós Plus | Clobutinol hydrochloride + Doxylamine succinate | União Química Farm. Nacional S/A, Taboão da Serra, SP, Brazil |
| Iodetox | Potassium iodine | Mariol Industrial Ltda., Barretos, SP, Brazil |

*100 mg granules bags

Total Soluble Solids Content (TSSC)

Bx readings were made by refractometry using an Abbé refractometer (PZO-RL1, Warszawa, Poland). As the refractive index of a sugar-containing solution is also temperature-dependent, refractometers are typically calibrated at 20°C. The equipment was calibrated with deionised water (refraction index= 1.3330 and 0° Brix at 20°C) and the readings of the samples were performed (Cavalcanti *et al.*, 2008).

Total Sugar Content

For determination of total sugar content, 5ml of concentrated hydrochloride acid were added to 25ml of each medication and put in double-boiler for 10min. After cooling, 5ml of diluted saturated lead acetate and distilled water base were added. The next stage consisted of the addition of 5ml of each one of the Fehling liquor solutions, followed by the addition of 40ml of distilled water and heating of the substance for 4min at the boiling point. A volume of

25ml of diluted filtrate was transferred and titrated against the Fehling liquor solution in the presence of methylene blue, discoloration occurred (formation of brick red precipitate). The wasted volume was recorded and the total sugar content of the sample was calculated using the following equation:

$$\text{Total sugar content (\%)} = \frac{F_{EQ} \times \text{dilution} \times 100}{V_{TITRATION}}$$

Where: F_{EQ} = Equivalence Factor; $V_{TITRATION}$ = volume wasted in the titration.

Results

Table 2 shows the distribution of the paediatric antitussive medications and their respective means and standard deviations for endogenous pH, titratable acidity, TSSC (%Brix) and total sugar content.

Table 2: Distribution of the means and standard deviations of endogenous pH, titratable acidity, TSSC (%Brix), and total sugar content of the paediatric antitussive medications evaluated

| Medications | Endogenous pH | | Titratable Acidity | | TSSC | | Total Sugar | |
|---|---------------|-------|--------------------|-------|-------|------|-------------|------|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Acebrophylline | 4.40 | 0.005 | 0.21 | 0.007 | 38.91 | 0.14 | - | - |
| Acetylcysteine | 5.96 | 0.03 | 0.083 | 0.004 | 3.51 | 0.27 | - | - |
| Acetylcysteine | 3.00 | 0.005 | 0.088 | 0.01 | 3.25 | 0.43 | - | - |
| Aerofrin | 3.03 | 0.03 | 1.171 | 0.01 | 33.05 | 0.08 | 37.02 | 6.65 |
| Ambroxmel | 3.19 | 0.00 | 0.443 | 0.01 | 31.96 | 1.05 | - | - |
| Bispect | 4.14 | 0.01 | 0.118 | 0.004 | 32.79 | 0.08 | - | - |
| Bronquitós | 4.35 | 0.005 | 0.875 | 0.005 | 4.95 | 0.54 | - | - |
| Carbocysteine | 6.75 | 0.005 | 0.138 | 0.01 | 4.16 | 0.38 | - | - |
| Celergin | 3.13 | 0.01 | 0.415 | 0.02 | 62.26 | 0.40 | 59.60 | 6.66 |
| Clobutinol hydrochloride | 2.74 | 0.01 | 0.104 | 0.004 | 26.9 | 0.31 | - | - |
| Clobutinol hydrochloride + Doxylamine succinate | 3.02 | 0.02 | 0.152 | 0.002 | 38.43 | 0.16 | - | - |
| Detoss | 5.04 | 0.01 | 0.049 | 0.007 | 35.76 | 0.02 | 48.12 | 9.66 |
| Expectovic | 5.99 | 0.01 | 0.150 | 0.04 | 55.00 | 0.66 | 59.11 | 3.41 |
| Hytós Plus | 4.00 | 0.01 | 0.164 | 0.002 | 42.16 | 1.37 | - | - |
| Iodetox | 2.49 | 0.09 | 0.021 | 0.01 | 25.08 | 0.14 | 35.93 | 8.17 |

Endogenous pH values ranged from 2.49 ± 0.09 (Iodetox[®]) to 6.75 ± 0.005 (Carbocysteine[®]) and 12 medications showed pHs below the critical value of 5.5 for enamel demineralization. Iodetox[®] (0.021 ± 0.01) presented the lowest titratable acidity and Aerofrin[®] (1.171 ± 0.01) presented the highest titratable acidity. Celergin[®] presented the highest TSSC (62.26 ± 0.40), Acetylcysteine[®] (100mg granules bags) presented the lowest TSSC (3.25 ± 0.43). Only 5 medications contained sugar, with total sugar content ranging from $35.93\% \pm 6.65$ (Iodetox[®]) to $59.60\% \pm 6.66$ (Celergin[®]).

Discussion

Several paediatric liquid medications may contain components named excipients or “inactive ingredients”, which can be deleterious to the dental structures, causing dental caries or erosion. Among these components, the most common are fermentable sugars and acids (Marquezan *et al.*, 2007). Because of the bitter taste of most medications, sugar is combined with other ingredients to give a more pleasant taste to the medications in order to increase acceptance and treatment compliance of patients, especially children (Hobson, 1985). Although there are artificial substitutes, such as sodium saccharine, sodium cyclamate, aspartame (Sasaki *et al.*, 2002) and sorbitol (Kumar *et al.*, 1993), sucrose is most widely used by the pharmaceutical industry because it has a lower cost, has antioxidant properties, preserves the formulation, and has an easy processing (Bigear, 2000; Chu *et al.*, 2001).

In a previous study, 82% of the syrup formulations evaluated contained sugar, which contraindicates their use by diabetic children and may increase the risk for caries in case of regular use (Kulkarni *et al.*, 1993). Several studies have shown higher dental caries prevalence in children under long-term use of liquid medications and that the severity of carious lesions got worse as treatment rates increased (Passos *et al.*, 2010; Sahgal *et al.*, 2002; Sunitha *et al.*, 2009).

Paediatric medications may also contain several types of acids that contribute to produce low pH values. However, some of the medications evaluated in this study did not contain information on the acid component in the product label. Among those that had this information, citric acid was by far the most common, followed by hydrochloride, tartaric or benzoic acids. It has been well demonstrated that citric acid can produce high levels of erosion, possibly due to its strong chelating properties (Lussi & Jaeggi, 2008).

The analysis of endogenous pH revealed that 12 medications presented pH values lower than the pH value that is considered critical for enamel demineralization (pH<5.5), varying between 2.49 (Iodetox[®]) and 6.75 (Carbocysteine[®]). This result is in accordance with those of previous studies (Maguire *et al.*, 2007; Marquezan *et al.*, 2007; Cavalcanti *et al.*, 2008; Sunitha *et al.*, 2009), which also found that these substances are erosive to the dental tissues.

Titrateable acidity was another physicochemical property analyzed in this study. It represents the total content of acids and is considered as an indication of the strength of the erosive potential (Shaw & Smith, 1998). Titrateable acidity values varied between 0.021 (Iodetox[®]) and 1.171 (Aerofrin[®]). A previous study also revealed high titrateable acidity in liquid medications (Maguire *et al.*, 2007), confirming their erosive nature.

The total soluble solids content is a measure of total content of soluble solids (proteins, lipids, glucides, mineral salts, vitamins, organic acids, pigments and other substances) in a sample (Ball, 2006), which has a direct relationship with the viscosity of the ingested foods, possibly facilitating the retention of diet components on the dental surfaces. One of the products analyzed in the study presented high %Brix (above 62%).

Regarding the total sugar content, only 5 medications presented sucrose in their composition, with values ranging from 35 to 59%. The other medications presented artificial sucrose substitutes, with predominance for the use of sodium saccharine. It is important to highlight that these are extremely high values and thus the long-term administration of these products can be a risk factor for the development of carious lesions in children under treatment with sweetened medications without an adequate control of oral hygiene. However, as caries is a multifactorial disease, long-term use of liquid oral medications must be associated with other factors for caries onset (Bankel *et al.*, 2006).

In addition to the properties of the medications, the indiscriminate use of liquid formulations (syrups) by young children can increase the risk for development of caries disease and dental erosion because the administration of liquid oral medications at bedtime frequently is not followed by proper oral hygiene after ingestion of the substance. Ingestion of sweetened medications or foods by children at bedtime or during the night is especially harmful to the teeth because the reduced salivary flow during sleep limits the natural cleansing action of saliva. This means that the sugar-containing medication or food remains in contact with tooth surfaces for a long period (Shaw & Glenwright, 1989). The liquid oral medications are usually viscous syrups that penetrate into the fissures and proximal areas, which are inaccessible to the toothbrush. Children should also be encouraged to rinse their mouths with water after taking liquid medications.

Most parents are not aware that several foods, beverages and paediatric medications in the form of syrups or granules to be dissolved contain sugar, and associate caries disease only with the consumption of candies and cookies (Mentes, 2001). Non-cariogenic or sugar-free medications should be prescribed whenever possible (Hunter *et al.*, 2000; Passos *et al.*, 2010).

Considering the cariogenic and erosive potential of sweetened and acidic medications prescribed to children, it is important that health professionals, especially paediatricians and paediatric dentists, are engaged in educating parents to ensure adequate oral clearance after each dose of medication as a primary step for minimizing the risk of dental caries and erosion of dental structures related to long-term, and sometimes unsupervised, regimens with sugar-containing liquid oral medications.

In conclusion, the paediatric antitussive medications evaluated in this study showed low endogenous pH values, some of them even below the critical value for enamel dissolution (pH<5.5), high titratable acidity and high sugar concentration (when sugar was presented in the formulation), being potentially cariogenic and erosive to the dental structures if frequently used, especially when adequate oral clearance is not performed after administration of each dose.

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