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CARIOGENICIDADE DE MEDICAMENTOS INFANTIS: AVALIAÇÃO DESTE POTENCIAL EM ESTUDO IN VITRO

CARIOGENICITY OF CHILDREN'S MEDICINES: EVALUATION OF THIS POTENTIAL IN AN IN VITRO STUDY

CARIOGENICIDAD DE MEDICAMENTOS INFANTILES: EVALUACIÓN DE ESTE POTENCIAL EN UN ESTUDIO IN VITRO

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RESUMO: Os medicamentos infantis possuem compostos aromatizantes e adoçantes utilizados para facilitar a aceitação das crianças por amenizarem o sabor desagradável. Por outro lado, a alta concentração de açúcares adicionada às fórmulas pode favorecer a desmineralização dos tecidos dentais e a formação de uma lesão cariosa, na ausência de uma higiene bucal adequada. O objetivo central deste estudo foi analisar o potencial de cariogenicidade de diferentes medicamentos pediátricos. Foram analisados oito medicamentos pediátricos, sendo eles: Amoxicilina, Dipirona monosódica, Paracetamol, Dropropizina, Ibuprofeno, Maleato de bronfeniramina + cloridrato de fenilefrina, Nitazoxanida, Sulfametoxazol + trimetoprima; nas quais os teores de açúcares totais e redutores existentes em cada amostra foram determinados, em triplicata, pelo método de Lane-Eynon (Fehling). Foi observado que o maior teor de açúcar total (37,26%), bem como de açúcar redutor (22,98%) foi encontrado em uma das amostras de Amoxicilina (A3 e AR3) e seus valores de pH foram os mais baixos: 5,6 e 5,7, respectivamente. O menor teor de açúcar total (17,87%), assim como o de açúcar redutor (3,13%) esteve presente em uma das amostras de Dropropizina. Os demais medicamentos não apresentaram açúcares fermentáveis, mas apenas substâncias adoçantes. Conclui-se que a Amoxicilina foi o medicamento com maior potencial cariogênico, seguida pela Dropropizina; entretanto, também existem os que apresentam formulações isentas de açúcares, refletindo um avanço da indústria na substituição por adoçantes não cariogênicos.

Palavras-chave: Cárie dentária. Açúcares adicionados. Soluções orais.

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ABSTRACT: Children's medications contain flavorings and sweeteners used to ease children's acceptance by lessening their unpleasant taste. On the other hand, the high concentration of sugars added to formulas can promote demineralization of dental tissue and the formation of caries lesions in the absence of adequate oral hygiene. The main objective of this study was to analyze the cariogenic potential of different pediatric medications. Eight pediatric medications were analyzed: Amoxicillin, Dipyrone Monosodium, Paracetamol, Dropropizine, Ibuprofen, Bronpheniramine Maleate + Phenylephrine Hydrochloride, Nitazoxanide, Sulfamethoxazole + Trimethoprim. The total and reducing sugar levels in each sample were determined in triplicate using the Lane-Eynon (Fehling) method. It was observed that the highest total sugar content (37.26%), as well as reducing sugar (22.98%) was found in one of the Amoxicillin samples (A3 and AR3), and their pH values were the lowest: 5.6 and 5.7, respectively. The lowest total sugar content (17.87%), as well as reducing sugar (3.13%) was present in one of the Dropropizine samples. The other medications did not present fermentable sugars, but only sweetening substances. It is concluded that Amoxicillin was the medication with the greatest cariogenic potential, followed by Dropropizine; however, there are also those that present sugar-free formulations, reflecting an advance in the industry in the replacement by non-cariogenic sweeteners.

Keywords: Dental caries. Added sugars. Oral solutions.

RESUMEN: Los medicamentos infantiles contienen saborizantes y edulcorantes que se utilizan para facilitar su aceptación por parte de los niños, disminuyendo su sabor desagradable. Por otro lado, la alta concentración de azúcares añadidos a las fórmulas puede promover la desmineralización del tejido dental y la formación de lesiones de caries en ausencia de una higiene bucal adecuada. El objetivo principal de este estudio fue analizar el potencial cariogénico de diferentes medicamentos pediátricos. Se analizaron ocho medicamentos pediátricos: amoxicilina, dipirona monosódica, paracetamol, dropropizina, ibuprofeno, maleato de bromfeniramina + clorhidrato de fenilefrina, nitazoxanida, sulfametoxazol + trimetoprima. Los niveles de azúcares totales y reductores en cada muestra se determinaron por triplicado mediante el método de Lane-Eynon (Fehling). Se observó que el mayor contenido de azúcar total (37,26%), así como de azúcar reductor (22,98%), se encontró en una de las muestras de amoxicilina (A3 y AR3), y sus valores de pH fueron los más bajos: 5,6 y 5,7, respectivamente. El menor contenido de azúcar total (17,87%), así como de azúcar reductor (3,13%), estuvo presente en una de las muestras de dropropizina. Los demás medicamentos no presentaron azúcares fermentables, sino únicamente sustancias edulcorantes. Se concluye que la amoxicilina fue el medicamento con mayor potencial cariogénico, seguido de la dropropizina; sin embargo, también existen aquellos que presentan formulaciones sin azúcar, lo que refleja un avance en la industria en sustituirlos por edulcorantes no cariogénicos.

Palabras clave: Caries. Azúcares añadidos. Soluciones orales.

INTRODUCTION

Regular medication use is very common in childhood, particularly in children with seizures, chronic illnesses, asthma, respiratory allergies, or those that trigger acute conditions such as sinusitis, tonsillitis, otitis media, and allergic rhinitis (LEAL et al., 2015). Although their action is systemic in controlling infection and/or inflammation, locally in the oral cavity,

medications can reduce salivary flow and salivary buffering capacity, favoring the development of caries (XAVIER et al., 2013; PEREIRA, 2023).

Dental caries is a chronic disease commonly developing in childhood. It results from the localized chemical dissolution of the tooth surface caused by metabolic events occurring in the biofilm covering the affected area (FEJERSKOV, 2015). The disease has a multifactorial etiology. Several factors, such as diet, saliva composition, buffering capacity, hygiene, and social class, among others, interact to promote demineralization of dental tissues (LOSSO et al., 2009).

Children's medications contain flavorings and sweeteners intended to alleviate unpleasant tastes that children dislike (JUNG and JUN, 2021; SILVA et al., 2022). For this purpose, a high amount of sugar may be added to formulas, with sucrose being the main culprit, followed by fructose and glucose. These, when used frequently, can alter the oral microbiota (BABU, 2014; LOZANO et al., 2018).

Recent studies confirm that pediatric formulations with non-cariogenic sweeteners, such as xylitol and sorbitol, significantly reduce the incidence of tooth decay compared to sugar-sweetened versions (LUO et al., 2024; LIANG et al., 2024). This fact is putting pressure on the pharmaceutical industry to develop sugar-free pediatric formulations. A recent meta-analysis concludes that low-intensity sweeteners, such as xylitol, sorbitol, and erythritol, not only reduce the number of cariogenic bacteria but also significantly reduce tooth decay rates in children and adolescents (LIANG et al., 2024).

Sucrose is a compound that promotes fermentation in the oral microbiota and exhibits significant acidogenic activity, resulting in a decrease in the pH of dental biofilm (DE AZEREDO et al., 2021). Furthermore, medications with a high sucrose percentage, low endogenous pH, and high titratable acidity have both cariogenic and erosive potential, as they promote a rapid drop in oral pH, which remains low for longer periods of time (SOUZA et al., 2010; VIEIRA, 2021).

The sugar content in each sample can be investigated using the Lane-Eynon (Fehling) method, which uses a Cu^{+2} solution. When heated in an alkaline solution, sugars with free groups readily transform into enediols, which are substances subject to the action of oxidizing agents. The end point of the reaction is indicated by methylene blue, which is reduced to its colorless form by a small excess of reducing sugar. However, as a brick-colored precipitate forms, the visible color change from blue to brick red. The methylene blue indicator is added only near the end point. The bleaching is almost instantaneous and the action of the indicator

is reversible, since the addition of traces of copper salts restores its color immediately (DOS SANTOS et al., 2016).

Considering that medications are part of many children's daily routines, and given the high sugar content of their formulations, this study evaluated the cariogenicity of pediatric medications. This study aims to inform the public, especially those responsible for them, about the risks associated with continued medication intake when there is a lack of adequate oral hygiene.

In this context, this study aimed to analyze the cariogenicity potential of different pediatric medications by analyzing their total and reducing sugar levels, as well as their potential hydrogenation (pH).

METHODS

Samples

The samples consisted of eight liquid pediatric medications: amoxicillin, dipyrone monosodium, dropropizine, ibuprofen, brompheniramine maleate + phenylephrine hydrochloride, nitazoxanide, paracetamol, and sulfamethoxazole + trimethoprim. The analyses were performed in December 2024 and January 2025 at the Instituto Federal de São Paulo, in Barretos. The selection of these drugs was based on national epidemiological data indicating their frequency of use among children in Brazil. Pons et al. (2024) demonstrated a high prevalence of childhood self-medication (22.2%), with a predominance of analgesics (dipyrone, paracetamol, ibuprofen), antibiotics (amoxicillin, sulfamethoxazole + trimethoprim), and antihistamines (brompheniramine + phenylephrine). Other studies confirm the prominent use of paracetamol, dipyrone, amoxicillin, and ibuprofen (COSTA et al., 2014; BERTOLDI et al., 2016) and nitazoxanide (against viral gastroenteritis) (REZENDE, 2022). Their chemical composition is shown in Table 1.

Table 1. Drug samples according to trade name, active ingredients and composition.

Commercial Name	Active Ingredients	Laboratory	Composition
Dipyrone (analgesic)	Dipyrone 500mg/ml	Farmace	Monobasic sodium phosphate, dibasic sodium phosphate, sodium saccharin, and purified water.
Paracetamol (analgesic/antipyretic)	Paracetamol 200mg/ml	EMS	Macrogol, sodium saccharin, sodium cyclamate, sodium benzoate, sodium metabisulfite, citric acid, sunset yellow dye,

Ibuprofen (anti-inflammatory/analgesic)	Ibuprofen 100mg/ml	Neo Química	vanilla essence, tangerine essence and purified water q.s. Citric acid, vanilla flavor, cherry flavor, strawberry flavor, sodium benzoate, sodium cyclamate, titanium dioxide, glycerol, xanthan gum, sodium lauryl sulfate, sodium saccharin dihydrate, simethicone, sucralose, purified water.
Amoxicillin (antibiotic)	Amoxicilin 250mg/5ml	Prati Donaduzzi	Carmellose sodium, microcrystalline cellulose, sodium saccharin, strawberry essence, sodium citrate dihydrate, sodium cyclamate, silicon dioxide and sucrose.
Benectrin (antibiotic)	Sulfamethoxazole 200mg/5ml + Trimethoprim 40mg/5ml	EMS	Carmellose sodium, microcrystalline cellulose, polysorbate 80, simethicone, sodium saccharin, propylparaben, methylparaben, glycerol, cherry essence, caramel essence, bordeaux red dye, sodium cyclamate, ethyl alcohol, citric acid and purified water.
Decongex (decongestant)	Bronpheniramine maleate 2mg/ml + Phenylephrine hydrochloride 2.5mg/ml	Neo Química	Citric acid, sodium citrate, sodium benzoate, glycerol, sorbitol, sucralose, artificial liq. purple grape flavor and water
Annita (anthelmintic)	Nitazoxanide 20mg/ml	Althaia	Sorbitol, microcrystalline cellulose, sodium carmellose, adipic acid, sodium benzoate, xanthan gum, strawberry essence, sodium citrate dihydrate, sucralose and red dye no. 33.
Dropropizine (antitussive)	Dropropizine 1,5 mg/mL	Biosintética	sodium benzoate, benzoic acid, sucrose, honey flavor, citric acid and purified water.

Source: Amoxicillin (2024), Benectrin (2024), Dipyrone (2024), Dropropizine (2024), Ibuprofen (2024), Bronpheniramine Maleate + Phenylephrine Hydrochloride (2024), Nitazoxanide (2024); Prepared by the authors (2024).

Standardization of Fehling's solution

The standardization of Fehling's solution was performed by titrating a 1% glucose standard solution against a mixture of 10 mL of Fehling's solution A and 10 mL of Fehling's solution B, and 40 mL of boiling distilled water. The titration was continued until the indicator became discolored. The titration time should not exceed 3 minutes. The standardization of Fehling's solution was calculated according to equation (1):

(1) FC = mL of glucose expenditure x 1

100

Determination of reducing sugar and total sugar content by the Lane-Eynon (Fehling) method

To determine the total sugar content, five grams (5 g) of each sample, weighed on an analytical balance, were transferred to a beaker and 50 mL of deionized water was added. The hydrogen potential was then analyzed using a digital pH meter (MS Tecnopon microprocessor pH meter, model MPA 210), duly calibrated with standard solutions of pH = 4.0 and pH = 7.0. Next, 2 mL of hydrochloric acid (HCl) was added and the solution was placed in a water bath for 60 minutes. The solution was subsequently neutralized with a 40% NaOH solution. The neutralized solutions were added to a 250 mL volumetric flask, and the volumes were completed with deionized water. These solutions were placed in a burette and titrated against a mixture containing 5 mL of Fehling's solution A and 5 mL of Fehling's solution B, followed by 40 mL of deionized water, and then a saturated methylene blue solution.

To determine the reducing sugar content, five grams (5 g) of each sample, weighed on an analytical balance, were transferred to a beaker with 50 mL of deionized water and stirred until completely dissolved. The solutions were added to a 250 mL volumetric flask and topped up with deionized water. These solutions were placed in a burette and titrated against a mixture containing 5 mL of Fehling's solution A and 5 mL of Fehling's solution B, followed by 40 mL of hot deionized water, and then 1 drop of 1% methylene blue solution. Figure 1 shows the materials used to prepare the Fehling's reagents and indicators (ZENEBON; PASCUET; TIGLEA, 2008).

Figure 1. Materials used to make Fehling's reagents and indicators (Potassium sodium tartrate tetrahydrate PA ($C_4H_4KNaO_6.4\ H_2O$), copper II sulfate pentahydrate ($CuSO4.5H_2O$) PA, sodium hydroxide microbeads PA ACS (NaOH) and methylene blue PA respectively from left to right).

Source: author's own

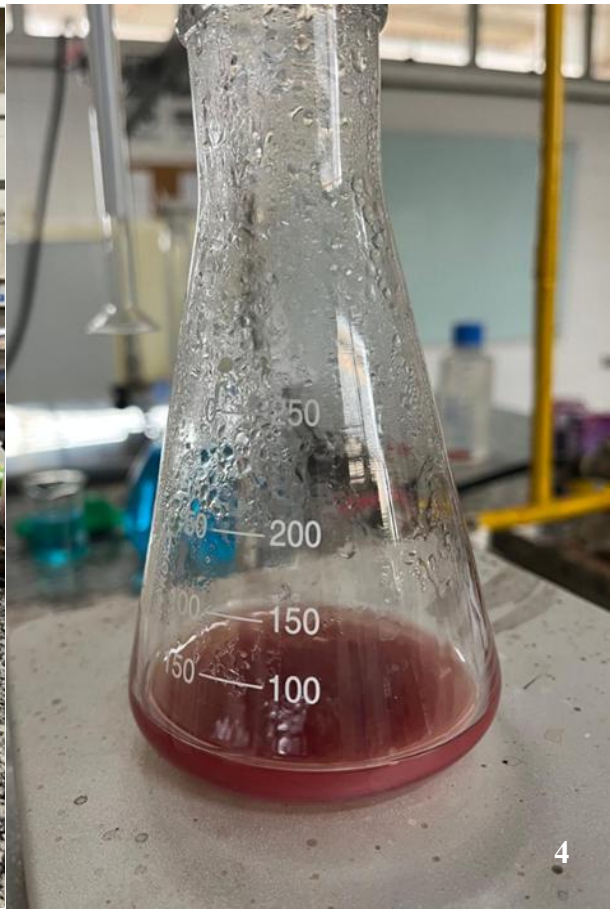
Figure 2 shows the prepared solutions: Glucose 1%, Fehling's Solution A ($CuSO_4$), Fehling's Solution B (tartrate) and methylene blue.

Figure 2. Solutions of 1% Glucose, Fehling's Solution A ($CuSO_4$), Fehling's Solution B (tartrate) and methylene blue.

Source: author's own

Figures 3 and 4 show the glucose sample titration and the titration turning point, respectively.

Figures 3 and 4. Glucose sample titration (blue) and the titration turning point (brick red), respectively.



Source: author's own

The total sugar content was calculated according to equation (2):

$$\text{Total sugars (\%)}: \frac{FC/2 \times 250 \times 100}{V \times m}$$

Where: FC = value obtained from the standardization of Fehling's solution, which indicates how many grams of reducing sugar are needed to reduce exactly 10 mL of the reagent. It adjusts the actual concentration of the solution and is essential for reliable results; V = volume of the sample used in the titration (mL); m = mass of the sample (g).

To ensure the reproducibility and reliability of the results, three samples of each medication analyzed were acquired, all from the same manufacturer, but from different batches, to account for possible variations between productions. Each sample was individually subjected to the tests proposed for determining the reducing and total sugar contents. Therefore, the analyses were performed in triplicate per medication, and the results were expressed as the mean and standard deviation of the three samples, representing the final value of each formulation evaluated.

RESULTS

The standardization of Fehling's solution resulted in a FC = 0.089. Table 2 presents the results obtained in the analyses, including the average levels of reducing sugars and total sugars, as well as the pH values. It is worth noting that the samples of Dipyrone monosodium, Ibuprofen, Brompheniramine maleate + phenylephrine hydrochloride, Nitazoxanide, Paracetamol, and Sulfamethoxazole + trimethoprim did not contain sugar in their composition, but did contain sweeteners, which was confirmed by the experimental analysis of their composition, as described in their package inserts.

It was observed that the highest total sugar content (37.26%), as well as reducing sugar (22.98%), was found in one of the Amoxicillin samples (A3 and AR3), and their pH values were the lowest: 5.6 and 5.7, respectively. The lowest total sugar content (17.87%) and reducing sugar content (3.13%) were found in one of the Dropropizine samples. The other medications contained no fermentable sugars, only sweetening substances. In turn, the Dropropizine samples had the lowest sugar content compared to the antibiotic Amoxicillin.

Table 2. Results obtained (pH, mean and standard deviation).

Total sugars			
Amoxicilin	pH	Average	Standard deviation
A1	5,91	24,38	2,27
A2	6,02	32,96	5,19
A3	5,66	37,26	6,47
Dropropizine	Ph	Average	Standard deviation
D1	4,30	17,87	5,50
D2	4,04	22,04	6,20
D3	4,26	29,85	7,39
Total reducing sugars			
Amoxicilin	pH	Average	Standard deviation
AR1	5,92	19,72	1,19
AR2	5,97	21,16	3,80
AR3	5,75	22,98	1,25
Dropropizine Reducer	pH	Average	Standard deviation
DR1	4,35	3,13	0,34
DR2	4,04	4,08	0,17
DR3	4,26	3,52	0,37

DISCUSSION

Historically, several pediatric medication formulations contained significant amounts of sugars, as exemplified by the previous version of Dipyrone Monohydrate marketed by Farmace, which included sucrose as an excipient (FARMACE, 2024). However, there is a current trend toward replacing these sugars with non-cariogenic sweeteners in pediatric pharmaceutical formulations, seeking to minimize the risks associated with excessive sugar consumption without compromising the therapeutic efficacy of the medications.

Therefore, this reformulation demonstrates a conscious move by the pharmaceutical industry to improve the quality of pediatric formulations, minimizing the negative impacts that sugary excipients can have on children's oral and systemic health. To this end, substitutes such as sodium saccharin, sodium cyclamate, carmellose, sorbitol, and sucralose have been used, which preserve the palatability of medications without posing a cariogenic risk or significantly increasing the glycemic index.

From a dental perspective, the results obtained in this study highlight the high cariogenic potential of some liquid pediatric formulations, especially those with high sugar content, such as the antibiotic Amoxicillin, which also contains a sweetener. This finding corroborates what is widely reported in the literature, which points to the presence of sucrose

as one of the main risk factors for dental caries in children who continuously use medications (DE AZEREDO et al., 2021; COUTINHO et al., 2022; AGRAWAL; TRIVEDI; BARODIA, 2024).

In addition to the sugar content, the acidic pH of medications is another factor that contributes to impaired oral health. Medications with a pH below 5.5, such as Dropropizine, promote enamel demineralization, even in the absence of sugars, by reducing the pH of the tooth surface to levels below the critical pH, causing the dissolution of hydroxyapatite (VIEIRA, 2021; PEREIRA, 2023). Even medications that did not have a pH below 5.5, such as Amoxicillin, demonstrated values close to the critical limit, which still poses a potential risk to the integrity of tooth enamel. This erosive effect is exacerbated when the drugs are administered at night, when salivation is reduced, limiting the buffering effect of saliva.

Acidic pH, when combined with high titratable acidity, can prolong tooth exposure to a demineralizing environment, favoring not only tooth decay but also dental erosion, which is characterized by the irreversible loss of dental tissue due to non-bacterial chemical action (SOUZA et al., 2010). Therefore, even sugar-free medications with a low pH can pose a risk to the integrity of tooth enamel, especially in children with poor oral hygiene habits or frequent consumption of liquid medications (FREITAS et al., 2013).

The finding that medications such as Dipyrone Monosodium, Ibuprofen, Bronpheniramine Maleate + Phenylephrine Hydrochloride, Nitazoxanide, Paracetamol, and Sulfamethoxazole + Trimethoprim did not contain sugar in their composition demonstrates a breakthrough on the part of the pharmaceutical industry. This change in profile can be attributed to the growing awareness of the negative impacts of added sugars in medications, both in terms of oral health and systemic conditions such as obesity (SILVA et al., 2022).

Replacing sugars with non-cariogenic sweeteners, such as sodium saccharin, sodium cyclamate, carmellose, sorbitol, and sucralose, as identified in this study, represents an effective alternative for preserving the palatability of medications without the deleterious effects on teeth (LOZANO et al., 2018; JUNG; JUN, 2021). This strategy has been widely adopted by the pharmaceutical industry as a way to reduce the negative impacts of sucrose consumption in children, particularly regarding the development of dental caries. In addition to contributing to the protection of oral health, sweeteners also contribute to the metabolic safety of pediatric patients, being especially beneficial for children at higher risk of systemic diseases, such as obesity or diabetes (SILVA et al., 2022).

Although sweeteners are considered safer alternatives to sugar, their use should be evaluated with caution. Recent studies demonstrate that polyols such as xylitol, erythritol, and sorbitol, widely used in infant formulas, are effective in reducing the incidence of cavities and inhibiting cariogenic bacteria (LUO et al., 2024; LIANG et al., 2024). These compounds have good metabolic tolerance and do not raise blood glucose levels, which reinforces their safety. However, when ingested in excessive doses, they can cause gastrointestinal effects, especially in younger children (FURNE et al., 2020; RUHNKE et al., 2022). Therefore, although they do not compromise oral health, sweeteners are not exempt from systemic adverse effects.

Furthermore, the literature indicates that many parents and guardians are still unaware of the presence of sugars in pediatric formulations and the risks associated with their prolonged consumption (LEAL et al., 2015). This data highlights the importance of educational initiatives aimed not only at healthcare professionals but also at the general population, with the aim of promoting the rational use of medications and the prevention of diet-related oral diseases. Raising awareness about label reading, choosing medications with sugar-free formulations, and preventive dental care are essential strategies for promoting oral health in childhood.

Therefore, although a positive trend in the reformulation of pediatric medications with the exclusion of sugars can be observed, this study highlights the need for greater health surveillance, specific public policies, and ongoing education for parents and healthcare professionals. Guidance on oral hygiene after medication use, combined with the choice of non-cariogenic and pH-neutral formulations, can significantly contribute to the prevention of tooth decay and erosion, and the promotion of a healthier childhood.

CONCLUSION

It was concluded that Amoxicillin was the medication with the greatest cariogenic potential, followed by Dropropizine. However, there are also medications that offer sugar-free formulations, reflecting the industry's progress in replacing them with non-cariogenic sweeteners.

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