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Evaluation of the cariogenic and erosive potential of pediatric liquid analgesics: An *in-vitro* study

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ABSTRACT

Objective: The objective of the present study is to analyze the endogenous pH, viscosity and total sugar content in 20 commonly prescribed pediatric liquid analgesics. Study design: The pH of each medicine was determined using a digital pH meter (Elico pH meter), viscosity measured using a calibrated digital rotational viscometer (Brookfield viscometer) and sugar content in these medicines was measured using Fehlings method. Results : The pH values of all syrups tested are below critical value of 5.5 with lowest pH in Syr. Ibuprofen group with mean value of 3.98 , sucrose was seen to be maximum in Syr. Ibuprofen group in the mean concentration of 43.13% ± 0.25% and viscosity was found to be higher in Syr. Combiflam group with mean value of 897 cP. Conclusion: In summary, our study showed that most PLA tested had pH values below the critical value, high viscosity and high total sugar content all of which increase the medicines cariogenic and erosive potential. The Pedodontist has a major role in educating the people at various levels of the society about the ill effects of using certain PLAs.

1. Introduction

Pediatric liquid analgesics (PLA) are widely prescribed and are easily accepted by both parents and children. However, these drugs can place patients at risk for dental caries and dental erosion, especially when used on a regular basis and over a long period of time**[1]**. The palatability of pediatric liquid medicaments (PLMs) is renowned in children as compared to its commonly used counter physical state tablet. The recognition is especially due in sweetened preparations of the former. Sucrose is widely used in the pharmaceutical industry due to its properties as preservative, antioxidant, solvent and thickening agent. It is also a low-cost, easily processed and pleasantly sweetish substance **[2]**. However, frequent ingestion of sugars can be rapidly fermented by oral bacteria producing sufficient acid to dissolve dental enamel. Acids are commonly used in medicines as buffering agents to maintain chemical stability, control tonicity or to ensure physiological compatibility. In addition, acids are used to improve flavor as well as promote the acid-base reactions that act to disperse effervescent and dispersible tablets on contact with water. However, when these medicines' pH is below 5.5, they may activate dental erosion. While the active ingredients in these medicines are necessary for improvement or maintenance of health, some inactive ingredients may pose dangers like dental caries and dental erosion**[3]**. This problem especially concerns chronically sick children who require long-term medication, and children who receive medications frequently because of various recurrent benign pathologies, such as cough and cold**[4,5].** However, there are only few studies which have quantified the erosive potential of pediatric liquid medications in primary teeth .Therefore, the aim of the present study was to analyze the endogenous pH, viscosity and total sugar content in these medicines.

2. Material and methods

The study was conducted on commonly prescribed 4 drug group of Pediatric Liquid Analgesics - which belong to NSAIDS group— with different brand names and pharmaceutical manufacturers. Under each group, 5 (n= 20) different commercial brands of syrups were taken. Samples of medicines were collected from local pharmacies. The determination of pH and viscosity of medicines was performed under the following steps.

A. Endogenous pH

The pH of each medicine was determined using a digital pH meter (Elico pH meter). The pH meter accurate to 0.01 was first calibrated. As much as 25 mL of each medicine was placed in a beaker, the electrode was immersed and then the value was recorded. All the readings were taken at room temperature and performed in triplicate.

B. Viscosity

The viscosity was measured in centipoises (cP) using a calibrated digital rotational viscometer (Brookfield

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viscometer). A suitable spindle was chosen and the speed of the spindle (rpm) was adjusted, so the percentage of full scale was between 15-95% (Fig 1).

Figure No. 1: Brookfield viscometer displaying viscosity value

C. Total sugar content

The determination of the total sugar content was made by the volumetric method (Fehling). Initially, it was made by the inversion of non-reducing sugars (sucrose) by acid hydrolysis. Five mL of medicine were measured by a pycnometer, diluted to a volume of 50 mL with distilled water. Then, 5 mL of hydrochloric acid (60%) was added to the solution, and the volume was made up to 100 mL. The diluted solution contained in a flask was heated to 70°C and kept in water bath for 10 minutes in order to obtain glucose and fructose molecules. The mixture was cooled immediately in cold water, had its pH neutralized by titrating with 20% NaOH, and the neutral solution was diluted to a final volume of 200 mL. For titration, 5 mL of solution A and 5 mL of solution B of the Fehling reagents, 5 mL of 15% ferrocyanide potassium, and 10 mL of distilled water were mixed in a conical flask and put on a burner to boil gently. The Fehling solution was first standardized with a standard invert sugar 2.5%, and the volume needed to change the color of Fehling solution from blue - green – yellow and then brown due to the presence of ferrocyanide potassium which acts as an indicator of the turning point was recorded. The neutralized diluted medicine was transferred to a 25-mL burette, added gradually to Fehling solution, and the volume required for titration was recorded.

Total sugars present in the sample were calculated according to the following equation:

$$\text{Sugars g/100ml (as invert sugar)} = \frac{F_{EQ} \times \text{Dilution} \times 100}{V_{TITRATION}}$$

F_{EQ}: Equivalence factor.

$V_{TITRATION}$ = Titration volume required for the sample.

3. Results

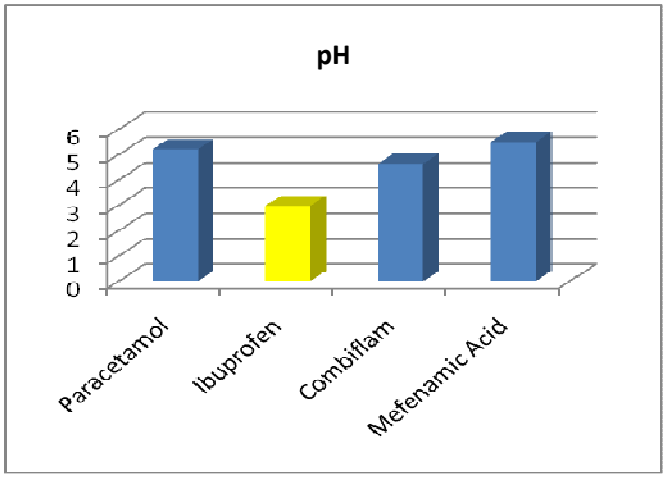
The results as obtained were subjected to statistical analysis using SPSS software. Table 1 shows endogenous pH, viscosity values and total sugar content of PLA.

Table No. 1: Means for Endogenous pH, viscosity values and total sugar content of 20 pediatric liquid analgesics and p values

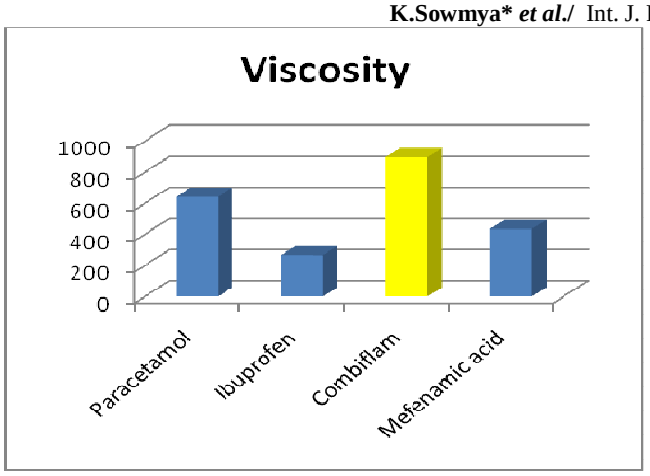
Active Ingredient	Mean pH	Mean viscosity (cP)	Mean total sugar content (g/100ml)	p-Value
Paracetamol	5.21	643	20.85	0.034*
Ibuprofen	3.98	267	43.13	0.017*
Combiflam	4.65	897	32.08	0.028*
Mefenamic Acid	5.5	435	25.29	0.033*

The statistical analysis was done using SPSS version 13 software and the intergroup comparison was done using ANOVA and post hoc test. On comparing all the groups significant difference was found in the ($p \leq 0.05$).Sucrose was seen to be maximum in Syr.Ibuprofen® in the mean concentration of 43.13% ± 0.25% and minimum in Syr. Paracetamol in the mean concentration of 20.85% ± 0.43%. The pH values of all syrups tested are below critical value of 5.5 with lowest ph in Syr.Ibuprofen and highest in Syr.Mefenamic acid whereas viscosity was found to be higher in Syr.Combiflam and lower in Syr.Ibuprofen.

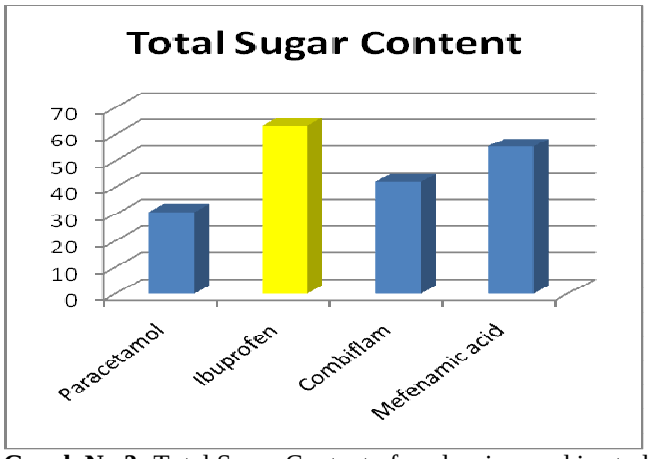
The graphical representation of pH, viscosity and sugar content of these analgesics is shown in graph 1,2,3 respectively.



Graph No. 1: pH values of analgesics used in study



Graph No.2: Viscosity values of analgesics used in study



Graph No.3: Total Sugar Content of analgesics used in study

4. Discussion

Many parents are aware that sugar causes tooth decay but they are often unaware of the hidden, added sugar in many foods and drinks, including PLAs[6]. Children on an average take medicine every eight hours daily or 10 times a week. Moreover, other healthy children who take medicines infrequently and for short periods are also at risk. In study conducted by Pradhan D *et al*, showed a fall in mean salivary pH below critical pH for up to 6 minutes after a 25% sucrose rinse, making children consuming sucrose containing PLA prone to dental caries[7].

Primary teeth are more liable to erosion as they are known to be less mineralized than permanent teeth and particularly as the enamel surface of deciduous teeth is not as mature as that of permanent teeth[8].

In the present study, each of the selected medications had a label clearly displaying the ingredients, but none contained any information regarding the pH of the solution. Therefore, the pH of each of the PLAs used in the present study was measured using a pH electrode meter. Our study showed that almost all of PLA had pH values ≤5.5 for enamel demineralization with pH values ranging between 3.93 and 5.68. A pH of 5.5 is traditionally considered to be the 'critical pH' for enamel dissolution although mineral loss may begin at higher pHs. The mean pH in our study was 4.83 ± 0.57, which was lower than in other studies. Passos *et al.*[9] and Xavier *et al.*[10] found that 44% and 56% of pediatric liquid medicines had pH values below 5.5, respectively.

Liquid oral medicines are usually viscous syrups that penetrate into fissures and proximal areas that are inaccessible to the toothbrush. Therefore, regular and long-term use of medications with prolonged oral clearance may increase the risk of dental caries if they contain sugars or dental erosion if they contain acids The present study showed that viscosity values ranged between 267 cP and 897 cP . Subramaniam *et al.*[11] found that viscosity of pediatric liquid medicines varied from 307.33 cP to 2408.3 cP, and ranged between 2.8 cP and 412.3 cP as reported by Neves *et al.*[12].

Most PLA evaluated contained sugar supporting previous findings that have shown that 50-71.43% of liquid medicines had sugar. Total sugar content varied considerably among sugar containing analgesics from 20.85-43.13 (g/100 mL), which is in accordance with previous studies that have shown a wide range in sugar content of pediatric syrups from 7.31-85.9%. Lima *et al.*[17]recorded that 58.3% of the medicines studied contained sucrose as a sweetening agent. As the sucrose concentration solution to form the cariogenic biofilm is 5%, it can be argued that all sweetened analgesics analyzed have the potential to provide conditions satisfactory to dental carious lesions. Not only the sucrose concentration but also the frequency of use, dose and patterns of use of any medication must be taken into account while determining its cariogenicity[13].

This study highlights the need to influence pharmaceutical industries to reformulate sugar-free liquid analgesics with low acid levels, low viscosity and reasonable prices as it is preferred for long-term treatment.

Another aspect of medication-induced erosion is that most syrup prescribed to children are given in 2 to 3 divided doses[14]. The night doses usually have a deleterious effect on enamel due to the following reasons- (1) at night, flow rate of saliva is diminished; some medications, such as anticonvulsants, sedatives or antihistamines also lower the salivary flow (2) in young children, the oral clearance process is less effective than adults due to lower salivary flow and less pronounced oral muscular co-ordination ability[15] and (3) sugar containing analgesics are given last thing at night to relieve pain; a night-time 'tickly cough' is soothed by a sugary cough syrup to help children go to sleep; the last daily dose of antibiotic syrup is given at bedtime.

Prevention of dental erosion caused by PLAs can be done only by a group effort. A number of steps should taken by pediatricians and parents of children who need to take oral liquid medications during early years. Pediatricians can arrange an early parental consultation with a pediatric dentist or general dentist. This will get oral hygiene measures underway as soon as the first incisors erupt. When the child is awake, the teeth should be brushed before the medication is given and a clearing drink of water offered after the medication. A topical fluoride gel may be used twice a week under the direction of the dentist, as total fluoride from all sources must be considered before supplementary fluoride is prescribed.

The following recommendations can be made at various levels of the society in order to decrease the dental erosion caused by PLAs**[16];**

1. Parents should know the importance of primary dentition and factors causing caries.

2. Sugar containing medications are better taken at meal times rather than before meals or in between meals.

3. Doctors (Pedodontists and Pediatricians) must prescribe medicines in non-cariogenic forms like tablets and capsules, and if a sweetened medication has to be given, prescribe the ones containing noncariogenic sugars like saccharin, aspartame and sorbitol.

4. Pharmaceutical Companies must display labels on all medications which indicate the type and amount of sweetener added, along with warning and possible negative effects on teeth.

5. Manufactures can come out with medicines having non-cariogenic sweeteners and "tooth friendly" symbols can be placed on these packs.

5. Conclusion

In summary, our study showed that most PLA tested had pH values below the critical value, high viscosity and high total sugar content all of which accentuate the medicines cariogenic and erosive potential. The Pedodontist has a major role in educating the people at various levels of the society about the ill effects of using certain PLAs. They should take the responsibility of informing pediatricians about the profile of the routinely prescribed analgesics so as to put in practice of oral health instructions.

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