

Original research article

Study of Cariogenic And Erosive Potential of Liquid Anti Epileptic Agent in Paediatric Population

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Abstract

Background: Dental caries is the most common chronic disease in children: it is about five times as common as asthma and seven times as common as hay fever. Dental caries may be considered as a disease of modern civilization. epilepsy affects 70 million people worldwide.

Material and Methods: A cross-sectional study was undertaken on a total of 84 children aged 2–12 years, who were suffering from epilepsy receiving liquid oral medication for, pediatric anti-epileptic liquid medicaments which are most commonly used in children for a prolonged period were obtained from local pharmacies after consulting pediatricians of Jamuhar Rohtas, Bihar. The physico-chemical analysis of endogenous pH, viscosity and sugar content of commonly prescribed ten anti-epileptic PLMs was done.

Conclusions: Most of the antiepileptic PLMs showed cariogenic and erosive potential. The study highlights the need to reformulate the antiepileptic PLMs with sugar substitutes or without sugar content.

Keywords: Dental caries; epilepsy; anti-epileptics; pediatric liquid medicaments.

Introduction

Dental caries is the most common chronic disease in children: it is about five times as common as asthma and seven times as common as hay fever. Epilepsy is also a common chronic neurologic disorder that affects 1–3% of the population, and almost 10% of the population will have one or more seizures at some time in their lives. The epilepsies form an array of more or less discrete epilepsy syndromes, characterized by age of onset, hereditary factors, seizure types, electroencephalogram (EEG) abnormalities, and prognosis. The current emphasis in epilepsy treatment is to improve quality of life, not only by suppressing seizure, but also by minimizing the side-effects of medications. Both the condition and its medical management can affect oral health. Prevention of oral disease and carefully planned dental treatment are essential to the well-being of people with epilepsy.¹ Children younger than 15 years constitute a large group among epileptic individuals, and a considerable proportion of them also have mental and motor deficits. Patients with epilepsy can be at increased risk of fracture because enzyme-inducing anti-epileptic drugs (AED; e.g., phenytoin, phenobarbital, carbamazepine) alter the metabolism and clearance of vitamin D and have been associated with osteopenia and osteomalacia.⁴ Dental treatment of patients with epilepsy and seizures should be carried out by dentists who are knowledgeable about these disorders.⁸ The medical literature contains little information on the influence of epilepsy in dental care. patients who have poorly

controlled epilepsy and who experience frequent generalized tonic-clonic seizures exhibit worse oral health in comparison with patients who are better controlled or only have seizures that do not involve the masticatory apparatus.⁹ Pediatric liquid medicaments are widely prescribed and are easily accepted by both parents and children. It is also a low-cost, easily processed and pleasantly sweetish substance. However, frequent ingestion of sugars can be rapidly fermented by oral bacteria producing sufficient acid to dissolve dental enamel.¹² 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. Viscosity of the medicated syrups is an important factor to be considered in erosion process. The syrup with high viscosity has more adhesiveness and less flow ability. The greater the adherence of the syrup, the longer will be the contact time with the tooth surface and higher the likelihood of erosion. The ingestion of liquid oral medications at bedtime is frequently not followed by proper oral hygiene. This problem especially concerns chronically sick children who require long-term medication. Although a public-health policy to limit sugar in medicines has been implemented in several developed countries, some developing countries do not have a policy for the use of pediatric medicines especially because of the lack of information on their sugar content and acidity. Patients living with epilepsy have special needs during dental treatment.

Objectives

To evaluate the viscosity of pediatric anti-epileptic liquid medicaments. To evaluate the total sugar content of pediatric anti-epileptic liquid medicaments.

Review of Literature

The purpose of this study was to determine the history of oral liquid medication usage and the incidence of dental caries from birth until about 36 months of age in a population of 20 such children. A pattern appeared in the frequency and dispensing characteristics of the 44 different drugs used for these children. Parents gave daily doses of syrupy medications and elixirs 3-4 times a day and at least two of these doses were given just before or during a designated nap or bedtime. Average age on examination was 31 months and the median number of def(t) was eight. The mean total amount of additional sugar from oral liquid medications was 8,696 g and the maximum sugar consumed by one child was over 20 kg. Physicians currently have no choice but to prescribe certain medications that contain 30 to 70 per cent sugar for patients who are already at higher than usual risk for dental caries due to chronic illness. The general medical practice survey showed that the prescribing of liquid oral medicines for prolonged periods was not confined to those children who had been referred to and were under the care of consultant paediatricians. The study took the form of in vitro measurement of endogenous pH and titratable acidity (mmol). Endogenous pH was measured using a pH meter, followed by titration to pH 7.0 with 0.1-M NaOH. Overall, 55 (57%) formulations had an endogenous pH of < 5.5. The mean (\pm SD) endogenous pH and titratable acidity for 41 SC formulations were 5.26 ± 1.30 and 0.139 ± 0.133 mmol, respectively; for 56 sugars-free (SF) formulations, these figures were 5.73 ± 1.53 and 0.413 ± 1.50 mmol ($P > 0.05$). Compared with their SC bioequivalents, eight SF medicines showed no significant differences for pH or titratable acidity, while 15 higher-strength medicines showed lower pH ($P = 0.035$) and greater titratable acidity ($P = 0.016$) than their lower-strength equivalents. This study was conducted to (i) assess concentration of sucrose in six paediatric drugs, (ii) determine endogenous pH of these drugs, and (iii) estimate drop in the plaque pH in the oral cavity in first 30 minutes after consumption of the drugs. Ten adult volunteers with mean age of 22 years were double blinded for the study. Concentration of

sucrose was assessed by volumetric method at Department of Chemical Branch of Engineering. Endogenous pH and drop in the plaque pH after consumption of the drugs were assessed using digital pH meter. SPSS software was used to assess the pH level at different time intervals and expressed as mean \pm SD. Changes in pH were assessed by one-way ANOVA followed by Wilcoxon's signed rank test. P-value was set at 0.05. Result: The data analysis was carried out by means of descriptive statistics using absolute and percentage values. The majority of the professionals (84.2%, n=16) stated they were unaware of the sucrose content in medicines. The instruction for the patients to brush their teeth after using a sweet medicine was reported by one professional only. There was a great variety (20 types) of medicines recommended by medical practitioners. The analysis of 103 medicines revealed that 67 (65.0%) had sucrose in their formula. To assess the general practices followed by parents in the use of common Pediatric liquid medications (PLM), knowledge of dosages, frequency of consumption, side effects and impact on oral health. The statistical test as undertaken was Pearson's correlation coefficient (r). Sucrose was seen to be present in Syr. Combiflam (35.75% \pm 0.25%) and Syr. Visyneral (18.48% \pm 0.43%). Acidic pH was observed for Syr. Visyneral (mean pH 3.63 \pm 0.04), Syr. Combiflam (mean pH 5.03 \pm 0.02) and Syr. Augmentin (mean pH 6.22 \pm 0.02). Highest calcium dissolution was seen with Syr. Combiflam (295.86 mg/ml) and the least with Syr. Orofer (25.51 mg/ml). No statistical significant correlation was observed with calcium dissolution potential of PLM in comparison with their respective pH. Syr. Combiflam can be regarded as the highest cariogenic and erosive potential medicament among the compared and tested PLM.¹¹ To assess and compare the effect of conventional and sugar free pediatric syrup formulations on primary tooth enamel hardness over a period of 14 days. An in vitro study was done on 40 noncarious deciduous teeth. To assess and compare dental caries experience in children under long term liquid oral medication with those not under such medication among 2-12 years old children suffering from epilepsy. A cross-sectional study was undertaken on a total of 84 children aged 2–12 years, who were suffering from epilepsy receiving liquid oral medication for more than 3 months were selected (study group) and for comparison 106 children of similar age group and disease but on other forms of medication were included as control group. Dental caries was assessed using DMFT/DMFS (Decayed, Missing, Filled Teeth / Surfaces), dmft/dft and dmfs/dfs indices. This study was conducted to provide basic understanding regarding possible enamel erosion by three kinds of first-aid antipyretic and analgesic medicines over a period of time, with comparison and analysis of the resulting deciduous teeth surface and microhardness changes. The Kruskal-Wallis test show differences in surface erosion and changes after 3, 5 and 8 days of treatment as well as before and after the treatment in each group. According to the results, there was no significant difference in the early deciduous teeth enamel surface microhardness ($p > 0.01$).

Material and Methods

A cross-sectional study was undertaken on a total of 84 children aged 2–12 years, who were suffering from epilepsy receiving liquid oral medication for, pediatric anti-epileptic liquid medicaments which are most commonly used in children for a prolonged period were obtained from local pharmacies after consulting pediatricians of Jamuhar Rohtas, Bihar. The physico-chemical analysis of endogenous pH, viscosity and sugar content of commonly prescribed ten anti-epileptic PLMs was done.

Pediatric Antiepileptic Liquid medicaments containing the following generic drugs were used in the study:

Phenytoin, Sodium Valproate, Levipril, Phenobarbitone

10 anti-epileptic Pediatric liquid medicaments which are most commonly used in children for a prolonged period were obtained from local pharmacies after consulting pediatricians of Jamuhar Sasaram Rohtas Bihar.

Inclusion Criteria

Pediatric anti-epileptic liquid medicaments which are commonly used for along duration.

Exclusion Criteria

Pediatric anti-epileptic liquid medicaments which are banned for use in children.

The physicochemical analysis for endogenous pH, viscosity and total sugar contents of all 10 pediatric anti-epileptic liquid medicaments was done in the biochemistry and pharmacy laboratories of Narayan medical college and Hospital, Jamuhar Sasaram, Rohtas Bihar. Analysis of pH of anti-epileptic pediatric liquid medicaments. The pH of each liquid medicament was determined using a digital pH meter (Eutech pH meter). The pH meter accurate to 0.01 was first calibrated. As much as 25 ml of each medicament was placed in a beaker, the electrode was immersed and then the value was recorded.

Analysis of Viscosity of antiepileptic pediatric liquid medicaments.

The viscosity was measured in centipoises (cP) using a calibrated digital rotational viscometer. A suitable spindle was chosen and the speed of the spindle (rpm) was adjusted, so that the percentage of full scale was between 15-95%.

Analysis of total sugar content of antiepileptic pediatric liquid medicaments. Sucrose concentration was determined by volumetric method (Fehling's test). As the Fehling's solution was added the blue copper (II) ions were reduced to copper (I) ions. These were precipitated out of solution as red copper (I) oxide.

Results

viscosity and sugar content of pediatric anti-epileptic liquid medicaments were analysed. All the readings were taken in triplicates. Data was entered in Microsoft excel sheet and analysed using SPSS (Statistical Package for Social Science, Ver.10.0.5) package

Table 1: Comparison between two samples of Phenytoin pediatric liquid medicament (Mean \pm SD)

Dependent Variables	Sample-1 (Eptoin) (Mean \pm SD)	Sample-2 (Dilantin) (Mean \pm SD)	P-value
PH	5.17 \pm 0.02	5.47 \pm 0	0.0001
Viscosity(cP)	160.00 \pm 0.00	573.33 \pm 10.40	0.0001
Total Sugar (gm%)	17.16 \pm 0.87	26.62 \pm 1.80	0.001

Comparison using T test

Comparison between two samples of phenytoin pediatric liquid medicament, in terms of pH, viscosity and total sugar content. The statistical analysis used for comparison was T test. The difference was statistically significant (p=0.0001) for all three parameters.

Table 2: Comparison between two samples of sodium valproate pediatric liquid medicament (Mean \pm SD).

Dependent Variables	Sample-3(valparin) (Mean \pm SD)	Sample-4 (valpex) (Mean \pm SD)	P-value
PH	7.66 \pm 0.01	6.93 \pm 0.02	0.0001
Viscosity(cP)	34.33 \pm 2.08	35.00 \pm 5.00	0.842
Total Sugar (gm%)	0	23.13 \pm 1.61	0.002

Comparison using T test

Comparison between two samples of Sodium valproate pediatric liquid medicament in terms of pH, viscosity and total sugar content. The statistical analysis used for comparison was T test. The difference was statistically significant ($p=0.0001$) for pH and total sugar content. There was no statistically significant difference in terms of viscosity.

Table 3: Comparison between two samples of Carbamazepine pediatric liquid medicament (Mean \pm SD).

Dependent Variables	Sample-5 (Oxcarbazine) (Mean \pm SD)	Sample-6 (Tegrital) (Mean \pm SD)	P-value
PH	3.08 \pm 0.01	3.95 \pm 0.01	0.0001
Viscosity(cP)	150.00 \pm 5.0	193.67 \pm 3.21	0.0001
Total Sugar (gm%)	12.00 \pm 0.42	16.48 \pm 0.31	0.0001

Comparison using T test

Table 4: Comparison between two samples of Levipril pediatric liquid medicament (Mean \pm SD).

Dependent Variables	Sample-7 (Levipil) (Mean \pm SD)	Sample-8 (levroxa) (Mean \pm SD)	P-value
PH	5.50 \pm 0.03	5.26 \pm 0.02	0.001
Viscosity(cP)	56.67 \pm 2.88	24.33 \pm 1.155	0.001
Total Sugar (gm%)	8.14 \pm 0.15	6.14 \pm 0.09	0.001

Comparison using T test

Comparison between two samples of Levipril pediatric liquid medicament in terms of pH, viscosity and total sugar content. The statistical analysis used for comparison was T test. The difference was statistically significant ($p=0.0001$) for all three parameters.

Table 5: Comparison between two samples of Phenobarbitone pediatric liquid medicament (Mean \pm SD).

Dependent Variables	Sample-9 (Gardinal) (Mean \pm SD)	Sample-10 (Barbinol) (Mean \pm SD)	P-value
PH	7.31 \pm 0	6.91 \pm 0.1	0.001
Viscosity(Cp)	214.00 \pm 1.7	219.67 \pm 4.5	0.112
Total Sugar (gm%)	0	0	

Comparison using T test

Comparison between two samples of Phenobarbitone pediatric liquid medicament in terms of pH, viscosity and total sugar content. The statistical analysis used for comparison was T test. A statistically significant difference was observed in terms of pH ($p=0.001$), whereas there was

no significant difference in terms of viscosity. No statistical test was applied for total sugar content among the two samples because the value was null for both the PLMs.

Table 6: Comparison of pH, viscosity and total sugar contents among 5 Generic anti-epileptic liquid medicaments (Mean± SD).

Dependent variables	Phenytoin (Mean± SD)	Sodium valproate (Mean± SD)	Carbamazepine (Mean± SD)	Levipril (Mean± SD)	Phenobarbitone (Mean± SD)	P value
PH	5.32± 0.16	7.29± 0.46	3.52± 0.47	5.38± 0.13	7.11± 0.21	0.0001
Viscosity (cP)	366.67± 226.4	34.67± 3.45	171.83± 24.21	40.50± 17.81	216.83± 4.35	0.0001
Total Sugar content (gm%)	21.89± 5.33	11.56± 12.71	14.24± 2.47	7.14± 1.09	0	0.0001

*comparison using ANOVA test: $p < 0.05$ is significant

comparison of pH, viscosity and total sugar contents among 5 Generic anti-epileptic liquid medicaments (Mean± SD) using statistical analysis one way ANOVA. The difference was statistically significant ($p=0.0001$) among the 5 generic pediatric anti-epileptic liquid medicaments in terms of pH, viscosity and sugar content.

Discussion

Dental caries is a multifactorial disease caused by the interaction between cariogenic bacteria with the appropriate substrate, in a susceptible host, within a certain time. The loss of tooth minerals during caries progression is caused by the formation of acids by bacteria, which lowers the pH to the point where the hydroxyapatite mineral of enamel dissolves (Nikiforuk, 1985), a process called demineralization. With increase in pH, the inverse process occurs called remineralization, in which there is a reprecipitation of minerals in the damaged area. Thus, the dental caries is a dynamic process which over a period of time may result in a net loss of mineral and subsequently lead to cavitation (Pierro et al, 2004). Time factor in caries development is associated with frequency of sugar exposure. Classical example is Vipeholm dental caries study (Newburn, 1989). In children who have to use medicines several times per day for long periods of time, sucrose-based medicines with acidic pH have potential for increasing dental caries (Girish et al, 2008). Caries as expressed by dmft index (decayed missing, filled teeth) increases significantly with increasing number of times the intake of snacks and drinks per day (Holt, 1991). Children suffering with epilepsy have multiple risk factors for occurrence of oral diseases such as poor oral hygiene practices, lack of visit to dentists, lack of preventive behaviour, incorrect dietary habits, and others. Along with these factors, the medication they take also has a profound effect on oral health. The use of PLM is usually for a short duration, but for chronically ill children like epilepsy it may be a daily occurrence. The active ingredients in these medicines are necessary for improvement or maintenance of health; some inactive ingredients pose a risk to dental health. Many liquid medications have an endogenous low pH that may itself contribute to demineralization or at least inhibit the demineralization–remineralisation process in newly erupted teeth. Although the prevalence of dental caries in children has decreased significantly in the past decades in many developed countries, it continues to be a major public health problem, especially in poor and disadvantaged groups of several developing economies. Regular use of sugar-containing liquid medicines is often implicated in the development of dental caries in children. Children on an average take medicine every eight hours daily or 10 times a week. Liquid preparations are usually sweetened

with sucrose, which can be readily fermented by oral acidogenic bacteria. Medicines in the form of syrups intended for pediatric use contain 10% to 80% sucrose, on an average about 55%. However, the sugar content is not the only factor responsible for the detrimental effects on dental health. Frequency of intake, bedtime ingestion, high viscosity, and low intrinsic pH also increase the risk for caries. The pH is an accurate indicator and an important variable in investigating the erosive potential of liquid medicines. In addition to pH and neutralizable acidity, viscosity of the syrup also influences degree of surface enamel dissolution. Syrups with high viscosity will be retained on the tooth surface for a longer duration leading to enamel erosion. Liquid medicines with low pH and high viscosity when administered frequently have greater synergetic potential to cause dental erosion. The frequent use of liquid oral medicines put children at risk of dental caries and erosion, as demonstrated by various clinical studies. Maguire, Rugg Gunn and Butler, in a survey conducted found that the dental health of children taking long term liquid medication to be worse than their siblings in relation to anterior teeth decay in deciduous dentition which can be substantiated with the results of this study. In another 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 PLM prone to dental caries.

Conclusion

*Most Pediatric antiepileptic liquid medicaments tested had acidic pH values which were below the critical pH except sodium valproate and phenobarbitone.

*Most Pediatric antiepileptic liquid medicaments tested had high viscosity

*Most Pediatric antiepileptic liquid medicaments tested had high total sugar content except phenobarbitone all of which increase the PLMs' cariogenic and erosive potential.

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