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Are sugars-free medicines more erosive than sugars-containing medicines? An *in vitro* study of paediatric medicines with prolonged oral clearance used regularly and long-term by children

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Objective. The reduced use of sugars-containing (SC) liquid medicines has increased the use of other dose forms, potentially resulting in more widespread dental effects, including tooth wear. The aim of this study was to assess the erosive potential of 97 paediatric medicines *in vitro*.

Methods. 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.

Results. Overall, 55 (57%) formulations had an endogenous pH of < 5.5. The mean (± 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. Chewable and dispersible tablets ($P < 0.001$), gastrointestinal medicines ($P = 0.002$) and antibiotics ($P = 0.007$) were significant predictors of higher pH. In contrast, effervescent tablets ($P < 0.001$), and nutrition and blood preparations ($P = 0.021$) were significant predictors of higher titratable acidity.

Conclusions. Paediatric SF medicines were not more erosive than SC medicines *in vitro*; a more significant predictor of their erosive potential was dose form.

Introduction

Tooth wear is increasingly being recognized as a problem in patients of all ages[1,2]. Of particular concern is tooth wear caused by dietary erosion, which is seen in individuals consuming fruit juices and carbonated soft drinks, and in those patients taking certain acidic medicines regularly and long-term, where the effects of dental erosion can add to their considerable burden of ill health[3].

Clinical evidence has shown the dentally erosive effects of aspirin[4], vitamin preparations in chewable tablet and lozenge form and anti-asthmatic drugs[5,6]. In addition, *in vitro* studies have shown the demineralizing potential of iron tonics[7], effervescent vitamin preparations[8], proprietary mouth rinses[9], and medicines used in the treatment of phenylketonuria[10] and renal disease[11,12]. The results of these studies, although limited to a small number of medicines, have led to concern over the detrimental dental effects of use of medicines with an endogenous pH lower than 5.5, the critical pH for enamel.

In extensive studies of medication use by children[13,14] as well as older people[15], a significant number of medicines with prolonged oral clearance when used regularly and long-term have been identified, along with their sugar content. While there has been a welcome reduction in the overall use of sugars-containing (SC) medicines in recent years, particularly in paediatrics, the use of certain dose forms, particularly effervescent and chewable tablet formulations, is increasing[16,17]. With these dose form and formulation changes, the potential for more

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widespread dental effects, including tooth wear, has increased. Hellwig and Lussi[18] emphasized that consumers should be aware of the potential for tooth erosion from medicines, particularly chewable and effervescent formulations, especially when such patients are also experiencing drug-induced xerostomia. Acids are commonly used in medicines as buffering agents to maintain chemical stability, control tonicity or to ensure physiological compatibility. In addition, acids may be used to improve flavour, as well as promoting the acid-base reactions that act to disperse effervescent and dispersible tablets on contact with water.

With these changes in the prescribing and formulation of medicines, the question that now arises is: are we replacing SC medicines that may potentially cause dental caries with sugars-free (SF) medicines that may cause dental erosion?

Three properties of an acid contribute to its erosive potential: (1) the amount of acid available (the titratable acidity); (2) the amount of acid actually present (the concentration of the H^+ ion or the pH); and (3) the relative strength of the acid or ease with which the acid will give up free H^+ ions (the pKa)[19].

The aim of this study was to investigate the dentally erosive properties of a number of SC and SF medicines with prolonged oral clearance used regularly and long-term in children[14] as well as older people[15] by determining the endogenous pH and titratable acidity of these medicines. An additional aim was to explore the impact of sugars content, dose strength, dose form and brand (i.e. whether a product was generic or proprietary) on a medicine's erosive potential.

Materials and methods

Of the 67 paediatric medicines with prolonged oral clearance identified as being used regularly and long-term by children[14], 41 were selected for this study. These 41 medicines were those held in stock in the local hospital pharmacy, and once all generically bioequivalent and alternative dose forms had been included, they comprised 97 formulations, all of which have also been reported as used regularly and long-term by older people[15]. The medicines were supplied by the Pharmacy Department of the Royal Victoria Infirmary, Newcastle Hospitals NHS Trust, Newcastle upon Tyne, UK, and all testing was carried out in their pharmacy quality control laboratory.

Sample preparation

For liquid oral medicines, a 2-mL sample of the liquid was diluted with 40 mL of distilled water prior to testing. To prepare the solid oral doses, an additional step was required. Effervescent tablets, and soluble tablets and powders were reconstituted in 50 mL of water, from which a 2-mL sample was further diluted with 40 mL of distilled water and tested. Chewable and other noneffervescent or soluble tablets were crushed using a mortar and pestle, and 50 mL of water was added to make a solution, from which a 2-mL sample was further diluted with 40 mL of distilled water and tested. Using the methodology described by Ng[11], the endogenous pH of two samples of a standard dose of each medicine was determined at room temperature (20 °C) using a PW9418 pH meter (Pye-Unicam Ltd, Cambridge, UK) and the mean of the two values was recorded. Following this, each sample was titrated to pH 7.0 with 0.1-M sodium hydroxide (NaOH) solution using an automated titrometer (DL40RC Memotitrator, Mettler, Küsnacht, Switzerland). Once the endogenous pH had been recorded, an endpoint pH was entered into the titrator (pH 7.0) and the titration started. The titrator recorded the volume of 0.1-M NaOH, which was automatically added to the sample to allow it to reach the endpoint pH. This measurement was repeated twice and a mean value recorded.

To calculate the mean titratable acidity in millimoles: volume of 0.1-M NaOH needed to reach specified pH (7.0) = a (mL); divide by 2 (since sample was 2 mL) = $a/2$ (mL); multiply by 5 for standard 5 mL dose = $(a/2) \times 5$ (mL); multiply by 0.1 for titratable acidity in mmoL = $[(a/2) \times 5] \times 0.1$ (mmoL).

Using this information, the titratable acidity for each formulation was calculated for a 5-mL dose for liquid oral medicines and for a single tablet for solid oral doses.

Very viscous syrups and suspensions could not be pipetted, and therefore, the weight per millilitre was determined using a pycnometer.

This allowed the volume to be calculated using the following equation:

$$\text{Weight per mL} = \frac{\text{Weight of suspension that fills pycnometer (g)*}}{\text{Capacity of pycnometer (mL)}}$$

*At a specified temperature.

The capacity of the pycnometer equals the weight of water required fill the pycnometer and was calculated as follows: weight of pycnometer = x (g); weight of water plus pycnometer = y (g); weight of water = $y - x = z$ (g).

The weight of water[20] at 20 °C = 997.18 g L^{-1} = 0.99718 g mL^{-1}

For water at 20 °C, 1 mL = 0.99718 g and 1.0028279 mL = 1 g.

Therefore, the capacity of the pycnometer = $1.0028279 \times z$ (mL).

For example, when measuring lactulose:

1 mL lactulose = 1.324 g and 2 mL lactulose = 2.648 g.

Since these weights are difficult to measure accurately and since 1.5 mL = 2 g, 2 g of lactulose suspension was weighed into the titration cup and diluted with 40 mL of distilled water as before. Unlike other, less-viscous liquids, the volume used for titration of lactulose was 1.5 mL and this value was used in the calculation of its titratable acidity in millimoles.

Data analysis

The endogenous pH and titratable acidity for SF and SC medicines were compared using Student's *t*-test for independent samples. Medicines were also compared with regard to dose strength and sugars content using a Student's *t*-test for paired samples. In addition, linear regression methods were used to assess the impact on erosive potential (as determined by endogenous pH and titratable acidity) of other factors important in medicines formulation, such as dose form and brand (i.e. whether a product was generic or proprietary).

Results

Of the 97 formulations tested, 37% were generic preparations, the remainder being proprietary or brand-name preparations. Overall, 55 (57%) formulations had a mean endogenous pH below the critical pH for the dissolution of enamel (pH 5.5).

The distribution of the 97 formulations according to therapeutic group (and SF status) was as follows: anti-infectives, 38 formulations (61% SF); central nervous system, 23 formulations (48% SF); gastrointestinal, 12 formulations (58% SF); nutrition and blood, 13 formulations (77% SF); respiratory, seven formulations (29% SF); cardiovascular system, three formulations (67% SF); and endocrine, one formulation (100% SF).

Of the 97 formulations, 41 (42%) were SC with a mean endogenous pH of 5.20 (SD ± 1.28, range = 3.03–9.60) and mean titratable acidity (to pH 7.0) of 0.132 mmol (SD ± 0.129 mmol, range = 0.00–0.382 mmol). The mean endogenous pH for the 56 SF formulations was 5.82 (SD ± 1.54, range = 3.35–9.45) and the titratable acidity was 0.440 mmol (SD ± 1.494 mmol, range = 0.00–8.30 mmol). These differences between SF and SC medicines were not statistically significant for endogenous pH ($P = 0.115$) or titratable acidity ($P = 0.178$) when analysed using an independent samples *t*-test.

When the mean endogenous pH and titratable acidity were compared across therapeutic groups, the respiratory and cardiovascular medicines had the lowest mean endogenous pH (4.29 and 4.12, respectively), although the medicines with the highest titratable acidity were the nutrition and blood medicines with a mean titratable acidity of 1.386 mmol (Table 1).

With regard to dose form, the mean endogenous pH ranged from 5.31 (SD ± 1.21) for liquids and syrups to 8.09 (SD ± 1.49) for the chewable tablets (Table 2). In contrast, the titratable acidity ranged from 0.061 mmol (SD ± 0.122 mmol) for chewable tablets, to 5.798 mmol (SD ± 3.914 mmol) for effervescent tablets.

When the influence of dose strength on the mean endogenous pH and titratable acidity was compared for 15 paired groups of lower- versus higher-strength medicines, the mean endogenous pH was statistically significantly lower (paired sample *t*-test, $P = 0.035$) in higher-strength (mean pH = 5.53, SD ± 1.51) compared with lower-strength (mean pH = 5.73, SD ± 1.42) medicines. Similarly, with regard to titratable

Table 1. Mean endogenous pH and titratable acidity (mmol) for 97 medicines by therapeutic group.

	Medicine					
	Sugars-free (n = 56)		Sugars-containing (n = 41)		All 97 formulations	
Therapeutic group	Mean pH	Titratable acidity	Mean pH	Titratable acidity	Mean pH (SD)	Titratable acidity (SD)
Gastrointestinal	7.51	0.203	4.57	0.030	6.28 (1.88)	0.131 (0.365)
Respiratory	4.20	0.253	4.32	0.300	4.29 (1.10)	0.286 (0.170)
Central nervous system	5.18	0.082	6.03	0.091	5.63 (1.64)	0.087 (0.110)
Infections	5.72	0.125	5.32	0.124	5.56 (1.10)	0.125 (0.079)
Nutrition and blood	5.67	1.714	4.90	0.292	5.50 (1.47)	1.386 (2.964)
Cardiovascular system	4.05	0.043	4.25	0.219	4.12 (0.37)	0.102 (0.106)
Endocrine	6.40	0.175	–	–	6.40 (0.00)	0.175 (0.000)
All groups	5.73	0.413	5.26	0.139	5.53 (1.447)	0.300 (1.144)

Table 2. Endogenous pH and titratable acidity of 97 medicines with prolonged oral clearance, according to dose form.

Dose form	Number	Percentage sugars-free	pH (SD)	Titratable acidity to pH 7 (SD)
Liquids and syrups	86	55	5.31 (1.21)	0.128 (0.118)
Effervescent tablets	3	100	4.96 (1.41)	5.798 (3.914)
Dispersible tablets	4	50	8.10 (1.66)	0.044 (0.088)
Chewable tablets	4	100	8.09 (1.49)	0.061 (0.122)
Total	97	58	5.53 (1.45)	0.297 (1.144)

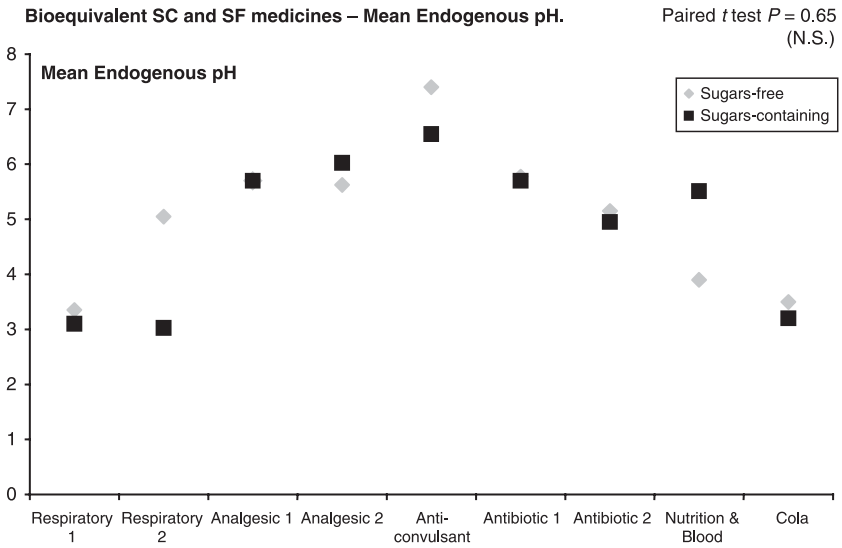

Fig. 1. Mean endogenous pH for eight bioequivalent sugars-free and sugars-containing medicines (with the results for a cola drink included for comparison).

acidity, higher-strength medicines had a statistically significantly higher titratable acidity (mean = 0.166 mmol, SD ± 0.105) compared with their paired equivalent lower-strength medicines (mean = 0.121 mmol, SD ± 0.091) (P = 0.016).

The overall difference in mean endogenous pH and titratable acidity between SF and SC medicines was not statistically significant (for endogenous pH, P = 0.12; for titratable acidity, P = 0.18) when compared using a Student's t-test for independent samples. In addition, when a subgroup of eight SF medicines were compared with their bioequivalent SC medicines using a paired samples t-test, no statistically significant differences were found for pH (P = 0.650) or titratable acidity (P = 0.310) (Figs 1 & 2).

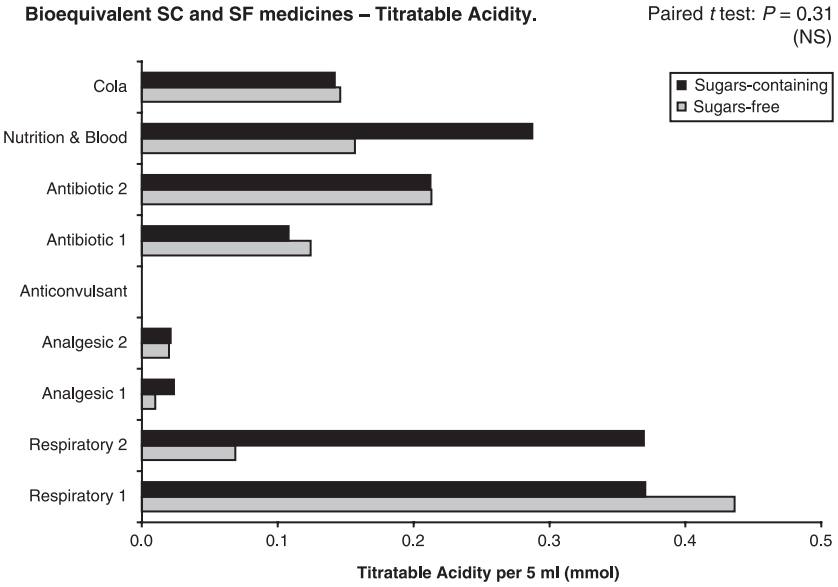

Fig. 2. Titratable acidity to pH 7 (mmol) for eight bioequivalent sugars-free (SF) and sugars-containing (SC) medicines (with the results for a cola drink included for comparison). NB: Mean endogenous pHs for the SF and SC anticonvulsants were close to pH 7.0, and no titratable acidity could be recorded.

Table 3. Regression analysis model: statistically significant predictors for higher mean endogenous pH.

	Regression coefficients for mean endogenous pH			
Dose form	***B***	**Standard error**	**Ninety-five per cent confidence interval**	***P*-value**
Chewable tablets	2.777	0.545	3.845, 1.709	< 0.001
Dispersible tablets	3.641	0.696	5.005, 2.277	< 0.001
Gastrointestinal medicines	1.211	0.379	1.954, 0.468	0.002
Antibiotics	0.722	0.262	1.236, 0.208	0.007

Table 4. Regression analysis model: statistically significant predictors for higher (*lower) titratable acidity to pH 7.

	Regression coefficients for titratable acidity to pH 7			
Dose form	***B***	**Standard error**	**Upper and lower confidence intervals**	***P*-value**
Effervescent tablets	5.554	0.336	6.213, 4.895	< 0.001
Nutrition/blood medicines	0.403	0.171	0.738, 0.068	0.021
Gastrointestinal medicines*	–0.460	0.171	–0.125, –0.795	0.009

The results of regression analysis for factors influencing the mean endogenous pH and titratable acidity are shown in Tables 3 and 4.

Gastrointestinal medicines, antibiotics, dispersible tablets and chewable tablets were statistically significant predictors of a higher endogenous pH, i.e. possibly lower erosive potential (Table 3).

In terms of erosive potential as measured by titratable acidity, effervescent tablets, and nutrition and blood medicines were statistically significant predictors of higher titratable acidity, while gastrointestinal medicines predicted lower titratable acidity (Table 4).

Discussion

Sixty-seven medicines used regularly and long-term in children were identified in a study carried out across the north-east of England[14]. Since then, the manufacture of a number of the identified medicines has been reformulated or discontinued. In addition, a small number of

medicines were used very rarely, and therefore, were not readily available from the central hospital pharmacy used to supply the study with samples; however, those medicines which were currently being used regularly in children were available for testing.

The range of medicines tested was fairly extensive, but did include a number of anti-infectives, which are less likely to be prescribed regularly and long-term since their main therapeutic indication is for short-term use for acute infection. Thirty-six per cent of the medicines tested were either gastrointestinal or central nervous system medicines, reflecting the main areas of regular and long-term prescribing identified in previous studies of paediatric[13,14,16] and geriatric prescribing[15,17].

In terms of dose form, the effervescent tablets had the highest capacity for erosion *in vitro*. The liquids and syrups formed the largest group, representing 89% of the medicines tested and their mean endogenous pH at 5.31 was less than the critical pH for enamel dissolution. Although the mean endogenous pH for the effervescent tablets was 4.96, their mean titratable acidity was high at 5.798 mmol, reflecting the incorporation of citric acid in excess in their formulation.

Citric acid was the main acid used in these prolonged oral clearance medicines, both in effervescent tablets and other dose forms. It has pKa values of 3.1, 4.8 and 6.4[19], and as such, is a weak acid, dissociating in solutions of a higher pH and able to act as a buffer over a range of pHs. Citric acid, however, is a potent erosive agent because of its ability to chelate calcium in hydroxyapatite, thus increasing enamel's rate of dissolution on exposure to the acid[21].

The inclusion of citric acid in excess in effervescent tablets, which rely on an acid-base reaction to release carbon dioxide on contact with water, is of some concern in terms of the potential risk for erosive wear in patients who require this type of medication regularly and long-term.

The mean endogenous pH for the SF medicines at 5.73 was greater than the critical pH for enamel (5.5), while for the SC medicines, it was lower at 5.26. Overall, however, 57% of the formulations tested had a mean endogenous pH below the critical pH for the dissolution of enamel, with a systemic nasal decongestant, pseudoephedrine hydrochloride 30 mg/5 mL, having the lowest endogenous pH at 3.03 while ranking ninth highest in terms of titratable acidity. In contrast, an oral calcium supplement in effervescent tablet form had the highest titratable acidity at 8.30 mmol for a single tablet, although its endogenous pH was higher than the pseudoephedrine hydrochloride preparation at 4.35.

The exact contribution of the various acidic properties of medicines to erosive potential is unclear, especially when the *in vivo* situation is considered. The mechanism of salivary buffering of pH is complex – the capacity of saliva to buffer a low initial pH as well as a potentially sustained low pH because of a high titratable acidity will be increased by the stimulatory effect of citric acid on salivary flow[22].

In view of the welcome move to the prescribing and dispensing of the SF option in medicines, it is reassuring to find that reformulating a medicine as SF does not increase the erosive potential of the medicine *in vitro*. It is important to realize, however, that SC and SF medicines still carry an erosive potential that is similar *in vitro*. How this potential translates to the *in vivo* situation is unclear and is an area for further research.

The statistically significantly lower endogenous pH and higher titratable acidity of higher strength medicines compared with their lower strength equivalent formulations was an interesting although not unexpected finding. The greater quantities of active ingredient in the higher strength forms would tend to require greater taste-masking and buffering with an appropriate weak acid (e.g. citric acid), resulting in the incorporation of larger quantities of citric acid in the higher-strength formulations.

In terms of identifying factors that predict a higher erosive potential, this study has shown that nutrition and blood medicines, and effervescent tablets were significant predictors of higher titratable acidity. This information will be of use to manufacturers, as well as prescribers and dispensers of these types of medicines so that consumers can be provided with adequate information and advice to try to avoid tooth erosion when using these medicines in the long term.

It could be expected that gastrointestinal medicines would be predictors of a higher mean

endogenous pH and lower titratable acidity since many of those tested were antacids, commonly used regularly and long-term, especially by older people who suffer from gastric irritation, a common side-effect of polypharmacy. Dispersible tablets predicted a higher mean pH, but this group of medicines was quite small ($n = 4$), primarily comprising minor analgesics and anticonvulsants, and may not be totally representative of this dose form as a group.

Regular and long-term use of medication with prolonged oral clearance may increase the risk of dental caries if it contains sugars, and dental erosion if it contains acids. It would appear that reformulating the medicine as SF will reduce the risk of dental caries while not increasing its erosive potential relative to the SC form.

For comparison, when the erosive potential of soft drinks was measured *in vitro* using the same methodology, the endogenous pH and titratable acidity to pH 5.5 (mmol) and pH 7.0 (mmol) were 3.5, 0.068 mmol and 0.146 mmol, respectively, for a 5 mL sample of diet cola drink. For pure orange juice, the respective values were 4.2, 0.384 mmol and 0.593 mmol, while for sparkling mineral water, they were 4.9, 0.021 mmol and 0.092 mmol, respectively. To put this into context, of all the medicines tested, those in the SF nutrition and blood groups had a mean titratable acidity (1.7 mmol per 5 mL) that was nearly three times that of pure orange juice (0.59 mmol per 5 mL). In addition, in medically compromised children or older people, many of these medicines may be taken at times remote from food intakes or at night when saliva flow is reduced, and these factors may add to the potential erosive challenge.

What this paper adds

- Information on the erosive potential of paediatric medicines and knowledge of the risk benefit of sugared and sugars-free medicines.
- A perspective on risk factors for children with chronic disease on long-term medication.

Why this paper is important to paediatric dentists

- Paediatric dentists need to be aware of patients potentially at risk of tooth surface loss from their medication.
- Clinically, the paper informs decision-making on risk status for preventive dental care and raises awareness of the balance of risk to be considered in chronically sick children.

In summary, sugars content does not affect the erosive potential of paediatric medicines tested *in vitro*: a more accurate predictor is dose form.

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