Cariogenic and erosive potential of liquid oral pediatric medicines of long-term use for children: an *in vitro* analysis

Ola B. Al-Batayneh (olabt@just.edu.jo)
Jordan University of Science and Technology https://orcid.org/0000-0003-1670-497X
Ala'a B. Al-Bataina
Jordan University of Science and Technology
Yousef S. Khader
Jordan University of Science and Technology
Arwa I. Owais
Jordan University of Science and Technology

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Abstract

Background

Liquid oral pediatric medicines (LOPM) contain sucrose and glucose and can have a low pH; their chronic administration may increase the risk for dental caries and erosion in children. The aim of this study was to determine sucrose and glucose concentrations, and pH of LOPMs of long-term use by children.

Methods

A cross sectional survey was conducted among 95/381 pharmacies to assess the most commonly prescribed LOPM by pharmacists in North Jordan, yielding 42 medicines which were analyzed for sucrose and glucose concentrations (mg/g) using HPLC-RID, and pH measurement using pH-meter CP-505. Data were analyzed using SPSS version 19.0. Differences were considered significant at $P \leq 0.05$.

Results

The lowest and highest sucrose concentrations were for Ramlac® (0.9%) from the gastrointestinal medicines and Varolex® (79.5%) from the nutritional medicines, respectively. The lowest and highest glucose concentrations were for Adol® (0.0%) from the central nervous medicines and Pediavit-D® (81.1%) from the nutritional medicines, respectively. The pH ranged from 3.2 for Varolex® from the nutritional medicines to 10.0 for Zithromax® from the antibiotics medicines.

Conclusions

Some of the LOPMs studied had high sucrose or glucose concentrations (or both) and low pH which could increase their potential of causing dental caries and erosion when ingested frequently and chronically.

Background

The National Center for Health Statistics considers an illness chronic if its duration exceeds three months. Long term is defined as daily or alternate days for more than three months.[1] It is noteworthy that many liquid oral pediatric medicines (**LOPM**) are embedded with carbohydrates, such as sucrose and glucose that can directly influence the cariogenic potential of the drugs.[2–5] Many pharmaceutical companies argue that improving the palatability of liquid medicines with sucrose increases compliance.[6] Liquid medicines can be part of a daily routine for children with chronic diseases.[3, 5, 6] As a result, these children are likely to take in more sugar from liquid medicines, which may increase the potential or severity of dental caries.[6] There is an increasing prevalence in prescription drug therapy to treat chronic conditions in children.[7] Due to the fact that medications in low and middle income countries can be

easily obtained by people, the risk for caries and erosion would be high due to the use of liquid sugared medications (syrups) by young children [8] along with ineffective oral hygiene standards to washout the remains of the medication after consumption of each dose, especially at bedtime.[9]

Previous studies with liquid pediatric medicines have shown sucrose concentrations ranging from 3.7–80% by weight (wt/wt).[3,6] In addition to the sucrose content in medicines and the caries risk in children, these products sometimes have a low pH, which increases the risk of dental erosion.[3] The combination of sugar and low pH of these medicines is sometimes complemented by a low salivary flow rate as a supplemental risk factor for dental problems such as early childhood caries and dental erosion. Early childhood caries is a disease of high prevalence worldwide ranging between 23.8% and 57.3% in children younger than 36 months and children aged 36 to 71 months, respectively. [10] To the best of our knowledge, there were no studies focusing on the cariogenic or erosive potential in terms of pH and sugar content of LOPM used in long-term by children in Jordan. Therefore, the aim of this study was to determine the pH and sugar content in LOPMs that are frequently used by Jordanian children for long-term in order to estimate the potential risk of these drugs for dental caries and dental erosion.

Methods

The aim of this study was to determine the pH and sugar content in LOPMs that are frequently used by Jordanian children for long-term in order to estimate the potential risk of these drugs for dental caries and dental erosion.

Phase I. The Cross-sectional Survey

A preliminary cross-sectional survey among pharmacies in Irbid governorate, Jordan was performed to identify the most commonly prescribed LOPMs for children. The total number of pharmacies was obtained from the Jordanian Pharmaceutical Association; these were listed in tables according to geographic location. Based on that, power calculations were performed to include a representative sample of 25% of pharmacies per geographic region. In total, 95 out of 381 pharmacies were randomly selected from tables using a systematic sampling technique. The study questionnaire was distributed to the pharmacists working in these pharmacies between May and July, 2017 who were asked to fill the questionnaire through a face to face interview. The study questionnaire included information on pharmacy location and requested the pharmacist to select the most three dispensed medications from a list per therapeutic class of medication brand names. There were five main categories of drugs (respiratory, central nervous, gastrointestinal antibiotics and nutritional drugs), each category was divided into subdivisions according to therapeutic use, with a total of (n = 197) medications surveyed. The questionnaire was test piloted on a group of pharmacists (n = 10) not included in the study. The study protocol had been approved by the Institutional Review Board at Jordan University of Science and Technology (JUST), Irbid, Jordan (Approval Number 42/105/2017). Prior written consent explaining objectives of the study was obtained from participating pharmacists before filling the questionnaire.

Phase Ii. Laboratory Analysis

The CRIS (Checklist for Reporting In vitro Studies) guidelines were adhered to in the reporting of this in vitro study. [11] According to the survey, pediatric medicines of long-term use were obtained for laboratory analysis. To ensure blindness, the medication bottles were concealed and labeled (numbered) by a laboratory technician not involved in the study, and remained blinded to the investigators and statistician. The medication names were not revealed until after the data analysis was performed.

Determination of acidity (pH) of the drug

The pH of the drug was measured using pH-METER CP-505 (Elmetron, Spain) with a glass combined electrode and temperature sensor. The device gives a direct digital reading of the pH with a range 2–16. A piloting phase with random drugs was tested for 3 samples each in order to test reproducibility of the readings. For the analysis of pH, 5 g of the drug was taken and dissolved in 100 ml distilled water, and measured using the pH meter at room temperature, the average of 3 readings was calculated per sample. A rinse was done between each sample by placing the electrode in distilled water to ensure reliable readings.

Determination of glucose and sucrose content

The analysis of sucrose and glucose content was done using the HPLC01-RID (Retractive Index Detector with system controller SCL-10AVP, RID-10A,LC-10ADVP liquid chromatography,CTO-20A column oven, Shimadzu, Japan), with an HPLC-Amine Column (Thermo Amine C18-Amine, dimensions of 5M, 50 × 4.6). The method was adapted from Valinoti et al., 2016 with modifying the sample size. [12] The mobile phase was prepared by adding 830 mL of acetonitrile to 170 mL of distilled water and was filtered, and then sonication was done to get it ready for use in a separate compartment in the HPLC device. The preparation of the drug sample included the following steps:

1. 1g of the drug was weighed in a 100mL volumetric flask and dissolved in 25ml of distilled water, then 75mL acetonitrile was added (total volume was 100mL). The sample was shook in the Vortex for 30 seconds.
2. A 10ml volume of the sample was withdrawn using a plastic test tube which was labeled according to the name of the drug and sample number.
3. The plastic test tubes were centrifuged using a centrifugation device (Hermle, Germany) for 15 minutes with a speed of 4000 RPM.
4. The centrifuged sample was filtered by withdrawing the upper layer using a 0.45µm filter syringe.
5. The drug sample was injected in another compartment of the HPLC device using a 20µl syringe.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, United States of America, version 19.0). Data were described using the ranges, means, medians, and standard deviations. A $P \leq 0.05$ was considered statistically significant.

Results

The preliminary survey performed with pharmacists to report the most commonly prescribed LOPM used by children yielded 49 medicines, 7 medicines weren't available in the market at the time of the research (Bendazol®, Medolin®, Salbutamol®, Ramzol®, Triomax®, Ultracillin Fort®, Atarax®). So, the total number of analyzed medicines was 42 drugs that were identified and analyzed for pH, sucrose and glucose content. The distribution of these medicines according to category are shown in Table 1.

Table 1
The distribution of studied LOPMs for long term use, according to category, (total n = 42).

Category name	Drugs in each category
Respiratory (n = 6)	Bronchodialators: Asmadil®
	Antihistamines: Allerfin®, Histazin®
	Cough preparation: Trifed®, Jospan®, Hatsu cold®
Central Nervous System (n = 9)	Analgesics: Adol®, Revanin®, Panda®
	Non-steroidal Anti-inflammatory drugs: Pangesic®, Doloraz®, Fenamic®
	Anti-epileptics: Tegretol®, Depakin®, Rivotril®.
Antibiotics (n = 15)	Antibacterial: Moxiclav Fort®, Zinnat®
	Macrolides: Zithromax®, Erythrodar®, Claritop®
	Miocamycin: Miocamen®.
	Trimethoprim with Sulfamethoxazole: Balkatrin®, Trimol®
	Antiprotozoal: Flagyl®, Nidazol®
	Antiviral: Zovirax®
	Antihelminthics: Vermox®
	Antifungal: Micozol Oral gel®, Mycoheal oral gel®, Mycosat®
Gastrointestinal (n = 9)	Antiflatulants: Deflat®, Gasix®, Restropinal®
	Antiemetics: Motilat®, Clopram® Motilium®
	Laxatives: Ezilax®, Duphalac®, Ramlac®
Nutritional (n = 3)	Vit-C: Varolex®.
	Multivitamin: Kiddi Pharmaton®
	Vit-D: Pediavit-D®

Table 2 shows the mean pH, sucrose and glucose in the LOPMs studied and their ranks for each measured parameter. Comparing values between categories, pH ranged between 3.2 and 10.0 for Varolex® from the nutritional category and Zithromax® from the antibiotics category, respectively. All the LOPMs investigated contained sugar; either sucrose, glucose or both. The sucrose concentration (mg/g) ranged from 0.9–79.5% for Ramlac® from the gastrointestinal category and Varolex® from the nutritional category, respectively. The glucose concentration (mg/g) ranged from 0–81.1% for Adol® from the central nervous system category and Pediavit-D® from the nutritional category.

Table 2
The mean pH, sucrose and glucose in LOPMs and their ranks among n = 42 medications studied.

Category	Drug	pH		Sucrose (mg/g)		Glucose (mg/g)	
		Mean	**Rank**	**Mean**	**Rank**	**Mean**	**Rank**
Respiratory	Asmadil®	3.5	5	21.2	38	14.5	27
	Allerfine®	3.3	2	3.4	12	1.2	6
	Histazin®	3.3	3	3.7	15	17.4	29
	Trifed plus®	5.3	26	5.7	27	26.6	35
	Jospan®	4.6	19	11.0	37	18.3	30
	Hatsu cold®	4.5	17	5.0	24	1.1	5
Central Nervous System	Adol®	5.6	30	3.9	17	0.0*	1
	Revanin®	5.5	28	4.0	20	2.8	10
	Panda®	5.5	27	6.9	31	36.3	39
	Pangesic®	5.2	25	2.1	5	13.6	24
	Doloraz®	4.0	9	9.4	35	23.8	34
	Fenamic®	4.8	21	3.5	13	14.0	25
	Tegretol®	4.2	14	2.7	7	14.3	26
	Depakin®	7.8	39	9.1	34	1.0	4
	Rivotril®	3.5	4	9.6	36	4.6	15
Antibiotics	Moxiclav fort®	4.8	20	4.3	23	1.6	7
	Zinnat®	5.0	22	1.4	3	0.9	3
	Zithromax®	10.0*	42	5.3	25	2.3	8
	Erythrodar®	8.0	40	4.3	22	8.2	17
	Claritop®	4.5	18	6.6	30	6.1	16
	Miocamin®	8.1	41	23.4	39	3.0	11
	Balkatrin®	5.6	29	3.0	9	13.3	23
	Trimol®	5.0	23	32.9	41	27.7	37
	Flagyl®	6.5	36	3.5	14	12.6	21

*Lowest and highest in rank

	Nidazol®	4.3	15	3.8	16	62.1	41
	Zovirax®	6.4	33	2.9	8	10.4	18
	Vermox®	5.8	31	7.9	32	12.9	22
	Mycozol oral gel®	6.3	32	1.1	2	15.5	28
	Mycoheal oral gel®	6.9	38	1.4	4	4.2	12
	Mycosat®	6.6	37	6.6	29	4.5	14
Gastrointestinal	Deflat®	3.7	7	3.0	10	27.5	36
	Gasix®	3.9	8	8.5	33	2.3	9
	Restropinal®	5.2	24	6.2	28	11.7	20
	Motilat®	6.5	35	3.1	11	21.8	32
	Clopram®	4.1	12	5.5	26	0.7	2
	Motilium®	6.4	34	3.9	18	32.1	38
	Ezilax®	4.4	16	4.0	19	11.5	19
	Duphalac®	4.0	11	4.2	21	4.2	13
	Ramlac®	3.7	6	0.9*	1	23.2	33
Nutritional	Varolex®	3.2*	1	79.5*	42	20.4	31
	Kiddi pharmaton®	4.0	10	2.5	6	42.5	40
	Pediavit-D®	4.2	13	24.0	40	81.1*	42
*Lowest and highest in rank							

Within each category, in the respiratory system medicines, the lowest pH (3.3), highest sucrose (21.2%) and glucose concentration (26.6%) was for drugs Allerfin®, Asmadil® and Trifed plus®, respectively. Among the central nervous system category medicines, Rivotril® had both the lowest pH (3.5) and highest sucrose concentration (9.6%), while Panda® had the highest glucose concentration (36.3%). For antibiotics, Nidazol® had the lowest pH (4.3) and highest glucose concentration (62.1%), while the highest sucrose concentration was for Trimol® (32.9%). In the gastrointestinal system medicines, the lowest pH (3.7), highest sucrose (8.5%) and glucose (32.1%) concentrations were for drugs Ramlac®, Gasix® and Motilium®, respectively. With the nutritional medicines, Varolex® had the lowest pH (3.2) and highest sucrose concentration (79.5%), the highest glucose concentration (81.1%) was found in Pediavit-D®.

Table 3 presents the range, median, and mean (SD) of pH, sucrose and glucose per therapeutic class of LOPMs studied. Comparing between categories, the least and highest pH median was 4.0 and 6.4 for the

nutritional and antibiotics categories, respectively. The least sucrose median was for central nervous system, antibiotics, and gastrointestinal system categories and was found to be 4.0%, whereas the highest sucrose median was 24.0% for the nutritional category. The least and highest glucose median was 9.3% and 42.5% for the antibiotics and nutritional categories, respectively.

Table 3
Range, median, mean (SD) of pH, sucrose and glucose per therapeutic class of LOPMs studied.

Variables	pH			Sucrose			Glucose		
Category	Range	Median	Mean (SD)	Range	Median	Mean (SD)	Range	Median	Mean (SD)
Respiratory System (n = 6)	(3.3–5.3)	4.5	4.1 (0.8)	(3.4–21.2)	5.7	8.1 (6.3)	(1.1–26.6)	14.5	12.2 (9.6)
Central nervous system (n = 9)	(3.5–7.8)	5.2	5.1 (1.3)	(2.1–9.6)	4.0	5.7 (3.1)	(0–36.3)	13.6	12.3 (12)
Antibiotics (n = 15)	(4.4–10.0)	6.4	6.4 (1.5)	(1.1–32.9)	4.0	7.3 (9.3)	(.9–62.1)	9.3	12.8 (15.9)
Gastro-intestinal system (n = 9)	(3.7–6.5)	4.1	4.7 (1.1)	(.9–8.6)	4.0	4.4 (2.2)	(.7–32.1)	11.7	15.0 (11.5)
Nutritional (n = 3)	(3.2–4.2)	4.0	3.8 (0.5)	(2.5–79.5)	24.0	35.3 (39.7)	(20.4–81.1)	42.5	48.0 (30.7)

Discussion

In Jordan, chronic illnesses have not been widely studied in terms of most frequent liquid oral drugs prescribed, and a search of the literature yielded no previous studies on cariogenic potential of drugs. This study included two phases; the first was a preliminary cross sectional survey (a questionnaire) distributed among pharmacies in Irbid governorate, Jordan that aimed to identify the most prescribed LOPMs for children. Then, an analysis of sucrose and glucose content, and pH of these drugs was performed.

Children on long-term use of liquid medications [13] and who take medications routinely due to coughs and common cold [9] are at risk of developing dental caries, as these preparations are made palatable by adding sugars like sucrose, glucose or fructose in order to gain patient compliance. The medicines analyzed in this study were considered for long term use since they can be used for illnesses in infants and young children in doses ranging from 1 to 6 times daily, and for periods ranging from 3 days to one month or more according to the National Center for Health Statistics. [1] The more frequent the intake, the higher the sugar exposure which could lead to an increase in cariogenic potential. [14–16]

In this study, the median of sucrose present in the LOPMs varied between 4 to 24%, the highest was found to be in the nutritional categories. When comparing with other studies, the amount of sucrose present in LOPMs varied from 0 to 67% [3, 17–19], and highest total sugar contents were identified in the antitussives and anticonvulsants. [18] As described in the drug inserts, sucrose was added in 47.5% of the formulations. The median of glucose present in the LOPMs varied between 9.3 to 42.5%, the highest was found to be for the nutritional drugs as well. Previous studies reported glucose concentrations between 6.6–33.6% [18], and 4.6–40.2%. [20]

The pH of the medications in this study ranged from 4 to 6.4, the lowest pH was for the nutritional drugs category. However, in other studies it was found to be between 2.6 and 5.7 [19], 2.3 to 10.6 [20], and 3.70 to 7.04. [21] Many liquid medications have an endogenous low pH [22, 23] that may itself contribute to demineralization of enamel. [24]

Without any doubts, pH is vital in the carious and erosion process; however sweeteners added to medicines are more likely of main significance to the development of dental caries [9] as they are fermentable by the acidogenic bacteria in the oral cavity thereby, enhancing the growth of *S. mutans*, eventually leading to enamel demineralization. A previous study reported that *S. mutans* growth was seen with a nutritional supplement which was due to the low pH and a higher content of sucrose in it [25], other medicines studied did not promote or inhibit *S. mutans* growth.[22, 23] Although antibiotics are antimicrobial in nature, their use in children who are on chronic use medication should not be unnoticed, as these formulations have an enamel-erosive potential. [22, 23] On the other hand, a significant drop in dental caries in adenoidectomized children who were on antimicrobial and antihistamine medications compared to a control group was reported. [26]

The intake of liquid oral medications if combined with a low oral hygiene is more likely to boost the formation of dental plaque through periods of intake causing unwanted consequences to oral health. Therefore, recommendations for limiting caries in these children include measures targeting parents, medical/dental professionals and the pharmaceutical industry.[18] Parental instructions by practitioners to immediate water rinsing and delayed tooth-brushing with fluoridated toothpaste after syrup medicines' ingestion could be proposed at the time of prescription [12], chewing sugar-free gum after taking the medicine; if possible, taking the medicine in tablet form, at meal-times rather than between meals; avoiding ingestion of the medicine before bed, home and dental-office fluoride applications and seeking regular preventive dental care.[27] The role of dietary control with regards to carbohydrates is paramount; a British survey reported that it would be futile to administer sugar-free medicine to a child consuming lot of sweets.[28] In Northern Ireland, 55% of doctors supported the principle of prescribing sugar-free medicines for children. The main sources of information about sugar-free preparations were drug company travelling representatives and professional journals, but a few doctors learned of this issue from other professionals, including dental practitioners.[4] The pharmaceutical industry should provide sugar-free medications [9] and include medicine's labels that alert parents for potential to cause dental caries and erosion when consumed for prolonged periods, several times a day, without adequate oral hygiene.[12] In a survey, 75% of pharmacists in Northern Ireland stated that they had not received formal

education concerning sugar in medication and its effect on dental health. The major factors influencing the provision of sugar-free medicines were parental request, health promotion literature, reports and media advertising. [29] There are some limitations of this study such as filling the questionnaire that was dependent on memory of the pharmacist, and some medicines could not be obtained at the time of the study to be analyzed.

Conclusions

Based on the results of this study, it can be concluded that the sweetener content of the most common prescribed oral liquid medications ranged from 0.9 to 79.5% for sucrose and from 0 to 81.1% for glucose, the highest drug category in sugar content was the nutritional drugs. The pH values ranged between 3.2 to10, most drugs had acidic pH values (below 7) and the lowest pH was in the nutritional drugs. Since caries is a multifactorial infectious disease caused by presence of carbohydrates and low pH, it can be assumed that such drugs can increase the likelihood of dental caries and erosion if ingested frequently and chronically. We recommend education for health-care providers who prescribe or dispense sweetened medications, provision of sugar-free medications by the pharmaceutical industry, and increasing parental awareness towards sweetened medications and their impact on oral health to avoid dental caries or erosion.

Abbreviations

LOPM
Liquid oral pediatric medicines

Declarations

Ethics approval and consent to participate

The study protocol had been approved by the Institutional Review Board at Jordan University of Science and Technology (JUST), Irbid, Jordan (Approval Number 42/105/2017). The pharmacists invited to participate received verbal and written information about the study and were requested to consent before filling the questionnaire.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The corresponding author is an Associate Editor in BMC Oral Health. Other authors declare that they have no competing interests.

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Authors' contributions

Ola B. Al-Batayneh and Arwa I. Owais conceived the idea Ola B. Al-Batayneh, Arwa I. Owais and Yousef S. Khader designed the study, Ala'a B. Al-Bataina collected the data, Yousef S. Khader conducted the data analysis, and all authors reviewed and agreed to the final version of the manuscript.

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Authors' information

Ola B. Al-Batayneh, BDS, MDSc, FRACDS (Paed) is Professor in Pediatric Dentistry, and currently the Head of Department of Preventive Dentistry, Faculty of Dentistry at Jordan University of Science and Technology. She is also a consultant in pediatric dentistry, and Head of the Pediatric Dental Division at King Abdullah University Teaching Hospital, Irbid, Jordan. Contact details: Post: PO Box 3030, Irbid 22110, Jordan. Tel: +962-2-7201000, Fax: +962-2-7095123, Email: olabt@just.edu.jo.

Ala'a B. Al-Bataina, Pharmacist, was a master student at the time of this study at the Department of Public Health, Faculty of Medicine, Jordan University of Science and Technology, PO Box 3030, Irbid 22110, Jordan. Email: alaabatina@gmail.com

Yousef Khader is a dentist and Professor of Epidemiology, Medical Education and Biostatistics at the Department of Public Health and Epidemiology, Faculty of Medicine, Jordan University of Science and Technology. Contact details: PO Box 3030, Irbid 22110, Jordan. Email: yskhader@just.edu.jo

Arwa I. Owais is Associate Professor in Paediatric Dentistry, Department of Preventive Dentistry, Faculty of Dentistry, Jordan University of Science and Technology. Contact details: PO Box 3030, Irbid 22110, Jordan. Email: aowais@just.edu.jo.

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Supplementary Files

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