Awareness of Healthcare Professionals About Sorbitol-Related Diarrhea in Pediatrics

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Abstract

Objective: We aimed to identify sorbitol content in liquid drugs and to spread awareness about sorbitol-related diarrhea to healthcare professionals. The aim of the study was to raise awareness of healthcare professionals about sorbitol-related side effects in certain situations, for example, when dealing with critically ill patients in intensive care units where drug administration and side effects are problematic, and to provide a reference list of sorbitol content in the most commonly used pediatric drugs to clinicians.

Material and Methods: The study was prospective and cross-sectional, consists of two parts including drug information database review and a survey of healthcare professionals. The drug information database review was undertaken in 2015 and survey questionnaires were delivered to healthcare professionals at a University Hospital in 2016. All liquid pharmaceutical preparations marketed in Turkey by the year of 2015 were included. The questionnaire were given to 22 doctors and 24 nurses. Of those, 15 doctors and 20 nurses were volunteered to participate in the study (response rate: 68% and 83%, respectively).

Results: There were 13,852 pharmaceutical products containing sorbitol as an "additive substance"; of those, 1726 were liquid preparations. The results revealed that 60% of nurses were aware and cautious of the additive substances in the drug while administering doses; however, only 20% of doctors considered additive substances during prescribing in pediatrics. More than 60% of the participants were concerned that additive substances may cause gastrointestinal side effects.

Conclusion: Clinicians should be aware of the risk of sorbitol related diarrhea in patients with fever, infections and gastrointestinal diseases, in particular for patients in intensive care units. Appropriate drug dosage forms or administration routes should be considered in vulnerable patients including pediatric and critically ill patients.

Keywords: Diarrhea, sorbitol, critical illness, pediatrics

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Introduction

Liquid dosage forms are convenient in drug dosing and administration for pediatrics (1). Sorbitol is a polyalcohol sugar that can be added to various liquid dosage forms to sweeten the solution, carry the active drug, and improve drug's stability. Because sorbitol is an inert substance, companies generally do not indicate the exact amount and osmolality of sorbitol on the product's label. Since the product's sorbitol contents may differ between companies, it is appropriate to contact the company to determine its accurate content in a product (2).

When a drug is administered via an enteral route, gastrointestinal (GI) side effects of sorbitol occur in approximately 50% of patients. The severity of sorbitol related GI side effects (gas, bloating and cramp/diarrhea) varies according to total daily amount of sorbitol (5, 10 and 20 g/day, respectively). Although many products include a small amount of sorbitol, total daily intake or cumulative dose of sorbitol should be considered when more than one drug containing sorbitol is being administered to the patient. It has been reported that nosocomial diarrhea begins within 72 hours after hospitalization and is often caused by medications (usually liquid medications containing sorbitol), enteral tube feedings, or superinfections (3). Therefore, if a sorbitol/drug-related sudden onset of osmotic diarrhea occurs, change of a drug or its administration route should be considered (2, 4). Reported dose-related GI side effects were generally applicable in adult and intensive care unit population where patients have heterogeneous metabolic and nutritional status and polypharmacy is frequent (5-7). However, there are not many studies undertaken in pediatric population (8-13). This problem was also noted in pediatric patients; a 5-year-old child who received valproic acid syrup has been reported to develop diarrhea because of the sorbitol content (9 g/day) of the drug, and the diarrhea resolved within 24 h after the dosage form was changed (14).

Similar concerns are also applicable in febrile children who have received antipyretics, cough suppressants, or any other combined treatment that includes sorbitol in the liquid dosage forms. It can be difficult to differentiate whether diarrhea in a child is related to fever or a pharmaceutical product.

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Healthcare professionals are generally not aware of all ingredients of the pharmaceutical products that they prescribe or administer to patients. It is well-known that the active substance of a drug is responsible for its clinical effects as well as side effects; however, the effect of additive substances or excipients, pharmaceutical dosage forms, is less likely to be known.

Although sorbitol is an inert excipient in pharmaceutical or nutritional products, identification and quantification of its content are necessary to evaluate its potential effects on patient's therapy. Most drug companies document the total amount of sorbitol in drug formulation; however, in pediatric patients, anticipated and received amount of sorbitol may change and drug treatment may cause diarrhea even the total administered sorbitol amount has not reached the critical value.

To the best of our knowledge, there is no study that has evaluated awareness and knowledge of healthcare professionals on sorbitol-related side effects in Turkey. Therefore, aim of this study was to identify the awareness of healthcare professionals about sorbitol-related diarrhea in pediatric patients and to review and evaluate the sorbitol content of liquid dosage forms to guide clinicians in drug administration practices.

Material and Methods

The study was divided in two parts. In the first part, all liquid pharmaceutical preparations listed in commonly used "Drug Information Database-2015 (RxMediaPharma, Gemaş, İzmir)" by healthcare professionals in Turkey, were reviewed by the researcher pharmacist for their sorbitol contents. Sorbitol content of the pharmaceutical products were given as mg/mL, and the total daily amount of sorbitol was estimated for pediatric dosage.

The second part of the study was initiated after the analysis of the first part. In the second part, a five-item questionnaire was administered to a convenient sample of doctors and nurses in pediatric services (bone marrow transplant unit, intensive care, general pediatrics, urology, orthopedics, infectious disease, cardiovascular surgery, and brain surgery) at the University Pediatric Hospital during the last two weeks of July 2016. The questionnaire was designed by researchers according to the results of previously published studies. The first section of the questionnaire comprised demographic data of participants (age, gender, and years of experience) and the second section was related to general knowledge and attitudes of healthcare professionals on drug-related GI side effects, which mainly focused on sorbitol-related diarrhea.

A written informed consent was obtained from all participants, and an ethical approval was obtained from the Non-Trial Ethics Committee Clinical Trials Ethics Committee of the University. Collected data were indicated as mean, standard deviation, and percentages for related subgroups. No statistical analysis was performed for comparison due to limited number of participants.

Results

According to the Drug Information Database-2015, there were 13,852 pharmaceutical products containing sorbitol as an "additive substance" and of those, 1726 were liquid preparations. Of the total liquid preparations, 1138 were solutions, 229 were sachets, and 359 were oral suspensions. The highest sorbitol amount was identified as 10,000 mg/mL in a product containing "acetlycysteine", followed by the products containing active substance as butamirate citrate, paracetamol, cetirizine, ketotifen, ferrous, piracetam, sulphamethoxazole+trimethoprim, and ambroxol. Three pharmaceutical products (paracetamol and ibuprofen) containing high amount of sorbitol were also ranked as the 9th, 22nd, and 27th in the Intercontinental Marketing Services (IMS) 2014 list, which includes the top 100 products according to the number of boxes sold in Turkey.

Therapeutic indications and pediatric dosage of certain pharmaceutical products and estimated daily sorbitol exposure are summarized in Tables 1 and 2.

The questionnaire was given to 22 doctors and 24 nurses and returned by 15 doctors and 20 nurses (response rate: 68% and 83%, respectively) in pediatric units. The participants' demographics and responses to the questions are shown in Table 3.

Most nurses (60%) focus on the additive substances in the drugs during drug administration; however, only 20% of the doctors consider it during prescribing drugs. More than 60% of participants were concerned that additive substances may cause GI side effects, but they were less informed of the potential side effects of>15 g/day of consumption of sorbitol, particularly with products like those containing paracetamol, acetylcysteine, butamirate, and sulphamethoxazole+trim ethoprim.

Discussion

Sorbitol-related diarrhea is a commonly observed complication particularly seen in patients receiving enteral feeding or many medications for different chronic conditions. It is important to differentiate the main reason of diarrhea in this patient population, whether it is related to a product or metabolic dysfunction. According to the case report by Madigan et al. (15), a patient who underwent enteral feeding at home for 22 months via a percutaneous endoscopic gastrostomy (PEG) tube and received liquid forms of baclofen+trimethoprim treatment developed diarrhea; however, after a community pharmacist changed her liquid medication to its crushed form, the problem resolved.

Studies by Lutomski and Johnston have identified sorbitol-related side effects for pharmaceuticals marketed in the United States (14, 16); however, not many studies have been conducted in local pharmaceutical markets and not many manufacturers readily provide information on sorbitol content or osmolality.

A paracetamol-containing product includes 16 g sorbitol if administered daily to a pediatric patient, and over 10 g of sorbitol causes gas and bloating and long-term treatment has a risk of developing diarrhea. This result was consistent with the results of the study by Johnston where paracetamol-containing products were reported to have highest amount of sorbitol (16). Another study by Lutomski indicated that two forms of the same drug (paracetamol solution and elixir) had differences in their sorbitol content (14). In our study, it was observed that active components of drugs manufactured by different companies have different sorbitol contents; therefore, the total daily amount of sorbitol in drugs should be considered and switching to the counterpart with lower sorbitol content may be necessary at certain instances. Three pharmaceutical brands with high amount of sorbitol were listed in the top 100 marketed drug list of IMS-2014 in Turkey. Therefore, other pharmaceutically bioequivalent brands containing a high amount of sorbitol and not included in the list should also be carefully considered during treatment. Moreover, even if the amount of sorbitol per mL of the solution is less than 350 mg, the cumulative amount at the end of the treatment may be higher than expected, which can be problematic for the patient.

Table 1. The products containing ≥500 mg/mL of sorbitol in Turkey and expected maximum sorbitol exposure for pediatric patients

Pharmaceutical product (sorbitol content as mg/mL)	Active drugs	Therapeutic indication	Maximum estimated pediatric dosage*	Total sorbitol exposure/day
Oxxa Syrup and granules to be prepared© (10,000 mg/mL)	Acetlycysteine	Mucolytic	3×5 mL	3×(10,000×5)=150 g
Bactrim Suspensions© (900 mg/mL)	Sulphamethoxazole+trimethoprim	Antibacterial	2×10 mL	2×(900×10)=18 g
Ferro Sanol Drops© (650 mg/mL)	Ferrous sulphate	Anemia	4×10 drops (20 drops=1 mL)	4×(650×0.5)=1.3 g
Sekrol Syrup© (633 mg/mL)	Ambroxol	Mucolytic	3×2.5 mL	3×(633×2.5)=4.7 g
Pulmistat Syrup© (550 mg/mL)	Butamirate citrate	Antitussive	3×10 mL	3×(550×10)=16.5 g
Tuscod Syrup© (550 mg/mL)	Butamirate citrate	Antitussive	3×10 mL	3×(550×10)=16.5 g
Notuss Syrup© (500 mg/mL)	Butamirate citrate	Antitussive	3×10 mL	3×(500×10)=15 g
Ferro Sanol B Syrup© (500 mg/mL)	Ferrous sulphate+Riboflavin+ thiamine+pridoxine	Anemia	1×15 mL	1×(500×15)=7.5 g
Fluibron Ped Syrup© (500 mg/mL)	Ambroxol	Mucolytic	3×5 mL	3×(500×5)=7.5 g
Zaditen Syrup© (500 mg/mL)	Ketotifen	Allergic rhinitis and conjunctivitis	2×5 mL	2×(500×5)=5 g
Mitofen Syrup© (500 mg/mL)	Ketotifen	Allergic rhinitis and conjunctivitis	2×5 mL	2×(500×5)=5 g

*dosages are based on the Drug Information database 2015

Table 2. Products containing 100–500 mg/mL sorbitol in Turkey and expected maximum sorbitol exposure for pediatric patients

Pharmaceutical product (sorbitol content as mg/mL)	Active drugs	Therapeutic indication	Maximum estimated pediatric dosage*	Total sorbitol exposure/day
Yenizin Syrup© (450 mg/mL)	Cetirizine	Allergic rhinitis and urticaria	1×10 mL	1×(450×10)=4.5 g
Cetryn Syrup© (450 mg/mL)	Cetirizine	Allergic rhinitis and urticaria	1×10 mL	1×(450×10)=4.5 g
Termaset Plus Suspensions© (400 mg/mL)	Paracetamol	Analgesic and antipyretic	4×10 mL	4×(400×10)=16 g
Nootropil Syrup© (400 mg/mL)	Piracetam	Dyslexia	1×16 mL	1×(400×16)=6.4 g
Ferrozinc G Syrup© (385 mg/mL)	Ferrous+zinc	Anemia	1×5–10 mL	1×(385×10)=3.8 g
Anfezinc G Syrup© (385 mg/mL)	Ferrous+zinc	Anemia	1×5–10 mL	1×(385×10)=3.8 g
Minamol Plus Suspensions© (379 mg/mL)	Paracetamol	Analgesic and antipyretic	4×10 mL	4×(379×10)=15 g
Doxafin Syrup© (354 mg/mL)	Desloratadine	Allergic rhinitis and urticaria	1×5 mL	1×(354×5)=1.77 g
Zincoplex Syrup© (350 mg/mL)	Zinc sulphate	Zinc deficiency	1×3.33 mlL	1×(350×3.33)=1.16 g
Broksin Syrup© (350 mg/ml)	Guaiafenezin & ephedrine	Expectorant	3×10 mL	3×(350×10)=10.5 g
Alores Syrup© (350 mg/mL)	Desloratadine	Allergic rhinitis	1×5 mL	1×(350×5)=1.75 g
Enfluvir Suspensions© (342.84 mg/mL)	Oseltamivir	Influenza prophylaxis and treatment	1×6.25–12.5 mL	342.84×6.25=2.14 g 342.84×12.5=4.28 g
#Dolven Ped Syrup© (300 mg/mL)	Ibuprofen	Analgesic and Antipyretic	4×10 mL	4×(300×10)=12 g
#Aferin Plus Ped Syrup© (200 mg/mL)	Paracetamol+pseudoephedrine+ chlorpheniramine	Analgesic and Antipyretic Antihistaminic Decongestant	4×10 mL	4×(200×10)=8 g
Ferrum Hausmann Syrup© (200 mg/mL)	Ferrous	Anemia	2×5 mL	2×(200×5)=2 g
Aerius Oral Solution© (150 mg/mL)	Desloratadine	Rhinitis	1×5 mL	1×(150×5)=0.75 g
#Iburamin Cold Syrup© (100 mg/mL)	Ibuprofen+pseudoephedrine+ chlorpheniramine	Analgesic and Antipyretic Antihistaminic Decongestant	4×5 mL	4×(100×5)=2 g
Apireks Pediatric Suspensions© (100 mg/mL)	Ibuprofen	Analgesic and antipyretic and anti-inflammatory	4×10 mL	4×(100×10)=4 g

*dosages are based on the Drug Information database 2015
#liquid products that are listed in top 100 pharmaceutical products sold list in Turkey in 2014

Table 3. Healthcare professionals' attitudes in regards to the use of liquid dosage forms

	Doctors (n=15)	Nurses (n=20)
Age (mean±standard deviation)	27.6±3.2	30.0±4.9
Practiced years (mean±standard deviation)	2.8±2.2	7.5±4.6
Which of the following dosage forms are the most commonly used in the service:		
Tablets	4	17
Capsules	1	5
Injectables	2	13
Powder mixtures	0	4
Syrup/elixir/suspensions	8	10
Do you pay any attention to the additive substances within the liquid dosage forms?		
Yes	3 (20%)	12 (60%)
No	6 (40%)	3 (15%)
Sometimes	6 (40%)	5 (25%)
Do you have any concerns about additive substances in the dosage forms that may cause side effects?		
Yes	9 (60%)	14 (70%)
No	2 (13%)	1(5%)
Sometimes	4 (27%)	5 (25%)
Which of the products with the following ingredients may cause GI side effects such as gas, cramp, or diarrhea on daily dosing? (active substances were given in manufactured names/ brand names)		
Paracetamol	0	1 (5%)
Ibuprofen	3 (20%)	0
Ibuprofen+pseudoephedrine+chlorpheniramine	6 (40%)	5 (25%)
Acetlycysteine	2 (13%)	11 (55%)
Sulphamethoxazole+trimethoprim	4 (26%)	6 (30%)
Ferrous Sulphate	13 (87%)	17 (85%)
Ambroxol	3 (20%)	0
Guiafenezin+ephedrine	6 (40%)	0
Which of the following may cause these gastrointestinal side effects?		
Active substance	10 (67%)	17 (85%)
Additive substance	8 (53%)	9 (45%)

Although the total daily amount of sorbitol may not seem to exceed the threshold value for the risk of diarrhea (>20 g/day), GI side effects such as gas and bloating may by seen in pediatric patients regardless of active drugs. Given the fact that paracetamol-, oseltamivir-, and desloratadine-related diarrhea is seen in 3–8% of patients during drug treatment, sorbitol may increase the risk of diarrhea in patients who takes these medicines.

Regardless of sorbitol content, treatment with various drugs such as antibacterials, antineoplastics, antidiabetics, nonsteroidal anti-inflammatory drugs, and antihypertensives has a risk of developing diarrhea to different extents (17). Therefore, characteristics of a drug and patient's other co-morbid diseases should be considered to have an appropriate and rational drug treatment for patients. Febrile pediatric patients who have enteric bacterial infections also suffer from diarrhea. Concurrent use of antibiotic and antipyretic treatments in patients may cause misinterpretation of the reason of diarrhea in clinical practice. Similar concerns exit in patients who have persistent cough and fever. Therefore, it is important to recommend appropriate dosage forms for patients who have diarrhea to minimize the risk related to sorbitol.

Unfortunately, the sample size of the survey was small to make any statistical comparison between the opinions of healthcare professionals. Therefore, this can be considered as the main limitation of the study.

Conclusion

According to the results of this study, healthcare professionals in pediatric services did not seem to have much information about the effects of additive substances, which might change therapeutic outcomes during treatment. Although they have concerns about the effects of additives, lack of proper information about substances causes an incorrect alert for patient monitoring, which may lead to discontinuation of therapy unnecessarily. Particularly, it should be remembered that the risk assessment of cumulative dose is important for a pediatric patient who uses more than one drug containing sorbitol concurrently.

When sorbitol-related GI side effects occur, especially with cumulative doses, clinicians might prescribe another medication to solve this problem, which may cause an elevated risk of drug-related problems due to polypharmacy. Moreover, GI side effects related to total daily doses of sorbitol are defined for adult patients and the side effects might be seen with lower amounts of sorbitol in pediatric patients. Thus, awareness of sorbitol amounts in medications is important in clinical practice, especially in pediatric patients, to avoid drug-related problems. Although this study mainly focused on drug formulations and dosage forms in pediatric patients, use of drugs containing sorbitol as an additive ingredient is also common in intensive care unit patients during administration of medications through the feeding tube. Thus, increased awareness of clinicians in intensive care units is also essential for achieving improved healthcare practice.

This study was a small, cross-sectional, exploratory study that aimed to identify and raise the awareness of healthcare professionals in local settings. Large and multi-institutionally designed research in different units, including pharmacists, nurses, and doctors, is needed in further studies.

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