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Antibiotic use for patients with inherited metabolic diseases in outpatient clinical setting

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Abstract

Aim: In this report, we aimed to assess the the frequency and accuracy of antibiotic use for upper respiratory tract infection for children younger than 6 years of age with inherited metabolic diseases and also to identify possible associated factors in the outpatient clinic.

Materials and Methods: This study was a prospective, randomized, single center study in which children with upper respiratory tract infections were enrolled. A 25-question questionnaire was prepared to ask the patients' families. These survey questions were included age, gender, weight, parental ages, education levels, type of antibiotics given, antibiotic dose and frequency.

Results: Of the 415 individuals, 380 patients and caregivers agreed to participate in the study. The most prescribed antibiotics were amoxicillin/clavunate (31.57%), amoxicillin (21.31%) and clarithromycin (15.26%). We demonstrated that antibiotic dose was inappropriate in 42.89% of our patients. Dosing errors were categorized as follows: 62.6% involved dosing above the recommended amount, while 37.4% involved dosing below the prescribed amount.

Conclusion: The significance of administering precise dosages should be consistently emphasized by healthcare professionals when administering antibiotic suspensions especially in the case of inborn errors metabolism in order to avoid inappropriate treatment, adverse effects and antibiotic resistance.

Introduction

Over 30 % of children living in Turkey receive an antibiotic each year. As the majority of infectious diseases appear to be viral in nature, the majority of antibiotic prescriptions are deemed unnecessary. However, when they are necessary, it is vital that the appropriate dosage be administered to the patient. Antibiotic prescription errors may result in adverse effects and potentially harmful treatments for children. Treatment failure may occur as a consequence of subtherapeutic dosing, whereas the occurrence and severity of adverse effects and toxicity may be amplified at high doses [1,2]. By employing suitable delivery devices, it is possible to readily modify the dosage to suit the individual requirements of patients. Nonetheless, administering the correct dose in addition to performing precise dose calculations is what ensures safe and effective treatment. This is especially crucial for children, as their sensitivity to dosage errors is greater than that of adults.

Clinicians have access to a diverse assortment of oral antibiotic medications for the treatment of acute bacterial infections in children, including pharyngitis/tonsillitis, acute otitis media, and sinusitis. Bacterial infections in children younger than 6 years are typically treated with antibiotic suspensions because of the difficulty in swallowing the tablets and capsules.

Clinicians select antibiotic suspensions based on a variety of distinguishing characteristics, such as cost, pharmacokinetics, tolerability, antibacterial spectrum, palatability, duration of therapy, and number of daily doses [3]. Failure to adhere to the prescribed dosage and/or treatment duration can lead to unfavorable consequences, including disease recurrence and resistance, complications, more physician visits, increased school day looses and the need for additional prescriptions [4,5]. In addition, infections can cause metabolic decompensation in inherited metabolic diseases. Since consanguineous marriages are frequent in our country, inherited metabolic diseases are common. Infections may trigger acute metabolic decompensation in children with inborn metabolic diseases.

In this report, we aimed to assess the accuracy of antibiotic dosing that prescribed for children with inborn metabolic

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diseases younger than 6 years mainly diagnosed with upper tract infections and also to identify possible associated factors in the pediatric metabolism outpatient clinic.

Materials and Methods

This work was a prospective, randomized, single center research in which children with upper respiratory tract infections who were previously diagnosed to have an inborn errors of metabolism were enrolled between January 1, 2022 and june 31, 2022. Patients were eligible for enrollment if they were below six years of age; if they were using antibiotic suspension for upper respiratory tract infections at least for the 72 hours; and if written informed consent had been obtained from the parent or legal guardian. Antibiotic necessity could not be determined due to the fact that the patients were already taking antibiotics at the time of admission. The study enrolled individuals who were diagnosed with inborn error of metabolism, including phenylalanine metabolism disorder, biotinidase deficiency, ketogenesis defects, ketolysis defects, galactosemia, fatty acid oxidation defects and lysosomal storage diseases. Inborn errors of metabolism are very rare disorders. Hence, the maximum amount of patients had been detected to be included in the study.

Patients were not included for the study if they exhibited any of the following characteristics: a history of a significant medical condition other than inherited metabolic diseases (i.e. kidney, liver, hematologic or gastrointestinal diseases, etc.); using another constant medication; if the name of the prescribed medicine or the dose is not known; or the children with recurrent applications.

Following the acquisition of each subject's informed permission, their medical histories were documented. A 25-item questionnaire was prepared to ask the patients' families. The survey questions included age, gender, weight, parental ages, education levels, name of antibiotics given, antibiotic dose and frequency. In addition, parents/legal guardians were asked the reasons for bringing children to the emergency clinic. Lastly, parents or legal guardians were queried regarding the source of dosing information: doctor, nurse, pharmacist, personal experience, or prescribing information.

The appropriate dose (dose range) and frequency of administration for amoxicillin, amoxicillin-clavulanate, cefuroxime, cefdinir, cephalexin, cefixime, clarithromycin and azithromycin were determined as 45-90 mg/kg (2dd, maximum of 3g/day), 45-90 mg/kg (2dd, maximum of 3g/day), 30 mg/kg (2dd, maximum of 1 g/day), 14 mg/kg (1-2 dd, maximum of 600 mg/day), 40 mg/kg (2 dd, maximum of 1 g/day), 8 mg/kg (1-2dd, maximum of 400 mg/day), 15 mg/kg (2dd, maximum of 1 g/day) and 10 mg/kg (10 mg/kg on day one followed by 5 mg/kg, q24 hr for four days, maximum of 500 mg/day), respectively.

All of the patients' weight was remeasured at the hospital so that the dose of the antibiotic drug could be calculated correctly. Doses below the aforementioned values are classified as low doses, while doses above them are classified as high doses.

The Ethics Committee of the Gazi Yasargil Training and Research Hospital granted approval for our work under decision number 2022/129.

Statistical analysis

The SPSS software, version 16.0 (provided by SPSS Inc. of Chicago, Illinois, USA), was utilized throughout each and every statistical analysis. For continuous variables, descriptive statistics including mean, standard deviation, minimum, and maximum were presented. The results of the categorical variables were shown with their frequency and percentage values. The accuracy of antibiotic dosing and associated factors were evaluated using the Chi-squares test. The confidence interval was 95% and the accepted margin of error was 5%. The significance level was set at 0.05 for a value of p.

Results

Of the 415 subjects, 380 patients and caregivers agreed to participate in the study. Most of the participants were boys (58.4%, n=222). Demographic characteristics are summarized in the table (Table 1).

Overall, a total of eight different antibiotics were prescribed. The most prescribed antibiotics were amoxicillin/clavunate (31.57%), amoxicillin (21.31%) and clarithromycin (15.26%).

The distribution of antibiotics used by patients in low, normal, or high doses is shown in the table (Table 2). Twenty patients (24.7%) administered amoxicillin below the advised daily dose, while eighteen patients (22.2%) administered the medication in excess of the advised daily dose.

Table 1. Characteristics of children and caregivers.

Clinical characteristics		95% Confidence Interval of the Difference	
		Lower	Upper
Age of children, years (mean±SD)	3.26±1.28	3.13	3.39
Female /Male	158/222	-	-
Weight (mean±SD)	16.38±5.36	15.84	16.92
Mother's age (mean±SD)	28.58±4.84	28.09	29.07
Mother's education			
1-11 year	205	-	-
>11 year	175		
Father's age (mean±SD)	31.59±4.89	31.10	32.09
Father's education			
1-11 year	193	-	-
>11 year	187		

Table 2. Rates of inappropriate use of antibiotics.

Antibiotics	Underdose Number (%)	Acceptable dose Number (%)	Overdose Number (%)
Amoxicillin	20 (24.7)	43 (53.1)	18 (22.2)
Amoxicillin-clavunate	29 (24.2)	72 (60)	19 (15.8)
Cefuroxime	3 (18.8)	9 (56.2)	4 (25)
Cefdinir	4 (7.7)	14 (26.9)	34 (65.4)
Cephalexin	3 (10.4)	15 (51.7)	11 (37.9)
Cefixime	-	5 (55.5)	4 (44.5)
Clarithromycin	2 (3.5)	52 (89.6)	4 (6.9)
Azithromycin	-	7 (46.7)	8 (53.3)
Totally	61	217	102

Table 3. Factors determining the antibiotic dose in patients using inappropriate doses of antibiotics.

Factors	Patient Numbers (%)
Doctor	52 (31.9)
Prospectus	24 (14.8)
Nurse	8 (4.9)
Pharmacist	63 (38.6)
Personal experience	16 (9.8)

A total of 29 patients (24.2%) administered amoxicillin-clavunate below the advised daily dose, while 19 patients (15.8%) exceeded the daily dose. Three patients (18.8%) reported a daily dose of cefuroxime below the advised amount, while four patients (25%) reported a daily dose exceeding the advised amount. Four patients (7.7%) administered cefdinir in a quantity below the advised daily dose, while 34 patients (65.4%) exceeded the daily dose. A total of eleven patients (37.9%) exceeded the advised daily dose of cephalexin, while three patients (10.4%) administered less than the suggested daily dose. An excess of the prescribed daily dose of cefixime was observed in four patients (44.5%). Two patients (3.5%) administered clarithromycin in a quantity below the advised daily dose, while four patients (6.9%) exceeded the daily dose. An excess of the advised daily dose of azithromycin was observed in eight patients (53.3%).

Among participants who took antibiotics, 163 (42.89%) of them used inappropriately. Dosing below the advised quantity constituted 37.4% of dosing errors, whereas dosing above the suggested amount constituted 62.6%. Among these, a pharmacist provided drug dosage information to the caregivers of 63 patients (38.6%). A doctor provided drug dosage information to the guardians of fifty-two patients (31.9%). Twenty-four (14.8%) caregivers dosed the antibiotic according to the prescribing information. Interestingly, 16 (9.8%) caregivers based on their own personal experience to dose the antibiotic. A nurse provided drug dosage information to the guardians of eight patients (4.9%) (Table 3).

Discussion

Inborn errors of metabolism are inherited disorders caused by mutations in genes coding for proteins that function in metabolism [6]. These diseases result from defects in metabolic pathways associated with the breakdown or accumulation of carbohydrates, proteins, and fatty acids [6]. In addition, there are metabolic diseases that present with insufficiency in energy production. Inborn errors of metabolism are uncommon when observed individually, but prevalent when observed collectively. Due to their heterogeneous nature, the epidemiologies, clinical manifestations, and heritabilities of various disorders vary considerably. Although they are typically autosomal recessive in inheritance, autosomal dominant and X-linked forms also exist [6]. Decompensation is frequently precipitated by infections or fasting in the numerous metabolic diseases. In order to prevent decompensation, it is imperative to refrain from fasting and to administer antibiotics while dealing with any infection [7].

The significant finding of the present work was the presence of high levels of the inappropriate use of antibiotics. We demonstrated that antibiotic dose was inappropriate in 42.89% of our patients. Dosing below the advised quantity constituted 37.4% of dosing errors, whereas dosing above the suggested amount constituted 62.6%. Of these, 68.1% caregivers received dosing information from pharmacist, nurse, prescribing information and personal experience.

According to prior research, over forty percent of parents administer liquid medications improperly [8,9]. Other prevalent mistakes made by parents include administering antibiotics using an ordinary spoon instead of a dispenser, failing to verify the medication's expiration date on the packaging, dissolving the drug in the child's milk, discontinuing the antibiotics when the child's symptoms resolve [10]. Keeping at home antibiotics for potential future illnesses is regrettably a practice adopted by a significant number of parents. When the child gets sick, parents decide on the antibiotic treatment themselves and its duration without consulting the doctor.

Parents whose children have been diagnosed with inherited metabolic diseases typically encounter severe and acute metabolic decompensations. To mitigate the risk of such episodes recurring, they generally take some precautions including starting on antibiotics immediately. However this approach results in significant drug resistance and sometimes adverse effects. The results obtained from our study probably reflect this fact. Families should avoid unnecessary use of antibiotics when their children are sick. It is imperative that physicians consistently prescribe the most suitable antibiotics for a given disease [11].

The volume, frequency, and duration of daily doses are critical factors in promoting adherence among pediatric patients and ultimately lead to enhanced treatment effectiveness. Enhanced efficacy ultimately results in a reduction in the overall cost of disease treatment due to the decreased necessity for supplementary prescriptions and office visits [4,5,12]. Other contributing factors include smell, and taste [12-14].

In a study that compared color-coded oral syringes with traditional dosing devices (such as dosing cups, measuring spoons, household teaspoons, calibrated medication spoons, and medication droppers), 92% of caregivers who used a syringe marked with colored lines were able to accurately measure an acetaminophen liquid dose, while only 50% of caregivers who used their own device were able to do so [15]. Cifaldi et al. evaluated the use and compatibility of cefdinir and amoxicillin/clavunate [16]. They discovered that due to its palatability and flavor, cefdinir suspension was preferred by parents over low-dose amoxicillin/clavulanate suspension; this led to greater adherence [16]. In a series of six randomized studies, it was observed that children exhibited a preference for the taste and smell of cefdinir as compared to the comparators. These comparators included amoxicillin/clavulanate, cefprozil, and azithromycin [17]. There might be some additional obstacles such as mental and motor retardation in children with inherited metabolic diseases which contributes to incompliance with drug intake. Our study is a cross-sectional study, and the frequency of using inappropriate doses of

antibiotics was investigated. In addition, how families decide the antibiotic dose was examined. In our study, among participants who took antibiotics, 163 (42.89%) of them used inappropriately.

Evaluations of the dose accuracy of oral antibiotic suspensions in children with inherited metabolic diseases are scarce. Hospitalized children's medication administration error rate was examined by Al-Ramahi et al. They reported the drug dose error rate as 22.4% in their study [18]. In another study conducted in Saudi Arabia, they reported the percentage of dose errors as 22.1% [19]. According to a systematic review of the literature concerning medication errors, the prevalence of dose errors in Middle Eastern countries ranged from 0.15% to 34.8% of prescriptions [20]. Due to the fact that we utilized a unique approach to collect and report antibiotic dose mistakes, it is possible that our findings are not comparable with those of previously published studies in this field.

This study was limited by its relatively small number of subjects. Furthermore, we were unable explore the association between inaccurate antibiotic dose and smell, color, taste, and dosing cup. There is a need for randomized controlled studies in which factors such as taste, odor, number of daily doses and duration of treatment are evaluated together.

Particularly in the case of inherited metabolic disorders, prompt diagnosis and treatment of minor ailments are crucial regardless of age. Regrettably, caregivers frequently decide to the antibiotic dose according to the pharmacist, nurse, prospectus and personal experience in our country. The significance of administering antibiotic suspensions with an accurate dose should be routinely emphasized by healthcare professionals to prevent disease recurrence, complications, more physician visits, increased time lost from school and the need for additional prescriptions. It is urgently necessary to devise a plan for an efficient strategy that will promote the proper utilization of antibiotics.

Conflict of interest statement

No potential conflicts of interest exist.

Funding information

No financial or personal links exist between the authors and other people or organizations.

Ethical approval

Ethical approval was received for this study from Gazi Yaşargil Training and Research Hospital Ethics Committee (2022/129).

Informed consent

Every procedure that was executed adhered to the ethical principles set forth by the committee responsible for human experimentation, as well as the Helsinki Declaration. Prior to participation in the investigation, informed consent was received from every patient.

Author's contributions

H.B. was responsible for the design of the study, as well as the collection, analysis, and writing of the paper. A.A. was responsible for the collection of data, as well as its analysis and writing. The final text was reviewed and approved by all of the authors.

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