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Where Do We Go Wrong in the Pharmacologic Treatment of Functional Constipation in Children?

Çocuklarda Fonksiyonel Kabızlığın Farmakolojik Tedavisinde Nerede Yanlış Yapıyoruz?

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ABSTRACT

Objective: Constipation is often inadequately treated in childhood, which can lead to psychological problems. This study aimed to evaluate the adequacy of prescribed drugs, dosing, usage, and responses to these drugs in children with functional constipation.

Methods: This research comprised children who had consulted a pediatric gastroenterologist for functional constipation and had previously undergone constipation therapy. The name of the drug used, duration of drug usage, method of measurement, and what they took the drug with, the dose of drug, and response to the drug were recorded.

Results: Eighty-seven percent of the patients had received lactulose treatment. Only 31% of the patients received a medication dose greater than 1 mL/kg. In 58.3% of cases, the duration of drug use was shorter than one month. There was not a response in 62.9% of cases, a partial response in 23.1%, and a full response in 13.8% of cases. When the patients were compared based on response, there was a significant difference in the duration of drug usage, what they drank the drug with, the daily dose of the drug, and the daily dosage per weight of the drug. Patients who measured the drug using a milliliter scale responded better. The response to the drug increased as the drug dosage per weight increased. Response was obtained in 73% of patients who had no response or partial response after drug or dose adjustments.

Conclusion: For a comprehensive response, parents must be carefully taught the dosage of the drug and how to measure it.

Keywords: Constipation, treatment, lactulose, treatment period, response

ÖZ

Amaç: Kabızlık çocukluk çağında sıklıkla yetersiz tedavi edilir ve bu durum psikolojik sorunlara yol açabilir. Bu çalışmada fonksiyonel kabızlığı olan çocuklarda reçete edilen ilaçların yeterliliği, dozajı, kullanımı ve bu ilaçlara verilen yanıtların değerlendirilmesi amaçlandı.

Yöntemler: Bu araştırma, fonksiyonel kabızlık nedeniyle pediatrik gastroenteroloji uzmanına başvuran ve daha önce kabızlık tedavisi gören çocukları kapsamaktadır. Kullanılan ilacın adı, kullanım süresi, ölçüm yöntemi, ilacı neyle aldığı, ilacın dozu ve ilaca verdiği yanıt kaydedildi.

Bulgular: Hastaların %87'si laktuloz tedavisi almıştı. Hastaların yalnızca %31'i 1 mL/kg'ın üzerinde ilaç dozu aldı. Olguların %58,3'ünde ilaç kullanım süresi bir aydan kısaydı. Olguların %62,9'unda yanıt alınamadı, %23,1'inde kısmi yanıt, %13,8'inde ise tam yanıt oluştu. Hastalar yanıta göre karşılaştırıldığında ilaç kullanım süreleri, ilacı neyle içtikleri, ilacın günlük dozu ve kilo başına günlük dozaj arasında anlamlı fark vardı. İlacı mililitre ölçeği kullanarak ölçen hastalar daha iyi yanıt verdi. Ağırlık başına ilaç dozajı arttıkça ilaca verilen yanıt da arttı. İlaç veya doz ayarlaması sonrasında yanıt alınamayan veya kısmi yanıt alınamayan hastaların %73'ünden yanıt alındı.

Sonuç: Kapsamlı bir müdahale için ebeveynlere ilacın dozajı ve bunun nasıl ölçüleceği dikkatle öğretilmelidir.

Anahtar Sözcükler: Kabızlık, tedavi, laktuloz, tedavi süresi, cevap

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INTRODUCTION

Constipation is a prevalent condition among children (1). Its reported prevalence ranges from 0.7-29.6%, accounting for 3% of all pediatric outpatient clinic visits and 25% of cases in pediatric gastroenterology (1,2). Although constipation can stem from many etiologies, 95% of children with constipation have no organic pathology and are defined as having functional constipation (3). The diagnosis of functional constipation can be made by a careful history and physical examination without the need for laboratory tests or other examinations (4,5). According to recommendations from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), polyethylene glycol (PEG) is the first-line treatment for pediatric constipation, and lactulose is recommended in cases in which PEG is unavailable (4). However, it has been shown that childhood constipation is usually not treated adequately (6). Inadequately managed constipation can result in significant abdominal discomfort, fecal incontinence, and subsequently psychological problems and social withdrawal among children (7). This study aimed to evaluate the adequacy of prescribed drugs, dosing, usage, and response to these drugs in children diagnosed with functional constipation.

MATERIALS AND METHODS

The study was conducted retrospectively, focusing on children who had visited the pediatric gastroenterology outpatient clinic of a training and research hospital between January 2020 and March 2021. The clinical data of patients were extracted from an electronic database. Patients between the ages of 1 and 18 years with functional constipation as defined by Rome IV diagnostic criteria, as well as those who had received any treatment for constipation prior to the visit to pediatric gastroenterology and after the visit to the pediatric gastroenterology clinic, the drug dosage had been corrected according to NASPGHAN and ESPGHAN recommendations, were included in this study (4). Patients with 2 or more of the following symptoms at least 4 days per month and criteria satisfied at least once per week for a minimum of 1 month with inadequate criteria for a diagnosis of irritable bowel syndrome are described as having functional constipation, according to Rome IV criteria: 2 or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years, A minimum of one episode of fecal incontinence per week; a history of retentive posture or excessive volitional stool retention; painful and hard bowel movements; a big-diameter stool that can impede the toilet; and the appearance of a large fecal mass in the rectum. After a thorough examination, the symptoms cannot be explained entirely by another medical condition (8).

Patients under the age of one, with any organic condition for constipation or cerebral palsy, and those who had not received prior treatment were excluded from the study. In addition, patients who did not attend the follow-up visit were excluded.

Demographic information, including age and gender, of the patients was recorded. Anthropometric measurements such as height and weight standard deviation scores (SDS) were calculated using Turkish norms (9).

The duration of symptoms (1-3 months, 3-6 months, 6-12 months, and >12 months), the name of the drug administered, the duration of drug usage (1 month, 1-2 months, and >2 months), the method of measurement and what they took the drug with (tea spoon, dessert spoon, regular spoon or measuring with milliliters), the dosage of the drug, and the patient's response to the treatment were all documented.

Regarding treatment response, patients were categorized as follows:

- No response: If there was no improvement in stool shape, consistency, or painful defecation between or after treatments.

- Partial response: If there was some improvement in stool shape, consistency, and painful defecation between or after treatments, but not to the expected extent.

- Full response: If the patient experienced one or two soft bowel movements per day after treatment.

For measurement purposes, the teaspoon, dessert spoon, and regular spoon were considered equivalent to 2.5 milliliters (mL), 5 mL, and 10 mL, respectively.

The daily dosage of the drug was divided by the patient's body weight, and the dosage was calculated in milliliters per kilogram (mL/kg) accordingly.

The methodology for this study was approved by the Human Research Ethics Committee of the University of Malatya Turgut Özal (approval number: 2021/34).

Statistical Analysis

The variables were investigated using visual (histograms, probiblty plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. All variables were distributed normally. Normally distributed quantitative variables are presented as mean ± SD. Evaluation of differences between groups with respect to numerical variables was performed using t-test and one-way ANOVA if parametric test assumptions were checked. When the ANOVA test was significant, post-hoc tests were used to obtain the result between which pairs this difference was. Mann-Whitney U test was used to examine whether two samples given quantitative scale observations came from the same distribution.

Pearson's chi-square test was used to compare the ratios between the groups. Data were analyzed using IBM SPSS 16.0 statistical package program (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 were considered as statistically significant.

RESULTS

A total of 4,213 patients were initially assessed. Among them, 451 patients were consulted for constipation. Thirty-five of these patients were found to have constipation caused by an organic pathology, and those with cerebral palsy were excluded. Consequently, 416 patients were identified as having functional constipation according to the Rome IV criteria. From this group, 270 patients who had not previously used any medication for constipation were excluded. Additionally, 38 patients withdrew from the trial because of lack of follow-up or withdrawal of consent. A total of 108 patients were included in the study.

Among the 108 cases, 56 (51.9%) were girls. The mean age of patients was 4.4±3.7 years. The mean body weight SDS was -0.09±1 and mean height SDS was -0.09±0.9. Duration of symptom, used drug name, number of patients with disimpaction treatment given

or not given, numbers of what to give the drug with, duration of drug usage, and response to the drug given in Table 1.

When comparing patients based on their response categories (no response, partial response, and full response), no significant differences were observed in terms of gender, age, body weight SDS, height SDS, duration of symptoms, or name of the drug. However, significant differences were noted among the response groups when considering the duration of drug usage, method of drug measurement and what they drank the drug with, the daily dose of the drug, and the daily dose per weight of drug (Table 2).

When comparing the response groups based on the method of drug administration, a significant difference was found between those who utilized it with the milliliter sirup scale and those who used other spoons. The patients who had measured the drug in milliliters showed a better response rate. As the dosage of the drug and the dosage of the drug per weight increased, the response to the drug increased. After drug changes (lactulose, PEG) or dose adjustments, full response was obtained in 68 (73.1%) of 93 patients who did not respond or who had a partial response before.

DISCUSSION

Constipation is a common condition among children and is often challenging to manage (1,10). This study showed that choosing the first-line treatment prescribed to patients with functional constipation was appropriate according to the NASPGHAN and ESPGHAN recommendations. However, despite receiving the appropriate medication, approximately 80% of the patients did not respond to the appropriate drug. These findings suggest that both the dosage of the medication and its administration method play crucial roles for treating functional constipation. Specifically, increasing the drug dosage and dosage per weight, along with administering the drug using a milliliter scale, were associated with improved treatment responses. These observations highlight the significance of optimizing drug dosage and administration techniques for the management of functional constipation in children.

Table 1. Baseline characteristics of patients

Characteristics		Number of patients (%)
Gender	Girl	56 (51.9)
	Boy	52 (48.1)
Duration of symptoms	1-3 months	13 (12)
	3-6 months	31 (28.7)
	6-12 months	25 (23.1)
	>12 months	39 (36.1)
Used drug name	Lactulose	94 (87)
	Mineral oil	11 (10.2)
	Rectal laxatives	2 (1.9)
	Magnesium hydroxide	1 (0.9)
Disimpaction treatment	Not given	86 (79.6)
	Given	22 (20.3)
The method of measurement and administration of the drug	Tea spoon	22 (20.3)
	Dessert spoon	25 (23.1)
	Regular spoon	37 (34.3)
	Syrup scale milliliter	21 (19.4)
Duration of drug use	<1 month	63 (58.3)
	1 to 2 months	42 (38.9)
	>2 months	3 (2.8)
Respond to the drug	No response	68 (62.9)
	Partial response	25 (23.1)
	Full response	15 (13.8)

In this study, the vast majority of patients who visited pediatric gastroenterology were diagnosed with functional constipation according to the Rome IV criteria. Guidelines recommend PEG as the first-line maintenance treatment, with lactulose being an alternative if PEG is not available (4,11). In other studies, lactulose has been identified as one of the most powerful choices for the treatment of functional constipation (12,13). According to the Poddar et al. (14) study, lactulose and PEG are equally efficient in functional constipation. Similarly, Cao and Liu (15) showed that lactulose may successfully and safely treat chronic constipation in Chinese children. In this study, approximately 90% of the constipated patients received lactulose as the first-line treatment, indicating adherence to the recommended guidelines. However, despite the appropriate selection of first-line treatment, approximately 80% of the patients did not respond to the prescribed appropriate drug.

According to the guidelines of NASPGHAN and ESPGHAN, PEG with or without electrolytes is recommended as the first-line maintenance treatment for constipation, with a starting dose of 0.4 g/kg/day. The dose should be adjusted on the basis of the patient's clinical response. Alternatively, lactulose can be used as the first-line maintenance treatment, with a recommended dose of 1-2 g/kg, administered once or twice daily (4). The Canadian Pediatric Society, like NASPGHAN and ESPGHAN, advises lactulose at 1 mL/kg/day to 3 mL/kg/day in divided doses. Parents should be educated on adjusting the dosage based on the child's response to the stool softener. They are advised to gradually increase the dosage every 2 days until the child achieves one or two soft stools per day or to gradually decrease the dosage if the child experiences loose stools. It is important to inform parents that some leakage or soiling may occur at the beginning of therapy (5). A common reason for the lack of response to stool softening therapy is inadequate dosing (5). This study showed that choosing the first-line treatment prescribed to patients was appropriate. Even so, approximately 80% of the patients did not respond to the appropriate drug. This suggests that the underdose administered to patients is the first cause of the lack of response to correct stool softening therapy. Only 30% of the patients had used more than 1 mL/kg. The response to the drug increased as the dosage was increased in this trial. Response was obtained in 68 (73.1%) of 93 patients who did not respond or who had a partial response after drug (lactulose, PEG) or dose adjustments. This once again demonstrated the importance of dose regulation and appropriate drug changes.

Patients who received the medication measured using a milliliter scale had more accurate dosages than those who received it with a spoon. Approximately 75% of patients who received the medication in milliliters showed either partial or full response. These findings suggest that administering the medication using a milliliter dosage is more effective in eliciting a response than administering it with a spoon without a scale.

Table 2. Comparing baseline characteristics with response to drug

		No response (number or mean ± SD)	Partial response (number or mean ± SD)	Full response (number or mean ± SD)	p-value
Gender	Girl	35	9	8	0.40
	Boy	33	16	7	
Age		4.5±4.0	4.0±3.2	4.6±3.7	0.85
Body weight SDS		-0.10±1.07	0.04±0.99	-0.27±0.90	0.63
Height SDS		-0.14±0.94	-0.03±0.89	0.05±0.75	0.69
Duration of the symptoms	1-3 months	10	3	0	0.65
	3-6 months	17	8	6	
	6-12 months	15	7	3	
	>12 months	26	7	6	
Name of the drug	Lactulose	59	21	14	0.55
	Mineral oil	7	3	1	
	Magnesium hydroxide	0	1	0	
	Rectal laxatives	2	0	0	
Duration of drug use	<1 month	42	14	7	0.01
	1 to 2 months	26	11	5	
	>2 months	0	0	3	
The method of measurement and administration of the drug	Tea spoon	20	1	1	0.002
	Dessert spoon	18	6	1	
	Regular spoon	18	11	8	
	Syrup scale milliliter	10	6	5	
Daily dose of drug (mL)		11.2±7.7	18.1±10.6	24.6±11.8	0.001
Daily dose per weight (mL/kg)		0.66±0.43	1.07±0.58	1.4±0.61	0.001

SDS: Standard deviation scores.

According to the NASPGHAN and ESPGHAN guidelines, maintenance therapy for constipation should ideally last for a minimum of 2 months (4). However, in this study, approximately 90% of the patients had used the medication for less than 2 months. Insufficient duration of drug usage may be another reason for the lack of response observed in patients. Nonetheless, it is important to note that according to NASPGHAN and ESPGHAN, all constipation symptoms should be resolved for at least 1 month before discontinuing drugs (4). This underscores the significance of allowing an adequate period of time for drug usage before evaluating treatment response, highlighting insufficient duration of drug usage as the second most important factor contributing to patients' lack of response.

Study Limitations

The research's limitations were that it was a retrospective study with some patients.

CONCLUSION

In conclusion, constipation is a common and important problem in children. Constipation may be serious if not treated properly. No response is possible because the constipation drugs are not administered to the children in the proper manner and doses. To ensure a comprehensive response, the dosage of the drug and how they measure the drug must be disclosed to parents, and parents should be encouraged to alter the dose based on the response.

Ethics

Ethics Committee Approval: The methodology for this study was approved by the Human Research Ethics Committee of the University of Malatya Turgut Özal (approval number: 2021/34).

Informed Consent: Retrospective study.

Author Contributions

Concept: N.G.K., H.Ö., Design: N.G.K., Supervision: N.G.K., Resources: N.G.K., Materials: N.G.K., Data Collection or Processing: N.G.K., Analysis or Interpretation: H.Ö., Literature Search: N.G.K., Writing: N.G.K., Critical Review: N.G.K., H.Ö.

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