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Utility of Mosapride Citrate Combined With Osmotic Laxatives and Probiotics in the Initial Treatment of Pediatric Functional Constipation

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1. Abstract

Mosapride citrate (Mc) is one of 5-HT4-receptor agonists, and has a pharmacological action to promote physiological gastrointestinal peristalsis. This manuscript showed that Mc from the start of treatment was useful for functional constipation (FC) to satisfy Rome Ⅳ criteria in three infants including one male, mean age: 4 years old.

All patients revealed Bristol Stool Form Scale (BSFS) 1, and one case complicated paradoxical diarrhea. Two patients had lost the spontaneous defecation, and completely depended on glycerin enema.

Mc 0.29 mg/kg/day with magnesium oxide or lactulose added to probiotics was administered to the patients, who obtained the spontaneous defecation over once a day and BSFS 4 or 5 in the treatment period for five months.

Promotion of the spontaneous defecation by Mc from the start of treatment is useful for FC in infancy with lower or none defecation frequency.

2. Introduction

Functional constipation (FC) in children often requires medical treatment, including pharmacotherapy. Severe FC in children is associated with decreased or no spontaneous defecation (1, 2). Conventional laxatives (CLs) such as magnesium oxide (Mo), sodium picosulfate, lactulose, and carmellose sodium have long been used to treat FC. However, these drugs are often ineffective in patients with severe FC, requiring continual transanal treatments such as glycerin enema (GE) (3).

Mosapride citrate (Mc), a 5-HT4-receptor agonist, is a prokinetic agent that promotes physiological bowel peristalsis (4). One of similar agents of 5-HT4-receptor agonist, prucalopride, has already been used for chronic constipation in adult worldwide (5). Mc has traditionally been administered to pediatric patients with severe FC in Japan (6); however, no literature has been cited to support its use, and although its use is described in the Japanese guideline for FC in children, no citations supporting the recommendation were provided (7).

In 2019, we reported the first case-control study of Mc in the treatment of severe FC in children who did not respond to other CLs. Mc increased the therapeutic ratio from 0 to 55.6 % (3). However, the utility of Mc as an initial treatment for severe FC has not been examined. This study describes the outcomes of three children with severe FC who received Mc in the first-line setting.

3. Case Reports

3.1. All cases

Patients who met the Rome Ⅳ criteria for FC and who visited our center (Division of Pediatrics, Tohoku Medical and Pharmaceutical University) for 2 years starting in June 2016 were treated. We obtained informed consent from the caregivers of the patients regard-

ing the conduct and publication of this study. The Committee on Ethical Affairs in our center judged that Mc treatment did not carry any ethical problems (registry number: 2018-2-060).

Treatment was deemed effective when the patient did not meet the Rome IV FC criteria for more than 4 weeks (e.g., defecation frequency [DF] exceeded 3 days per week or stool consistency was consistently higher than type 3 on the Bristol Stool Form Scale [BSFS]) (8). De-escalation of laxatives including Mc was performed in a step-wise manner starting when efficacy was confirmed. Complete remission (CR) was defined as a laxative-free status for more than 4 weeks based on our previous clinical study and a previous investigation (8).

The characteristics of the patients prior to visiting our center and outcomes are presented in Table 1. The mean DF and BSFS score at the start of treatment were 0.3 day/week and 1, respectively. The daily dose of Mc was 0.3 mg/kg, which was administered in two equal doses under a basal treatment for FC together with probiotics and osmotic laxatives (6). The mean duration of treatment was 5.3 months, and the mean DF and BSFS score at the time of CR were 7 days/week and 4.3, respectively. All patients achieved spontaneous defecation at a rate of more than once a day, and they were released from the need for regular GE. No adverse events, including hepatic damage, occurred in any patients.

Table 1. Patient characteristics and outcomes.

Case	1	2	3
Sex	Male	Female	Female
Age at first visit (years)	4	4	5
DF at first visit (days/week)	0	1	0
BSFS score at first visit	1 and 6 with PD	1	1
Dependency on GE at the first visit	Regular	Frequent	Regular
Mosapride citrate (mg/kg/day)	0.29	0.28	0.29
Combined osmotic laxative (g/kg/day)	Lactulose (0.73)	Mo (0.056)	Lactulose (0.55)
Combined probiotics	Dual-agent	None	Single-agent
Duration of treatment (months)	5	4	5
DF at CR	7	7	7
BSFS score at CR	5	4	4
Release from dependency on GE	achievement	achievement	achievement

DF, defecation frequency; BSFS, Bristol Stool Form Scale; PD, paradoxical diarrhea; GE, glycerin enema; Mo, magnesium oxide; CR, complete remission.

3.2. Case 1

Case 1 was presented in Figure 1. A boy 4 years old had suffered severe FC as SF 0 and BSFS 1 with paradoxical diarrhea for two years. He was completely dependent on regular GE at home. Mo 0.29 mg/kg/day, lactulose 0.73 g/kg/day, and probiotics (C. butylricum, B. longum and B. infantis) were administered from the first visit. Mc was needed for only one month, and he was released from the basal treatment four months later. GE had never been performed until CR.

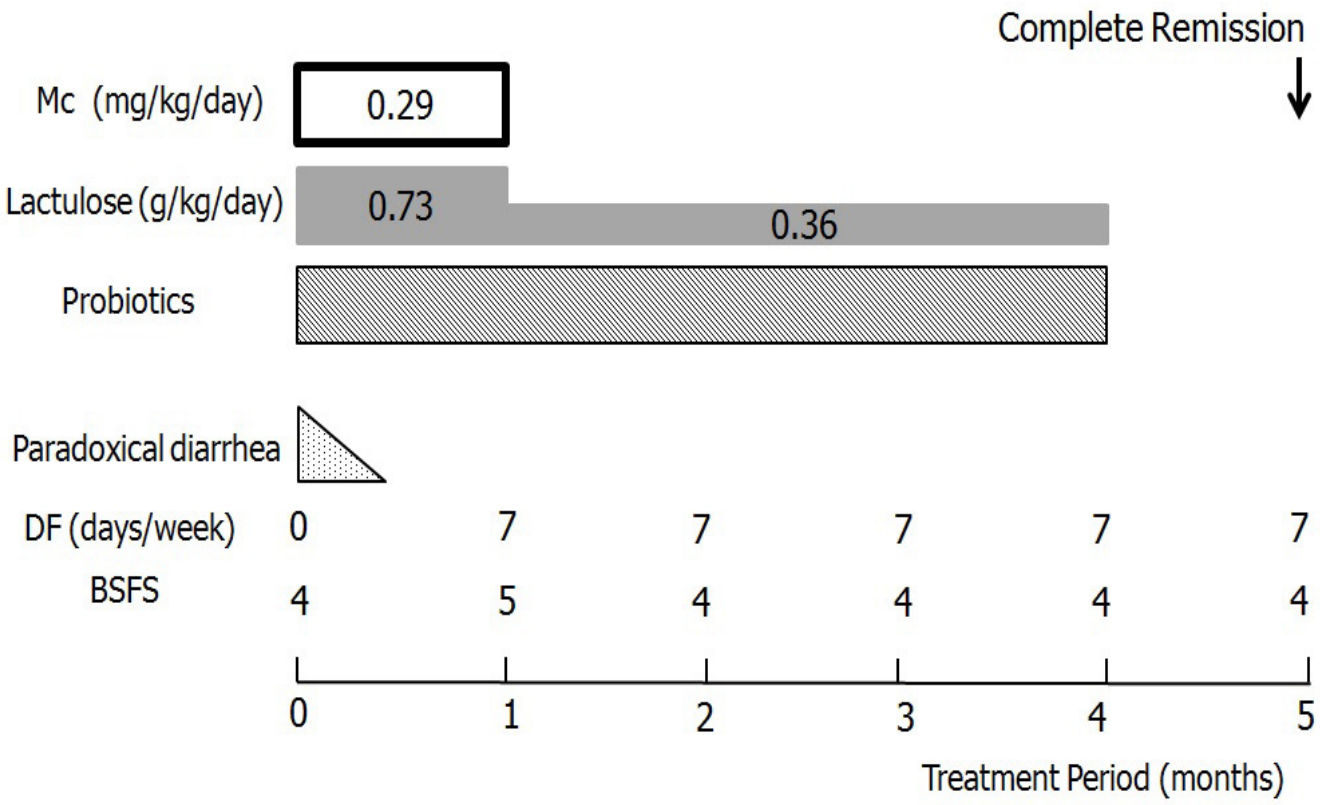

Figure 1: Clinical Course of Case 1

Abbreviations: DF, defecation frequency; BSFS, Bristol Stool Form Scale
Probiotics consists of *C. butylricum*, *B. longum* and *B. infantis*.

4. Discussion

Mc modulates gastrointestinal function by activating intramural cholinergic nerves (4). BSFS, but not DF, reflects the severity of mild FC (1). Prolonged stool hardness (low-grade BSFS [score of 1 or 2]) is the result of an impaired neuronal response for defecation caused by a disturbance in the colon wall. This vicious cycle leads to severe FC, for which DF reflects severity as accurately as BSFS (1, 2). Two of our patients exhibited a loss of spontaneous defecation, and the remaining patient defecated once per week. All patients required frequent GE with distress. These features suggested that our cases should have been diagnosed with comparatively severe FC. The outcome of the study consequently highlighted the utility of Mc for severe FC in the first-line setting with the aim of increasing DF.

One limitation of this study was that Mc was not compared with other treatments for FC. A comparison between Mc only and the basal treatment of probiotics and osmotic laxatives was not permitted ethically because the basal treatment should be ineffective for severe FC according to the previous reports (3, 6, 8, 9). However, the duration of Mc treatment did not exceed the treatment duration in previous studies (8, 9). Moreover, the period of Mc-treatment was definitely shorter than that of osmotic laxatives only (6). This result indicates that Mc should be used as an initial therapy to shorten the duration of treatment for severe FC

5. Conclusion

In conclusion, we recommend that Mc administration should be added to osmotic laxatives and probiotics as an initial treatment for severe FC in children with low or no DF.

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