www.mednet.gr/archives
ARCHIVES OF HELLENIC MEDICINE: ISSN 11-05-3992

ORIGINAL PAPER
ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

Racecadotril for treating acute diarrhea in children
A systematic review and meta-analysis

OBJECTIVE **To perform a review and meta-analysis concerning the efficacy of racecadotril administration for treating acute diarrhea in children.** METHOD **Published papers selected from PubMed, Embase, Cochrane, and Google Scholar were analyzed using a fixed or random-effect model.** RESULTS **A total of 11 relevant papers were included in the analysis, which showed that racecadotril administration, compared with control, was associated with reduced duration of diarrhea, with standardized mean difference (SMD): 0.98 (95% CI: 0.55–1.43, p<0.001) and stool volume, SMD: 4.93 (95% CI: 2.98–7.0, p=0.000). Conversely, dehydration (OR: 1.78 [95% CI: 0.70–4.53], p=0.226) and vomiting (OR: 1.44 [95% CI: 0.98–2.12], p=0.066) were not affected significantly by treatment with racecadotril.** CONCLUSIONS **Racecadotril administration appears to reduce diarrhea duration and stool volume in children with acute diarrhea.**

ARCHIVES OF HELLENIC MEDICINE 2021, 38(5):618–623
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2021, 38(5):618–623

F. Farahdina,[1]
F. Rizaliansyah,[2]
J.U. Aulya,[3]
J.K. Fajar[4]

[1]Faculty of Medicine, Universitas Brawijaya, Malang
[2]Faculty of Medicine, Universitas Airlangga, Surabaya
[3]Faculty of Medicine, Universitas Sumatera Utara, Medan
[4]Brawijaya Internal Medicine Research Center, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

Χορήγηση racecadotril για τη θεραπεία της οξείας διάρροιας σε παιδιά: Μια συστηματική ανασκόπηση και μετα-ανάλυση

Περίληψη στο τέλος του άρθρου

Key words

Acute diarrhea
Adjuvant therapy
Racecadotril

Submitted 27.10.2020
Accepted 26.12.2020

Acute diarrhea is one of the world's greatest health challenges for children. Reports reveal that 2.5 billion people suffer from diarrhea, and 1.5 million deaths are recorded annually from diarrhea.[1] Children are estimated to account for around 40% of this morbidity and 30% of mortality. The youngest children, particularly those before their second birthday, are the most vulnerable population.[2] The guidelines for the management of acute diarrhea in children have been well established and are updated periodically. The current guidelines recommend the use of oral rehydration solution for the treatment of acute diarrhea in children, but evidence revealed that oral rehydration solution did not provide a decrease in bowel movements, fluid loss, and duration of diarrhea.[3] On the other hand, the supplementary oral therapy was proven to reduce the period of dehydration and accelerate the return to normal conditions. Adjuvant treatments have recently been investigated for their effectiveness in conjunction with oral rehydration solutions, including antisecretory and anti-motility agents such as racecadotril.[3,4]

In the case of acute diarrhea, supplementation therapy is used to curtail fluid and electrolyte loss from the bowel.[5] Currently, supplementation therapy widely used in acute diarrhea includes probiotics, smectite, zinc, and racecadotril, the efficacy of which has been investigated in some studies. One study reported that racecadotril provided a superior effect compared with other supplementations in decreasing diarrheal duration and stool volume.[6] Previous studies to assess the impact of racecadotril for treating children with acute diarrhea reported inconsistent findings, which led us to attempt to clarify racecadotril efficacy in managing acute diarrhea in children, using a meta-analysis approach.

This study aimed to investigate the real effectiveness of racecadotril for treating children with acute diarrhea, based on the current literature.

MATERIAL AND METHOD

Study design

A review and meta-analysis were conducted from August to September 2020 to determine the effectiveness of racecadotril administration in managing acute diarrhea in children. Published papers from PubMed, Embase, Cochrane, and Google Scholar were collected, to calculate the pooled standardized mean difference (SMD) and 95% confidence interval (95% CI) using either a random or a fixed-effect model. The study applied the checklist from Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) to ensure that the protocols, including paper selection, data extraction, quality assessment, and statistical analysis, conformed to the PRISMA guidelines.[7]

Search strategy and data extraction

Several scientific databases (PubMed, Embase, Cochrane, and Google Scholar) were searched for papers assessing the effectiveness of racecadotril for the management of acute diarrhea in children, as of September 5, 2020, using the keywords "acute diarrhea" and "children" and "racecadotril". We did not limit the language of publication, but when articles with a publication language neither in English nor Indonesian were found, we consulted with the Language Center in our University. In our search strategy, if we found papers with the same study data, we only included the papers with a larger sample size. The following information of interest was extracted from each paper: (a) First author's name, (b) year of publication, (c) sample size of cases and controls, (d) age of participants, (e) ethnicity, (f) main findings, (g) duration of diarrhea of cases and controls, (h) frequency of dehydration in cases and controls, (i) stool volume of cases and controls, and (j) frequency of vomiting of cases and controls. To provide high-validity data, two independent authors performed data extraction to avoid human error (FF, JUA). If a discrepancy was found, a consensus and consultation was made with the senior researcher (JKF).

Eligibility criteria

The following inclusion criteria were used: (a) Assessment of the effectiveness of racecadotril administration in treating acute diarrhea in children; (b) sufficient data to calculate effect estimates.

The exclusion criteria were as follows: (a) unrelated titles and abstracts, (b) reviews and commentaries, (c) incomplete and or ungeneralized data, and (d) low-quality article.

Outcome measures

The determinant in our analysis was racecadotril administration, while the outcome measures were the duration of diarrhea, dehydration, stool volume, and vomiting, which were determined after initial covariates screening for inclusion in our meta-analysis.

Assessment of the methodological quality

The quality of each paper was assessed using the New Castle-Ottawa scale (NOS). The NOS score ranges from 0 to 9, based on three points: selection of patients (4 points), comparability of the groups (2 points), and ascertainment of exposure (3 points). A paper was interpreted as having low quality (for scores ≤4), moderate quality (for scores 5–6), or high quality (for scores ≥7). Papers with low quality were excluded from our study. Two independent investigators (FF and FR) performed the NOS assessment, and in the case of discrepancy, consultation with a senior researcher (JKF) was conducted.

Statistical analysis

The correlation and effect estimates of racecadotril administration on the duration of diarrhea, dehydration, stool volume, and vomiting among children with acute diarrhea were assessed using a Z test. Prior to identification of the significant factors, the data were evaluated for heterogeneity and potential publication bias. The heterogeneity among studies was assessed using the Q test, and when present ($p<0.10$), a model of random effect was adopted; otherwise, a fixed-effect model was applied. The test of Egger and funnel plot were used to determine reporting or publishing error ($p<0.05$ was considered as having publication bias). The correlation and effect estimates were then presented using a forest plot. The data were analyzed using Review Manager version 5.3 (Revman Cochrane, London, UK). To avoid methodological errors, two independent authors (FF and JKF) conducted the statistical analysis.

RESULTS

Eligible studies

The search strategy identified 211 potentially relevant papers, of which 191 papers were excluded because of irrelevant titles and abstracts. In total, 20 papers were included for review in full-text, of which 9 were excluded because of review (n=5), incomplete data (n=2), and low quality (n=2). Finally, 11 papers were included in our analysis. Figure 1 summarizes the paper selection pathway in our study, and table 1 outlines the baseline characteristics of the papers included in our meta-analysis.

Data synthesis

In data synthesis, we included 9 papers assessing the association between racecadotril administration and duration of diarrhea, 6 papers assessing the correlation between racecadotril administration and dehydration, 7 papers assessing the association between racecadotril administra-

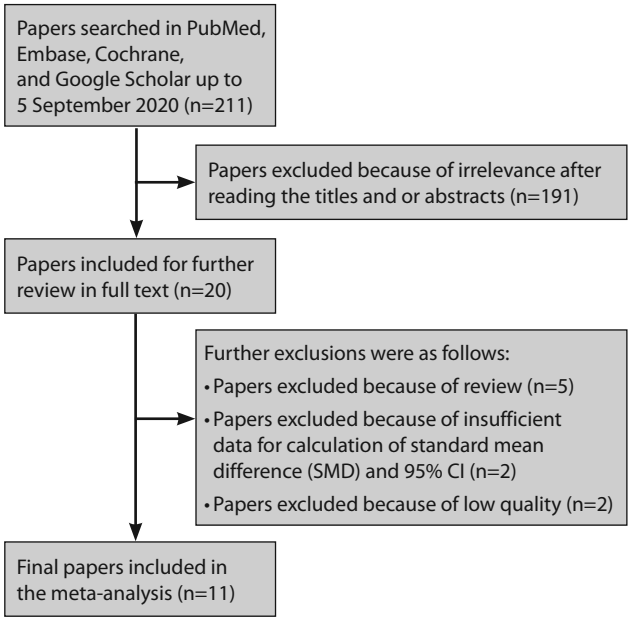

Figure 1. Flowchart of selection of papers for the meta-analysis study.

tion and stool volume, and 6 papers assessing the relation between racecadotril administration and vomiting. Our pooled analysis showed that racecadotril administration, compared with control, was associated with reduced duration of diarrhea (SMD: 0.98 [95% CI: 0.55–1.43], p=0.000) and reduced stool volume (SMD 4.93 [95% CI: 2.98–7.00], p=0.000). Dehydration (odds ratio [OR]: 1.78 [95% CI: 0.70–4.53], p=0.226) and vomiting (OR: 1.44 [95% CI: 0.98–2.12], p=0.066) showed no significant difference between treatment and control groups. The summary of the correlation and effect estimates between racecadotril administration and outcome measures is outlined in table 2.

Heterogeneity among studies

Our analysis found evidence for heterogeneity in the following covariates: duration of diarrhea, dehydration, and stool volume. For this reason, the random effect model was used to assess the association between racecadotril administration and the duration of diarrhea, dehydration, and stool volume. Conversely, as we found no evidence of heterogeneity in the vomiting covariate, the fixed-effect model was used to evaluate the correlation between racecadotril administration and vomiting. The evidence for heterogeneity among the studies in this meta-analysis is described in table 2.

Table 1. Baseline characteristics of articles included in the meta-analysis of effectiveness of racecadotril on acute diarrhea in children.

Author, year	Sample size		Case setting	Age, mean±SD (months)	Ethnicity	NOS	Main findings
	CON	RCC					
Alvarez et al, 2009	78	65	GEA	14.4±9.3	Caucasian	5	Racecadotril is associated with reducing the number of stools and shortening the course of disease
Cézard et al, 2001	82	85	Acute diarrhea	12.8±0.9	Caucasian	7	Racecadotril is associated with up to 50% reduction in stool output
Cojocaru et al, 2002	78	76	Acute diarrhea	12.1±6.7	Caucasian	6	Racecadotril provides efficacy in rehydration in the treatment of acute diarrhea
De-Tapobrata, 2016	338	64	Acute diarrhea	21.6±16.7	Asian	5	Racecadotril is likely to help in early recovery
Garcia et al, 2018	34	45	Acute diarrhea	17.5±8.9	Caucasian	5	Racecadotril is effective in reducing the number of diarrhea stools after 48 hours
Gharial et al, 2017	60	60	GEA	3–60	African	7	Racecadotril has no impact on the volume of stools at 48 hours, LOS, and duration of diarrhea
Kang et al, 2016	63	61	Acute diarrhea	13.2±8.9	Asian	7	Treatment with racecadotril does not reduce diarrheal duration, stool volume, or the requirement for fluid replacement
Michael et al, 2014	30	30	Acute diarrhea	42.0±31.6	Asian	7	Racecadotril is effective as adjuvant therapy for the treatment of acute diarrhea in children
Salazar-Lindo et al, 2000	67	68	Acute watery diarrhea	12.5±7.0	Caucasian	7	Racecadotril is an effective and safe treatment
Santos et al, 2009	66	71	GEA	11.8±7.8	Caucasian	7	The use of racecadotril does not improve the symptoms of diarrhea
Sreenivas et al, 2016	60	53	Acute watery diarrhea	27.7±20.8	Asian	6	Racecadotril is effective as an adjuvant therapy for diarrhea management among infants and children

NOS: Newcastle-Ottawa Scale, GEA: Gastroenteritis acute, CON: Control, RC: Racecadotril, SD: Standard deviation

Table 2. Meta-analysis of the association between racecadotril and outcome parameters among children with acute diarrhea.

Outcome parameters	NS	Model	Outcome measure		Std diff in mean/OR	95% CI	pE	pHet	p
			Control	Racecado tril					
Duration of diarrhea	9	Random	71.9±23.9	54.7±19.3	0.98	0.551–1.434	0.640	0.000	0.000
Dehydration	6	Random	16.52%	12.96%	1.78	0.700–4.527	0.966	0.000	0.226
Volume of stool	7	Random	290.0±61.3	165.6±47.9	4.93	2.975–7.001	2.647	0.000	0.000
Vomiting	6	Fixed	21.92%	17.10%	1.44	0.976–2.124	0.209	0.326	0.066

Data were presented in mean±SD

NS: Number of studies; OR: Odds ratio; CI: Confidence interval; pE: p Egger; pHet: p heterogeneity

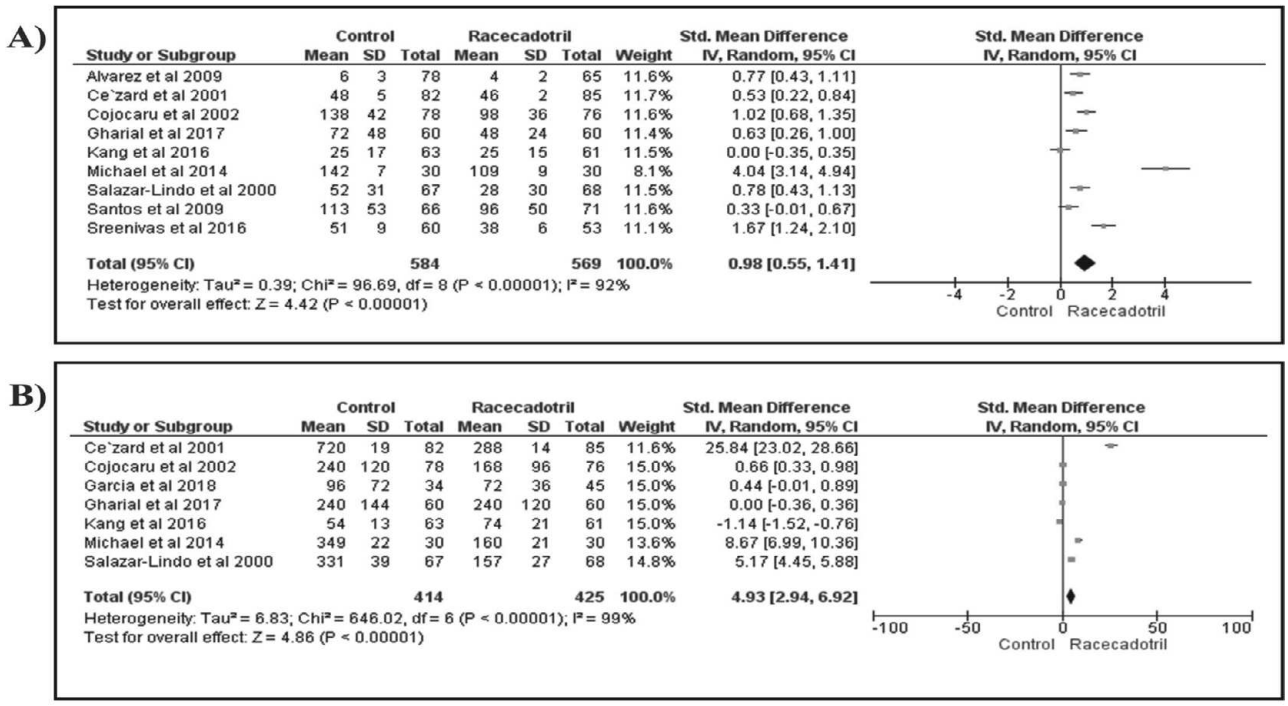

Figure 2. Forest plot of the association between racecadotril and outcome parameters among children with acute diarrhea. **(A)** Duration of diarrhea, and **(B)** volume of stool.

Potential publication bias

We used Egger's test to determine the potential publication bias among studies. Overall, no publication bias was detected, as described in table 2.

DISCUSSION

A total of 9 studies were analyzed to assess the correlation between racecadotril administration and the duration of diarrhea among children with acute diarrhea. In these, correlation was confirmed by 5 studies, but not by 4. Our pooled analysis revealed that shorter duration of diarrhea was observed in patients given racecadotril than in those not taking racecadotril, among children with acute diarrhea. This is consistent with previous studies that showed racecadotril administration to be correlated with a lower duration of diarrhea.[3,5,8] One study reported that racecadotril provided superior results compared to smectite and other probiotics.[6] Other studies, however, reported that racecadotril had no impact on the duration of diarrhea among children with acute diarrhea.[4,9] In other settings, a meta-analysis failed to clarify the correlation between racecadotril administration and the duration of diarrhea among adult patients with acute cholera.[10] This contradiction needs to be explored. Theoretically, the main pathological process in the devel-

opment of diarrhea is the excessive fluid accumulation discharged from the intestine, which cause a change of stool consistency.[11] The effect of racecadotril may be to restrict the pathological fluid loss and to prolong the transit time, providing sufficient opportunity for fluid reabsorption. Fluid secretion is considered to play the pivotal role, having the major responsibility for the development of diarrhea, particularly in the case of critically ill patients with diarrhea. In this condition, the risk related to dehydration may govern the level of severity. In this setting, racecadotril may play a crucial role in preventing fluid loss.[11,12] This explanation suggests that racecadotril might also have beneficial effects on secretory diarrhea. No beneficial effect has been documented for racecadotril when applied in the case of diarrhea related to rotavirus and cholera.[13] This might also be the reason for the contradictory reports regarding the impact of racecadotril in patients with acute diarrhea.

In addition to the duration of diarrhea, we assessed the impact of racecadotril administration on stool volume in children with acute diarrhea. We found 7 relevant papers, in 4 of which correlation was reported, while three papers showed no association. The pooled data indicated that racecadotril administration was indeed correlated with lower stool volume, compared with children with acute diarrhea not taking racecadotril, in line with previous meta-analyses. While our findings were consistent with previous studies in the setting of secretory diarrhea,[3–5,8] no correlation between racecadotril administration and stool volume was reported in the setting of cholera, either in children or adults.[10] Theoretically, racecadotril is a prodrug rapidly absorbed from the gut and hydrolyzed in the plasma to form the active metabolite thiorphan. These enkephalins are endogenous opioid neurotransmitters synthesized and secreted by enteric neurons acting on cholinergic neurons, enterochromaffin cells, and the epithelial secretory cells to coordinate their gastrointestinal function.[14] They may inhibit enkephalinase enzyme effects in the intestine, preventing the split of enkephalin and enhancing endogenous opioid levels in the intestinal mucosa. They act via delta receptors to increase luminal fluid absorption, and may therefore play a role in decreasing stool volume in children with acute diarrhea.[15] This possible mechanism might explain our findings that racecadotril was associated with decreased stool volume. Further studies are needed to investigate the exact mechanism of how racecadotril reduces stool volume.

The present study confirmed a decrease in stool volume and in the duration of diarrhea in children with acute diarrhea treated with racecadotril, compared to those without racecadotril treatment. Previous meta-analyses that had been performed to assess the effect of racecadotril in patients with diarrhea showed several crucial limitations. Several of the studies provided a small sample size,[3–5,9] while our present study had a larger sample size. One study involved multiple comparisons, and therefore, the high potency of bias might occur.[8] Another study assessed a variety of treatments, and the selection of articles was not clearly elucidated.[8] The present study addressed only the comparison between subjects with and without racecadotril administration, and all the procedures in the papers selected were well described, ensuring better association than previous studies. Our results emphasized that racecadotril could be beneficial as an adjuvant treatment for treating acute diarrhea in children, reducing stool volume and curtailing the duration. Therefore, in the near future, we expect that racecadotril might be considered as adjuvant treatment for acute diarrhea in children, but further studies are required to explore other considerations in the context of pharmacological, pharmacokinetic, and pharmacogenetic interaction.

Our current meta-analysis had some limitations. First, some essential factors that might govern the severity of acute diarrhea in children were not monitored and therefore not included in our analysis, including nutritional status, medication compliance, level of dehydration, congenital disorder and comorbid factors. Second, while we provide a larger sample size than previous meta-analyses, our cumulative sample was relatively small, and therefore, our results should be interpreted with care. Third, some papers included in our study had unequal proportions of sample populations, and this factor might cause heterogeneity, with the potential for bias.

In conclusion, our meta-analysis has identified that racecadotril administration provides efficacy in reducing diarrhea duration and stool volume in children with acute diarrhea. Dehydration and vomiting were not shown to be affected by racecadotril administration to children with acute diarrhea. Our study may help to clarify the effectiveness of racecadotril as adjuvant treatment in children with acute diarrhea.

ACKNOWLEDGMENTS

We thank Medsclub Research Club and DSKF Publishing Campus for supporting this study.

ΠΕΡΙΛΗΨΗ

Χορήγηση racecadotril για τη θεραπεία της οξείας διάρροιας σε παιδιά: Μια συστηματική ανασκόπηση και μετα-ανάλυση

F. FARAHDINA,[1] F. RIZALIANSYAH,[2] J.U. AULYA,[3] J.K. FAJAR[4]

[1]Faculty of Medicine, Universitas Brawijaya, Malang, [2]Faculty of Medicine, Universitas Airlangga, Surabaya, [3]Faculty of Medicine, Universitas Sumatera Utara, Medan, [4]Brawijaya Internal Medicine Research Center, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Ινδονησία

Αρχεία Ελληνικής Ιατρικής 2021, 38(5):618–623

ΣΚΟΠΟΣ Ανασκόπηση και μετα-ανάλυση σχετικά με την αποτελεσματικότητα της χορήγησης racecadotril για τη θεραπεία της οξείας διάρροιας σε παιδιά**. ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Άρθρα από PubMed, Embase, Cochrane και Google Scholar αναλύθηκαν χρησιμοποιώντας ένα μοντέλο σταθερού ή τυχαίου αποτελέσματος. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Έντεκα σχετικές εργασίες συμπεριλήφθηκαν στην ανάλυση. Από τη συγκεντρωτική ανάλυση διαπιστώθηκε ότι η χορήγηση racecadotril, σε σύγκριση με την ομάδα ελέγχου, συνοδευόταν από μειωμένη διάρκεια διάρροιας (μέση διαφορά: 0,98 [95% διάστημα εμπιστοσύνης [ΔΕ]: 0,55–1,43], p<0,001) και όγκου κοπράνων (μέση διαφορά: 4,93 [95% ΔΕ: 2,98–7,00], p=0,000). Ωστόσο, η αφυδάτωση (σχετικός λόγος [ΣΛ]: 1,78 [95% CI: 0,70–4,53], p=0,226) και ο έμετος (ΣΛ: 1,44 [95% CI: 0,98–2,12], p=0,066) δεν επηρεάστηκαν με τη χορήγηση racecadotril. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η χορήγηση του racecadotril φάνηκε να μειώνει τη διάρκεια της διάρροιας και τον όγκο των κοπράνων σε παιδιά με οξεία διάρροια.

Λέξεις ευρετηρίου: Ανοσοενισχυτική θεραπεία, Οξεία διάρροια, Racecadotril

References

1. SHARIF N, NOBEL NU, SAKIB N, LIZA SM, KHAN ST, BILLAH B ET AL. Molecular and epidemiologic analysis of diarrheal pathogens in children with acute gastroenteritis in Bangladesh during 2014–2019. *Pediatr Infect Dis J* 2020, 39:580–585
2. FENTA A, ALEMU K, ANGAW DA. Prevalence and associated factors of acute diarrhea among under-five children in Kamashi district, western Ethiopia: A community-based study. *BMC Pediatr* 2020, 20:236–242
3. HAO R, DE VERA M, RESURRECION E. Racecadoctril in the treatment of acute diarrhea in children: A meta-analysis. *PIDSP Journal* 2010, 11:19–32
4. LEHERT P, CHÉRON G, CALATAYUD G, CÉZARD JP, CASTRELLÓN PG, GARCIA JM ET AL. Racecadotril for childhood gastroenteritis: An individual patient data meta-analysis. *Dig Liver Dis* 2011, 43:707–713
5. GORDON M, AKOBENG A. Racecadotril for acute diarrhoea in children: Systematic review and meta-analyses. *Arch Dis Child* 2016, 101:234–240
6. GUTIÉRREZ-CASTRELLÓN P, ORTÍZ-HERNÁNDEZ AA, LLAMOSAS-GALLARDO B, ACOSTA-BASTIDAS MA, JIMÉNEZ-GUTIÉRREZ C, DIAZ-GARCÍA L ET AL. Efficacy of racecadotril vs smectite, probiotics or zinc as an integral part of treatment of acute diarrhea in children under five years: A meta-analysis of multiple treatments. *Gac Med Mex* 2015, 151:329–337
7. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG; PRISMA GROUP. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med* 2009, 151:264–269
8. EBERLIN M, CHEN M, MUECK T, DÄBRITZ J. Racecadotril in the treatment of acute diarrhea in children: A systematic, comprehensive review and meta-analysis of randomized controlled trials. *BMC Pediatr* 2018, 18:124
9. LIANG Y, ZHANG L, ZENG L, GORDON M, WEN J. Racecadotril for acute diarrhoea in children. *Cochrane Database Syst Rev* 2019, 12:CD009359
10. ALAM HN, ASHRAF H, KHAN WA, KARIM MM, FUCHS GJ. Efficacy and tolerability of racecadotril in the treatment of cholera in adults: A double-blind, randomised, controlled clinical trial. *Gut* 2003, 52:1419–1423
11. EBERLIN M, MÜCK T, MICHEL MC. A comprehensive review of the pharmacodynamics, pharmacokinetics, and clinical effects of the neutral endopeptidase inhibitor racecadotril. *Front Pharmacol* 2012, 3:93
12. SREENIVAS SK, LAKSHMI M, PAVITRA NA. Efficacy and safety of racecadotril as an adjunct to oral rehydration therapy for acute watery diarrhea in children. *Indian Journal of Child Health* 2017, 4:68–71
13. KANG G, THUPPAL VS, SRINIVASAN R, SARKAR R, SUBASHINI B, VENUGOPAL S ET AL. Racecadotril in the management of rotavirus and non-rotavirus diarrhea in under-five children: Two randomized, double-blind, placebo-controlled trials. *Indian Pediatr* 2016, 53:595–600
14. FAURE C. Role of antidiarrhoeal drugs as adjunctive therapies for acute diarrhoea in children. *Int J Pediatr* 2013, 2013:612403
15. SINGH, M, YADAV A, NANDA S. Racecadotril in acute watery diarrhea in children. *J Evol Med Dent Sci* 2016, 5:301–305

Corresponding author:

F. Farahdina, Faculty of Medicine, Universitas Brawijaya, Malang, 65145 Indonesia
e-mail: farahdina95@gmail.com