Open Access

Original Article

Efficacy of Oral Racecadotril in Children with Acute Watery Diarrhea

Rida Tahir, Muhammad Tariq Nadeem, Hira Javed*, Maryam Ijaz

Department of Paediatrics, Combined Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan, *Department of Paediatrics, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

***Objective*:** To determine the efficacy of Racecadotril in treating acute watery diarrhea among children under 5 years of age attending Combined Military Hospital, Rawalpindi Pakistan.

***Study Design*:** Quasi-experimental study.

***Place and Duration of Study*:** Department of Pediatrics, Combined Military Hospital, Rawalpindi Pakistan, from Jul to Dec 2022.

***Methodology*:** All patients aged 6 months to 5 years with acute watery diarrhea were consecutively enrolled. All children were randomly divided into a control group (Oral Rehydration Supplement) and a study group (Racecadotril 1.5 mg/kg every eight hours). Racecadotril administration lasted until diarrhea symptoms improved or five days after the start of the treatment. From day 1 to day 5, the quantity and consistency of stool were noted. On day 5, clinical effectiveness was indicated by three stools or fewer per day.

***Results*:** Of 90 children, the overall efficacy was 61(67.8%). A significant association of efficacy was observed with the treatment group (p <0.001), degree of dehydration (p <0.001), and mother's educational status (p 0.015). The efficacy was 4.82 times higher among children who received Racecadotril (aOR: 4.82, 95% CI 1.48-15.76), 3.21 times higher among intermediate or higher mothers' education (aOR: 3.23, 95% CI 1.32-7.91), 2.84 times higher among below matric mothers' education (aOR: 2.84, 95% CI 1.24-6.48) while 94% lower among children with severe dehydration (aOR: 0.06, 95% CI 0.01-0.27).

***Conclusion*:** Racecadotril's efficacy was higher in treating children with acute watery diarrhea than Oral Rehydration Supplement alone in children under 5 years old.

Keywords: Acute Watery Diarrhea, Children, Efficacy, Racecadotril.

How to Cite This Article: *Tahir R, Nadeem MT, Javed H, Ijaz M. Efficacy of Oral Racecadotril in Children with Acute Watery Diarrhea. Pak Armed Forces Med J 2024; 74(6): 1578-1583. DOI: https://doi.org/10.51253/pafmj.v74i6.10039*

INTRODUCTION

Children under the age of five years frequently die from diarrhea, particularly in low-income nations.[1,2] Diarrhea in children frequently results in frequent, watery bowel movements, which may result in an excessive loss of fluid and electrolytes. Dehydration brought on by diarrhea should be prevented and treated with fluid replacement.[3-5]

Racecadotril is an anti-secretory medication that hydrolyses the active metabolite thiorphan to produce its anti-diarrheal properties.[6] It lowers the hyper-secretion of water and electrolytes into the intestinal lumen without affecting motility by preventing the breakdown of endogenous enkephalins.[6,7]

Various studies have utilised Racecadotril as an adjuvant to oral rehydration treatment for acute diarrhea in children.[8-10] Racecadotril reportedly has the potential to lower the risk of rehydration. We are unsure if it affects the frequency of bowel movements or the length of the diarrhea. Due to its ability to decrease water absorption and electrolytes into the digestive system, Racecadotril has been used in addition to fluid replacement to treat diarrhea in children. The medication is intended to lessen the likelihood of dehydration failure while also easing diarrheal symptoms. Nevertheless, there are not a few studies that report on Pakistan's population. Therefore, this study aimed to assess the effectiveness of Racecadotril in treating acute watery diarrhea in children under five years.

Correspondence: Dr Rida Tahir, Department of Paediatrics, Combined Military Hospital, Rawalpindi Pakistan

Received:07 Mar 2023; revision received: 11 May 2023; accepted: 12 May 2023

METHODOLOGY

The quasi-experimental study was conducted at the Department of Paediatrics, Combined Military Hospital, Rawalpindi Pakistan, from Jul 2022 to Dec 2022. Ethical approval was obtained from the institute prior to the commencement of the study (IERB #: 329). Epi Info sample size calculator was used to estimate sample size, taking 95% confidence intervals (CI), power 80%, percentage outcome in the treatment group as reported in a previous study 22.4%, and percentage outcome in the control group as reported in a previous study 52.8%.[11]

Inclusion Criteria: All patients aged 6 months to 5 years with acute watery diarrhea were consecutively enrolled.

Exclusion Criteria: Children who were severely underweight, severely dehydrated, had chronic diarrhea, had received antibiotic treatment in the five days prior, had a known chronic, uncontrolled intestinal condition like celiac disease or pancreatic insufficiency, had co-morbid conditions like cardiac, respiratory, or renal disease, or had dysentery were all excluded.

More than three loose stools daily were considered a sign of acute watery diarrhea. Based on clinical symptoms, dehydration was divided into three categories: nil, some, and severe. According to WHO recommendations, the clinical examination was used to determine whether a patient had some dehydration or no dehydration (two or more of the following indications, including restlessness, irritability, sunken eyes, drinking eagerly, and skin pinch returning slowly).

All children who met the participation requirements were randomly split into two roups. The sample size was 90, i.e., 45 in each group. After explaining the study's pros and cons, signed informed consent was obtained from the parents/guardians of all study participants. The control group received only an oral rehydration supplement (ORS), while the Racecadotril group received 1.5 mg/kg of Racecadotril eight hours after commencement of the treatment (Figure). Racecadotril was administered for five days following the commencement of the treatment or until the symptoms of diarrhea improved. All children received the prescribed drugs following the WHO recommendations.

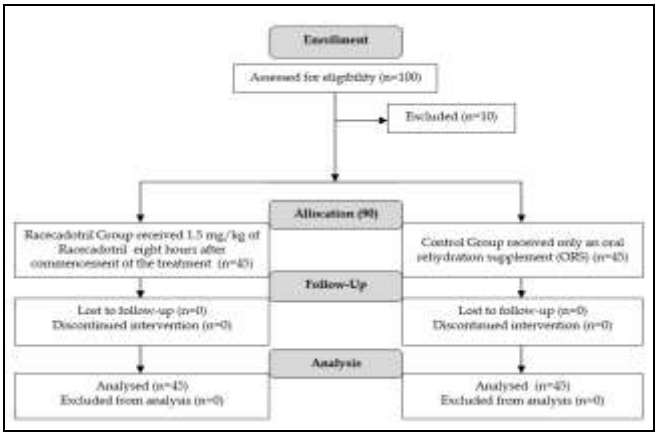

Figure: Patient Flow Diagram (n=90)

The age, gender, weight, maternal age, level of schooling, and degree of dehydration of the children, among other characteristics that may affect the result, were noted. The main measures were the total duration of diarrhea, mean quantity of stools per day, consistency of faeces, and length of stay in the hospital. The Bristol Criteria were used to define stools' consistency. Those with types 5-7 Bristol Criteria were classified as having diarrhea. From day 1 to day 5, the quantity and consistency of stools was noted. On day 5, clinical effectiveness was indicated by three stools or fewer per day.

Statistical Package for Social Sciences (SPSS) version 24.0 was employed for statistical analysis. While qualitative factors were reported as frequencies and percentages, quantitative data were expressed as Mean±SD. The Repeated Measure ANOVA test was used to investigate the mean difference between the daily quantity and consistency of stools. At the same time, the independent t-test was used to investigate the mean difference in the amount and consistency of stools each day in the two groups. In order to investigate the relationship between efficacy and baseline and clinical features, the Chi-square/Fisher-Exact test was used. The *p*-values lower than 0.05 were regarded as significant.

Additionally, binary logistic regression was used. All variables with univariate *p*-values of 0.25 were considered in multivariable logistic regression. The *p*-values, odds ratios, and 95% confidence intervals (CI) were presented.

RESULTS

Of 90 children with acute watery diarrhea, the overall mean age of the patients was 3.84±1.11 years. Most children were males, i.e., 61(67.8%). The mean weight of the children was 14.49±4.74 kg. The mean duration of diarrhea was 4.22±0.75 days, whereas the duration of hospital stay was 3.13±0.77 days.

The mean age of the mothers was 29.92±10.05 years. Most mothers were ≤30 years of age, i.e., 63(70%). There were 55(61.1%) children with intermediate or higher mother's educational status and 35(38.9%) below matric educational status. Most of the children, 151(59.9%), presented with some dehydration, followed by no dehydration in 72(28.6%) and severe dehydration in 29(11.5%).

For a time, there was a discernible decrease in the frequency of stools (*p*: 0.001). The mean number of stools on the first day was 5.44±0.91, which decreases

to 4.68±0.64 on day 2, 3.95±0.52 on day 3,2.97 ±0.94 on day 4, and 2.52±1.06 on day 5. Similarly, a substantial change in stools' consistency over time was also noted (*p*: 0.001). The mean consistency of stools on the first day was 6.62±0.49, which decreases to 6.04±0.65 on day 2, 6.04±0.75 on day 3, 5.84±1.06 on day 4, and 5.37±1.28 on day 5.

Insignificantly higher mean age was observed in the control than that of the treatment group, i.e., 4.01±1.17 years and 3.69±1.04 years, respectively (*p*: 0.187). At the same time, the mean weight was insignificantly higher in the treatment group than in the control roup, i.e., 14.68±4.77 vs 14.30±4.74, respectively (*p*: 0.703). The mother's age was also insignificantly higher in the control than the treatment group, i.e., 31.09±13.63 years and 28.75±4.01 years, respectively (*p*: 0.273). However, a significant mean difference of number of stools was observed on day 3 (*p*: 0.014), day 4 (*p*: 0.012), and day 5 (*p*: 0.003). Similarly, a non-significant difference in the mean consistency of stools was observed between groups on day 1 (*p*: 0.196) and day 2 (*p*: 0.106). However, a significant mean difference in the consistency of stools was observed on day 3 (*p*: 0.001), day 4 (*p*: 0.009), and day 5 (*p*: 0.040). (Table-I)

Table-I: Mean difference of Frequency and Consistency of Stools in Study Groups (n=90)

	Study Groups	Mean±SD	*p*-value	95% CI
Number of stools (Day 1)	Racecadotril	5.60±0.81	0.102	-0.06 to 0.68
	Control	5.28±0.97		
Number of stools (Day 2)	Racecadotril	4.78±0.56	0.194	-0.09 to 0.45
	Control	4.60±0.72		
Number of stools (Day 3)	Racecadotril	3.82±0.61	0.014	-0.48 to -0.05
	Control	4.08±0.36		
Number of stools (Day 4)	Racecadotril	2.73±0.88	0.012	-0.86 to -0.11
	Control	3.22±0.92		
Number of stools (Day 5)	Racecadotril	2.20±0.99	0.003	-1.07 to -0.22
	Control	2.84±1.04		
Consistency of stools (Day 1)	Racecadotril	6.68±0.47	0.196	-0.07 to 0.34
	Control	6.55±0.50		
Consistency of stools (Day 2)	Racecadotril	5.93±0.68	0.106	-0.49 to 0.05
	Control	6.15±0.60		
Consistency of stools (Day 3)	Racecadotril	5.78±0.70	0.001	-0.83 to -0.23
	Control	6.31±0.70		
Consistency of stools (Day 4)	Racecadotril	5.55±0.94	0.009	-1.01 to -0.15
	Control	6.13±1.09		
Consistency of stools (Day 5)	Racecadotril	5.08±1.43	0.040	-1.08 to -0.03
	Control	5.64±1.07		

The overall efficacy was found to be 61(67.8%). A significant association of efficacy was observed with the treatment Group (*p*: <0.001), degree of dehydration (*p*: <0.001), and mother's educational status (*p*: 0.015). (Table-II)

Table-II: Comparison of efficacy with demographics and clinical characteristics (n=90)

Groups	Efficacy		*p*-value
	Yes	No	
Group			
Racecadotril	39(86.7)	6(13.3)	<0.001
Control	22(48.9)	23(51.1)	
Degree of Dehydration			
No Dehydration	41(80.4)	10(19.6)	<0.001
Some dehydration	17(77.3)	5(22.7)	
Moderate/severe dehydration	3(17.6)	14(82.4)	
Age, years			
>3 years	4(40.0)	6(60.0)	0.076
≤3 years	57(71.3)	23(28.7)	
Gender			
Male	45(73.8)	16(26.2)	0.078
Female	16(55.2)	13(44.8)	
Weight			
≤15 kg	23(76.7)	7(23.3)	0.202
>15 kg	38(63.3)	22(36.7)	
Maternal age			
≤30 years	42(66.7)	21(33.3)	0.730
>30 years	19(70.4)	8(29.6)	
Duration of Diarrhea			
≤4 days	37(69.8)	16(30.2)	0.621
>4 days	24(64.9)	13(35.1)	
Mother's Educational Status			
Less than matric	32(58.2)	23(41.8)	0.015
More than equal to intermediate	29(82.9)	6(17.1)	

The findings of the univariate regression analysis revealed that the efficacy was 6.79 times higher among children in the probiotic roup than those in the control group (OR: 6.79, 95% CI 2.40-19.21). The efficacy was 3.47 times higher among children with mothers having more than equal to intermediate education than those with less than equal to matric education (OR: 3.47, 95% CI 1.24-9.72). The efficacy was 95% lower among children with severe dehydration than those without mild/moderate-severe dehydration (OR: .0.05, 95% CI 0.01-0.22). Findings of the multivariable analysis revealed that after adjustment for other covariates, the efficacy was 4.82 times higher among children in the treatment group compared to those in the control group (aOR: 4.82, 95% CI 1.48-15.76). The efficacy was 3.21 times higher among children with mothers having more than equal to intermediate education than those with less than equal to matric education (aOR: 3.23, 95% CI 1.32-7.91). The efficacy was 2.84 times higher among children with less than equal to matric

mother's education than those with more than equal to matric mother's education (aOR: 2.84, 95% CI 1.24-6.48). The efficacy was 94% lower among children with severe dehydration than those without mild/moderate-severe dehydration (aOR: 0.06, 95% CI 0.01-0.27). (Table-III)

0.001) and male gender (*p*: <0.001). While in patients with moderate/severe dehydration, efficacy was significantly associated with the treatment group (*p*: 0.006), more than 3 years of age (*p*: 0.006), and male gender (*p*: 0.006), and more than equal to intermediate education mother's education (*p*: 0.015). (Table-IV)

Table-III: Regression Analysis for Factors associated with Efficacy (n=90)

Groups	Study Parameter		Efficacy			
			OR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Group						
Racecadotril	39(86.7)	6(13.3)	6.79(2.40-19.21)	<0.001	4.82(1.48-15.76)	0.009
Control	22(48.9)	23(51.1)	Ref		Ref	
Mother's educational status						
More than equal to intermediate	29(82.9)	6(17.1)	3.47(1.24-9.72)	0.018	3.21(0.90-11.44)	0.072
Less than equal to matric	32(58.2)	23(41.8)	Ref		Ref	
Severe dehydration						
Yes	3(17.6)	14(82.4)	0.05(0.01-0.22)	<0.001	0.056(0.01-0.27)	<0.001
No	58(79.5)	15(20.5)	Ref		Ref	

Table-IV: Comparison of Efficacy with Demographics and Clinical Characteristics stratified on the basis of Dehydration Status (n=90)

Groups	No Dehydration (n=51)			Some Dehydration (n=22)			Moderate/Severe Dehydration (n=17)		
	Efficacy			Efficacy			Efficacy		
	Yes (n=41)	No (n=10)	*p*-value	Yes (n=17)	No (n=5)	*p*-value	Yes (n=3)	No (n=14)	*p*-value
Group									
Racecadotril	19(95.0)	1(50.0)	0.035	17(81.0)	4(19.0)	0.227	3(75.0)	1(25.0)	0.006
Control	22(71.0)	9(29.0)		0(0)	1(100)		0(0)	13(100)	
Age, years									
>3 years	1(50.0)	1(50.0)	0.357	0(0)	4(100)	0.001	3(75.0)	1(25.0)	0.006
≤3 years	40(81.6)	9(18.4)		17(94.4)	1(5.6)		0(0)	13(100)	
Gender									
Male	28(93.3)	2(6.7)	0.010	17(94.4)	1(5.6)	<0.001	3(75.0)	1(25.0)	0.006
Female	13(61.9)	8(38.1)		0(0)	4(100)		0(0)	13(100)	
Weight									
≤15 kg	23(76.7)	7(23.3)	0.495	-	-	-	-	-	-
>15 kg	18(85.7)	3(14.3)		17(77.3)	5(22.7)		3(17.6)	14(82.4)	
Maternal age									
≤30 years	28(80.0)	7(20.0)	>0.999	12(75.0)	4(25.0)	>0.999	2(16.7)	10(83.3)	0.999
>30 years	13(81.3)	3(18.8)		5(83.3)	1(16.7)		1(20.0)	4(80.0)	
Duration of diarrhea									
≤4 days	23(79.3)	6(20.7)	>0.999	11(78.6)	3(21.4)	>0.999	3(30.0)	7(70.0)	0.228
>4 days	18(81.8)	4(18.2)		6(75.0)	2(25.0)		0(0)	7(100)	
Mother's educational status									
Less than matric	21(77.8)	6(22.2)	0.731	11(68.8)	5(31.3)	0.266	0(0)	12(100)	0.015
More than equal to intermediate	20(83.3)	4(16.7)		6(100)	0(0)		3(60.0)	2(40.0)	

In patients with no dehydration, efficacy was significantly highly associated with the treatment group (*p*: 0.035) and male gender (*p*: 0.010). In patients with some dehydration, efficacy was significantly associated with more than years of age of children (*p*:

DISCUSSION

According to the current study findings, Racecadotril's efficacy in treating acute watery diarrhea was 4.82 times higher compared to the children treated with ORS alone. The similarities

between the current study findings and previous national and international studies further emphasise the positive role of Racecadotril in children with acute watery diarrhea. Previously published systematic reviews and meta-analyses have stated Racecadotril is superior to comparator treatments in both outpatients and hospitalised patients.[12,13] Racecadotril is said to lessen fluid loss, which might increase the efficacy of rehydration and relieve diarrheal symptoms by reducing the frequency of stools and shortening the length of the diarrhea.[6] Racecadotril, compared to a placebo, can decrease the length of diarrhea and lower the number of stools, according to a meta-analysis of randomised Controlled trials in adults.[14] Published trials indicate that Racecadotril is also well tolerated with side effects that are comparable to those who received ORS therapy alone.[15,16] According to another study, Racecadotril is a more cost-effective adjuvant medication for treating children's diarrhea than oral rehydration therapy alone.[17]

The current study also reported that the efficacy was 3.21 times higher among children with mothers having more than equal to intermediate education than those with less than equal to matric education. The efficacy was 2.84 times higher among children with less than equal to matric mother's education than those with more than equal to matric mother's education. The efficacy was 94% lower among children with severe dehydration than those without mild/moderate-severe dehydration. Published studies reported that one of the primary goals of utilising Racecadotril, according to the literature, is to improve the restoration of water-electrolyte imbalances.[18,19]

In several systematic reviews, Racecadotril has been evaluated for its effectiveness in treating children with acute diarrhea. However, the use of this medication is still debatable because of recently published trials that have shown conflicting results about its effectiveness.[6,20,21] In the current study, a considerable decline in the frequency and consistency of stools was observed in both groups. One recent meta-analysis has also reported Racecadotril as safe in acute diarrhea conditions among children under 5 years of age but has not recommended its use in routine practice.[6]

LIMITATION OF STUDY

There are certain limitations in the current study. First, the current study included only some important confounding variables such as hygiene practices, previous history of diarrhea, laboratory characteristics, and maternal and household characteristics. Secondly, a longer follow-up duration could not be ascertained due to time limitations and financial constraints.

CONCLUSION

The efficacy of Racecadotril was found to be higher in treating children with acute watery diarrhea than ORS alone, especially in children under 5 years old. However, it is important to note that Racecadotril should not replace ORS as the first-line treatment for acute diarrhea; instead, it can be used as adjunctive therapy to enhance its effectiveness.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

RT & MTN: Conception, study design, drafting the manuscript, approval of the final version to be published.

HJ & MI: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Liu L, Villavicencio F, Yeung D, Perin J, Lopez G, Strong KL, et al. National, regional, and global causes of mortality in 5-19-year-olds from 2000 to 2019: a systematic analysis. Lancet Glob Health 2022; 10(3): e337-e347. https://doi.org/10.1016/S2214-109X(21)00566-0
2. GBD 2016 Diarrheal Disease Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis 2018; 18(11): 1211-1228. https://doi.org/10.1016/S1473-3099(18)30362-1
3. Florez ID, Niño-Serna LF, Beltrán-Arroyave CP. Acute Infectious Diarrhea and Gastroenteritis in Children. Curr Infect Dis Rep 2020; 22(2): 4. https://doi.org/10.1007/s11908-020-0713-6
4. Anigilaje EA. Management of Diarrheal Dehydration in Childhood: A Review for Clinicians in Developing Countries. Front Pediatr 2018; 6: 28. https://doi.org/10.3389/fped.2018.00028
5. Santillanes G, Rose E. Evaluation and Management of Dehydration in Children. Emerg Med Clin North Am 2018; 36(2): 259-273. https://doi.org/10.1016/j.emc.2017.12.004
6. Liang Y, Zhang L, Zeng L, Gordon M, Wen J. Racecadotril for acute diarrhea in children. Cochrane Database Syst Rev 2019; 12(12): CD009359. https://doi.org/10.1002/14651858.CD009359.pub2
7. Sultana A, Bishwas P, Islam S, Ghosh UK, Iman K, Afroze S, et al. Role of Racecadotril in Children with Acute Diarrhea. Dhaka Shishu Hosp J. 2020; 36(1): 8-13. https://doi.org/10.3329/dshj.v36i1.52617
8. Pienar C, Benninga MA, Broekaert IJ, Dolinsek J, Mas E, Miele E, et al. Drugs in Focus: The Use of Racecadotril in Paediatric Gastrointestinal Disease. J Pediatr Gastroenterol Nutr 2020; 70(2): 162-164. https://doi.org/10.1097/MPG.0000000000002574

9. Rautenberg TA, Downes M, Kiet PHT, Ashoush N, Dennis AR, Kim K. Evaluating the cost utility of racecadotril in addition to oral rehydration solution versus oral rehydration solution alone for children with acute watery diarrhea in four low middle-income countries: Egypt, Morocco, Philippines and Vietnam. J Med Econ 2022; 25(1): 274-281. https://doi.org/10.1080/13696998.2022.2037918
10. Florez ID, Veroniki AA, Al Khalifah R, Yepes-Nuñez JJ, Sierra JM, Vernooij RWM, et al. Comparative effectiveness and safety of interventions for acute diarrhea and gastroenteritis in children: A systematic review and network meta-analysis. PLoS One 2018; 13(12): e0207701. https://doi.org/10.1371/journal.pone.0207701
11. Turck D, Berard H, Fretault N, Lecomte JM. Comparison of racecadotril and loperamide in children with acute diarrhea. Aliment Pharmacol Ther 1999; Suppl 6: 27-302. https://doi.org/10.1046/j.1365-2036.1999.00004.x-i1
12. 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(1): 124. https://doi.org/10.1186/s12887-018-1095-x
13. 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(3): 329-337.
14. Coffin B, Hamza H, Vetel JM, Lehert P. Racecadotril in the treatment of acute diarrhea in adults. An individual patient data based meta-analysis. Int J Clin Med 2014; 5(7): 345. https://doi.org/10.4236/ ijcm.2014.57051
15. Alam NH, 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(10): 1419-1423. https://doi.org/10.1136/gut.52.10.1419
16. Cézard JP, Duhamel JF, Meyer M, Pharaon I, Bellaiche M, Maurage C, et al. Efficacy and tolerability of racecadotril in acute diarrhea in children. Gastroenterology 2001; 120(4): 799-805. https://doi.org/10.1053/gast.2001.22544
17. Rautenberg TA, Zerwes U, Foerster D, Aultman R. Evaluating the cost utility of racecadotril for the treatment of acute watery diarrhea in children: the RAWD model. Clinicoecon Outcomes Res 2012; 4: 109-116. https://doi.org/10.2147/CEOR.S31238
18. Gordon M, Akobeng A. Racecadotril for acute diarrhea in children: systematic review and meta-analyses. Arch Dis Child 2016; 101(3): 234-240. https://doi.org/10.1136/archdischild-2015-309676
19. Lehert P, Chéron G, Calatayud GA, Cézard JP, Castrellón PG, Garcia JM, et al. Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis. Dig Liver Dis 2011; 43(9): 707-713. https://doi.org/10.1016/j.dld.2011.03.001
20. Kang G, Thuppal SV, 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(7): 595-600. https://doi.org/10.1007/s13312-016-0894-0
21. Sreenivas SK, Lakshmi M, Pavitra NA. Efficacy and safety of racecadotril as an adjunct to oral rehydration therapy for acute watery diarrhea in children. Ind J Child Health 2017; 4(1): 68-71. https://doi.org/10.32677/IJCH.2017.v04.i01.018