

Use of Racecadotril as Outpatient Treatment for Acute Gastroenteritis: A Prospective, Randomized, Parallel Study

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Objective To compare the efficacy of therapy with racecadotril plus oral rehydration versus oral rehydration alone in children with gastroenteritis in an outpatient setting care.

Study design Prospective, randomized, open and parallel study performed in a Pediatric Emergency Service of a tertiary care hospital. The study included 189 patients, ages 3 to 36 months, with acute gastroenteritis: 94 were administered an oral rehydration solution (OR), 94 received oral rehydration solution plus racecadotril (OR + R). The principal variable studied was the number of bowel movements in 48 hours after initiating treatment.

Results The groups were comparable clinically and epidemiologically at enrollment. No significant differences were found in the number of bowel movements between the 2 groups 48 hours after initiating treatment (4.1 ± 2.7 bowel movements in the OR group vs 3.8 ± 2.4 bowel movements in the OR + R group). No differences were found in the average duration of gastroenteritis (4.7 ± 2.2 days in the OR group, 4.0 ± 2.1 days in the OR + R group; $P = .15$). The incidence of adverse events was similar in both groups (19 patients [20.2%] in the OR group, 18 patients [19.1%] in the OR + R group).

Conclusions In our study group, the use of racecadotril did not improve the symptoms of diarrhea compared with standard rehydration therapy. (*J Pediatr* 2009;155:62-7).

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Acute gastroenteritis is a common disease among the pediatric population, with an estimated incidence of 1.8 billion cases per year. It carries a significant morbidity and it is responsible for 1.8 million deaths among children each year. The treatment is based on oral rehydration using a World Health Organization–defined standard solution with early re-introduction of food.¹⁻⁴

Over the past few years, new drugs have been developed for the treatment of acute gastroenteritis, including inhibitors of encephalins.⁵ Enkephalins are endogenous opioid peptides that function as intestinal neurotransmitters. Among their functions is the inhibition of intestinal secretions. Racecadotril is a propeptide form of thiorphan, a potent inhibitor of intestinal encephalins.⁶⁻⁸ The drug increases the activity of endogenous enkephalins, causing a reduction in intracellular cAMP levels and a decrease in the secretion of water and electrolytes.^{4,9} These effects occur without altering the motility or duration of intestinal transit and without promoting bacterial overgrowth. In addition, it does not affect basal absorption of water or electrolytes.^{5,6,10,11}

The objective of this study was to compare the efficacy of combined therapy with racecadotril and oral rehydration with that of oral rehydration alone in children and patients with gastroenteritis as outpatient care.

Methods

This was a single-center, prospective, randomized, open and parallel study conducted from June 2005 to December 2006 in the Pediatric Emergency Service of a tertiary-care hospital. It was approved by the ethics committee of the hospital and informed consent was obtained from the parents or legal guardians of all children.

Children were eligible for enrollment in the study if they were 3 to 36 months of age with acute gastroenteritis, as defined by having at least 3 loose stools within the previous 24 hours. Patients with gastroenteritis requiring hospitalization, with more than 7 days of symptoms, allergic to any of the components of the drug, receiving drugs that may interact with racecadotril, such as antibiotics, salicylates, or other antidiarrhea drugs were excluded from the study.

BMI	Body mass index
CF	Cardiac frequency
DBP	Diastolic blood pressure
OR	Oral rehydration
OR + R	Oral rehydration plus racecadotril
RF	Respiratory frequency
SBP	Systolic blood pressure

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Patients in both treatment groups received a standard rehydration solution, following the recommendations of the American Academy of Pediatrics.¹ One of the groups also received racecadotril additionally (OR + R). The doses were as follows: 10 mg every 8 hours for children weighing less than 9 kg; 20 mg every 8 hours for children weighing 9 to 13 kg; and 30 mg every 8 hours for children weighing more than 13 kg. The investigator was allowed to prescribe other therapy to treat the gastroenteritis or any other concomitant disease as needed, as long as it did not interfere with the study drug. Randomization of each of the treatment groups was performed using a computer program, which creates a random number list, divided into 2 blocks, 1 for each group. The numbers were assigned consecutively to each patient that was included in the trial, and the lowest number was assigned at first. The sample size was based on the median number of stools for each group and its standard deviation (SD), using the study of Cojacorcu et al as a reference. In this study, the median number of bowel movements was 6.8 (SD, 3.8) in the racecadotril plus oral rehydration group and 9.5 (SD, 4.5) in oral rehydration group. Therefore, with a sample size of 73 children in each group, we may detect, with a power of 90%, significant differences between the groups. We estimated a loss of 10% of children planned to enroll was 82 per groups.

Racecadotril treatment was discontinued when the patient had 2 stools of normal consistency, when they had no bowel movements in 12 hours, or after the maximum duration for treatment established of 7 days.

There were 2 follow-up visits after enrollment at 48 hours and at 7 days. Additionally, the parents or caregivers had were provided a notebook to record the time of each bowel movement, its consistency, the maximum temperature, and the need to go to another healthcare center. At the inclusion visit, the parents were trained on when to discontinue treatment and how to fill out the notebook.

During the initial visit, the following data were collected: demographic variables, family history of gastrointestinal disease, patient's medical history, characteristics of the current gastroenteritis, physical examination including weight, body temperature, heart and respiration rates, blood pressure, degree of dehydration, as well as any additional test required.

During the 48-hour visit, tolerance to treatment, side effects, changes in concomitant medication, visits to the pediatrician or the emergency room, as well as data regarding the outcome of the gastroenteritis (number of bowel movements per day and consistency, vomiting, and weight) were monitored. Therapeutic adherence was evaluated based on the number of doses received in 48 hours of treatment: good compliance was defined as when the patients received 75% or more of doses according to the patient's weight.

On day 7, the same variables were measured at the 48-hour visit, focusing on symptoms observed within the previous 24 hours.

The main objective of this study was to determine the efficacy of treatment according to the number of bowel move-

ments within 48 hours after imitation of therapy with oral rehydration plus racecadotril versus oral rehydration alone. Secondary objectives were to evaluate differences in the length of the diarrhea, the number of visits to the emergency room or primary doctor, and the safety and tolerance to the study drug.

To analyze the safety of the drug, we included data from all of treated patients, using a regression model. The result of drug efficacy and the primary and secondary objectives were analyzed as intent to treat as per protocol populations. For the analysis of the main variable, we used a linear generalized model fitted to the severity of the presentation, the age of the patient, and the family history, with application of the Wald bilateral test, with a significance level of .05. We compared the outcome of the number of bowel movements and the length of duration of symptoms using the Wilcoxon and Mann-Whiney *U* tests. To compare the changes in the consistency of the bowel movements, the symptomatology, and the child's weight, we applied general models of repeated measurements or equations of general estimates. We used a Poisson model of linear regression in order to monitor the evolution of the symptoms.

Results

A total of 189 children were included in the study. Among them, 188 (94 per group) were included in the safety analysis. The analysis of efficacy was performed on 179 children; 91 in the oral rehydration (OR) and 88 in the oral rehydration+racecadotril (OR + R) group. The study per protocol was performed on 133 children, 64 in OR group and 69 in OR + R Group. From the 179 patients who could be included in the intent-to-treat study, only 137 children returned for evaluation 48 hours later (66 in the OR group, 71 in the OR + R group) and 103 returned for the 7-day visit (53 in the OR group and 50 in thr OR + R group).

Thirty patients did not comply with the study protocol. The reasons included adverse events ($n = 4$), doctor's decision ($n = 1$), protocol violation ($n = 3$), decision of parents/legal guardians ($n = 19$), and no clear motive ($n = 3$). Another 50 children did not return for further monitoring.

The median age of percentile was 12 months (percentile 25: 7.5, percentile 75: 18); 12.5 months (percentile 25: 8.75, percentile 75: 18.5) in OR + R group and 11.0 months (percentile 25: 6.75, percentile 75: 18) in the OR group); 109 (58.9%) patient were male, with no statistically significant differences between the 2 treatment groups. The **Table** shows the medical history, initial clinical data, and concomitant treatments, with no significant differences between groups except for the incidence of previous episodes of acute gastroenteritis, which was higher in OR + R group than in OR group (45.7% vs 29.8%). We concluded that this difference could be a selection bias. Thirty-eight patients showed signs of dehydration: 21 (22.3%) in the OR group and 16 (17%) in the OR + R group. The grade of dehydration was mild in all patients except 1 in the OR + R group who had moderate dehydration. The mean duration of gastroenteritis before

Table. Medical history, physical data at admission, and concomitant treatments and disease

	S + R	S	Total	P
Medical history				
Breast milk	28 (29.8%)	38 (41.9)	67 (35.8%)	.21
Formula	41 (43.6%)	32 (34.4%)	73 (39%)	
Mixed breast milk and formula	25 (26.6%)	22 (23.7%)	47 (25.1%)	
Unmonitored pregnancy	2 (2.1%)	2 (2.1%)	4 (2.1%)	.68
Preterm delivery	5 (5.5%)	12 (12.9%)	17 (9.2%)	.08
Instrument-assisted delivery	40 (42.6%)	33 (35.9%)	73 (39.2%)	.35
Hospitalization during neonatal period	12 (12.8%)	14 (14.9%)	26 (13.8%)	.67
History of gastroenteritis	43 (45.7%)	28 (29.8%)	71 (37.8%)	.02
Physical at admission				
Weight (kg)	10 ± 2.4	9.6 ± 2.4	9.8 ± 2.4	.29
Height (cm)	78.1 ± 9.8	76.3 ± 10	77.2 ± 9.9	.19
BMI	16.4 ± 2.3	16.4 ± 1.9	16.4 ± 2.1	.62
% Dehydration	0.8 ± 1.4	0.8 ± 1.3	0.8 ± 1.3	.14
Axillary temperature	37.1 ± 0.8	36.9 ± 0.8	37.0 ± 0.8	.68
CF (lpm)	135.8 ± 21.6	133.1 ± 24.6	134.5 ± 23.1	.28
RF (rpm)	30.3 ± 10.4	29.8 ± 10.5	30.1 ± 10.4	.43
SBP (mm Hg)	103.0 ± 16.5	101.0 ± 16.4	102.0 ± 16.4	.28
DBP (mm Hg)	64.2 ± 13.2	64 ± 11.9	64.1 ± 12.7	.99
Concomitant treatments				
With other treatments	54 (57.4%)	58 (61.7%)	112 (59.6%)	.55

inclusion was 2.2 days (SD ± 1.5) in the OR + R group and 2.0 days (SD ± 1.3) in the OR group.

Bacterial stool cultures were performed in 127 patients (69%): 65 (69.9%) from the OR group and 62 (68.1%) from the OR +R group. The yield of a positive result was 8.7% (n=16). Viruses were tested in 93 children (50.5%); 22 of them (23.6 %) were positive for rotavirus, 11 in each group. No significant differences were observed between the groups.

Clinical Outcome and Response to Treatment

No significant differences were observed in the average number of bowel movements at the beginning of the study: 7.5 (±3.6 SD) in the OR group compared with 7.7 in the OR +R group (±3.5 SD). After 24 hours, these were reduced to

4.6 (±2.7 SD in the OR +R group and ±2.5 in the OR group) and to 4.1 by 48 hours (±2.7 SD) in the OR group and to 3.8 (±2.4 SD) in the OR +R group (Figure 1). A Poisson linear regression test confirmed a rapid decline in the number of bowel movements in both groups without any statistically significant differences by 48 hours after the beginning of therapy. The same results were obtained in both the intent to treat and per protocol analysis.

A decline in the number of loose stools and an increase in solid bowel movements was noted after the initial visit and at the 7-day visit in both groups (Figure 2).

We compared the number of bowel movements at different time points according to microbiological results (bacterial and viral) of the stools cultures, with no significant differences observed between groups at any of the visits. Only when we analyzed together the bowel movements in children with positive cultures (bacterial or rotavirus), the OR + R group showed a significant decrease in the number of bowel movements after 48 hours, which was not observed in the OR group [OR + R group, 8 (±2.3 SD) positive bacterial culture initially, 4.4 (±2.5 SD) at 48 hours (P < .01), 8.9 (± 4.3 SD) rotavirus positive initially, 4.8 (±3.7 SD) after 48 hours].

The evolution of other symptoms was similar in both groups. After 48 hours of treatment, 15 (21.1%) patients in the OR + R group and 9 (13.6%) in the OR group were asymptomatic. By day 7, 43 children (86%) in the OR + R group and 41 (77.4%) in the OR group did not present any gastrointestinal symptoms (P = .73).

After 48 hours of starting treatment, 13 children (5 in the OR + R group and 8 in the OR group) had revisited the emergency room and another 12 (6 from each group) had been to their pediatrician’s office. By day 7, 7 children revisited to the emergency room (5 from the OR + R group, 2 from the OR group) and 4 had been to their pediatrician’s office (1 from

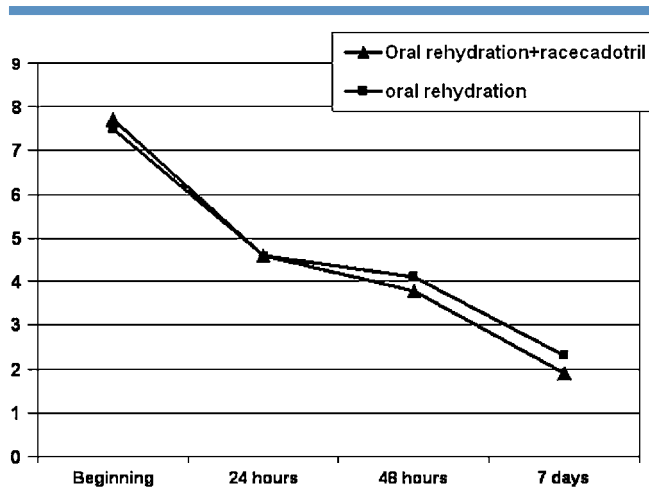


Figure 1. Evolution in number of bowel movements (ITT).

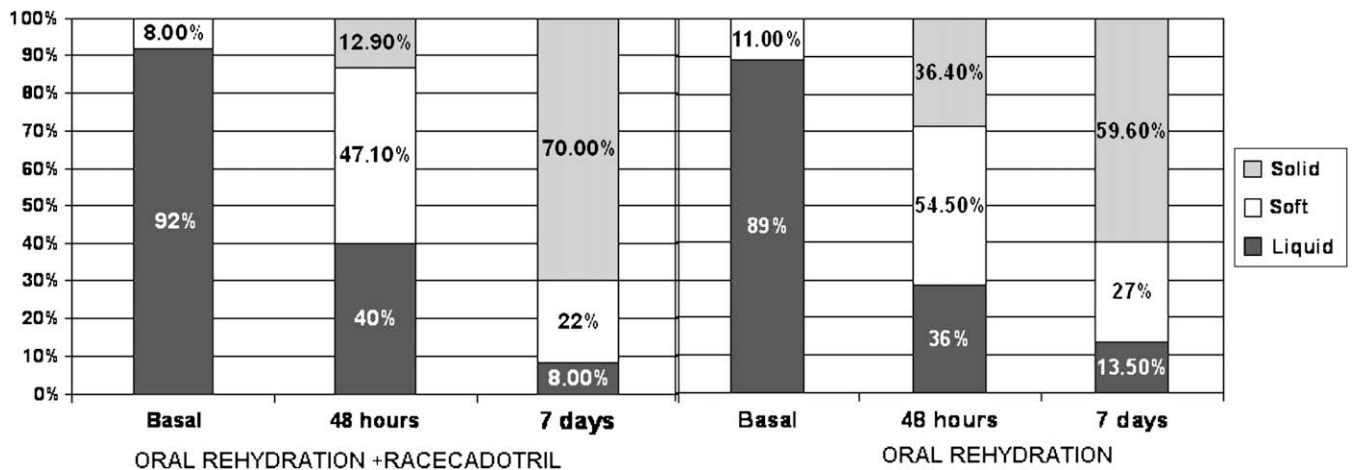


Figure 2. Evolution in bowel movement consistency.

the OR + R group, 3 from the OR group). Within this variable, no statistically significant differences were found between the 2 groups.

The average duration of the gastroenteritis was 4.0 days (± 2.1 SD) in OR + R patients and 4.7 days (± 2.2 SD) in OR patients; ($P = .15$). After 48 hours, 6 of 71 (8.5%) OR + R patients and 2 of 66 (3%) OR patients ($P = .27$) had recovered. After day 7, 35 of 50 (70%) OR + R patients and 30 of 53 (56.6%) OR patients ($P = .15$) had recovered, with no statistically significant differences between the two treatment groups.

Therapeutic Adherence and Adverse Effects

Forty-four patients (66.7%) showed good therapeutic compliance. Adverse effects were seen in 18 (19.1%) OR + R children and 19 (20.2%) OR children ($P = .85$). The most frequent adverse effects in both groups were respiratory illness (rhinitis, bronchitis, coughing, pneumonia, and upper respiratory infection): 13 (9.6%) OR + R children and 5 (5.3%) OR children. Other adverse effects were exanthema 5 (5.3%) in the OR + R group and 3 (3.2%) in the OR group, followed by gastrointestinal symptoms (vomiting and blood in stools), 4 (4.3%) patients in the treatment group, and in 5 (5.3%) control patients. There were 3 serious adverse effects. One child from the OR + R group showed an elevation in transaminases (ALT, 957 UI/L; AST, 1357 UI/L) requiring hospitalization for 1 week, decreasing thereafter until they normalized 3 months later; a viral infection was suspected. Two patients from the OR group patients were admitted to the hospital, one due to vomits and another due to mild dehydration.

Discussion

In this study, performed in a pediatric population younger than 3 years of age with acute gastroenteritis who did not require hospitalization, we found that treatment with raceca-

dotril associated with OR did not significantly improve the symptoms when compared with treatment with an oral rehydration solution alone. Both treatment groups had similar symptoms; therefore patient selection probably did not influence the results. Previous studies in pediatric populations found that the use of racecadotril to treat moderate-severe diarrhea reduced the volume of bowel movements by 56% to 60% after 48 hours of treatment when compared with placebo,^{4,12,13} and racecadotril-treated children required less rehydration solution, as they lost less water. However, the studies by Salazar-Lindo and Cèzard were performed using hospitalized children who had more severe dehydration with more serious clinical manifestations.^{12,13} Moreover, in those studies, medication was given under supervision, but in our study, we did not directly observe the administration of the drug. The study by Cojocaru et al, described studies performed in a pediatric population under ambulatory care.¹⁴ The study design was similar to ours: patients were not hospitalized, the control group did not receive a placebo, and there was no direct monitoring of drug administration. In that study, however, the use of racecadotril diminished the number of bowel movements after 48 hours and lowered the number of visits to the emergency room or to the primary care doctor.¹⁴

In adults, the data showed greater disparity. In a study by Alam et al looking at adults with severe cholera, no differences were found in the total volume of bowel movements, the ingestion of rehydration solution, or the duration of the gastroenteritis when racecadotril was compared with the placebo.¹⁵⁻¹⁷ Other studies in adults showed that racecadotril was more effective against acute diarrhea when compared with the placebo, reducing the number and volume of the bowel movements, the required oral dehydration solution, the length of disease, and the need for emergency care.^{6,7,15,18-21} Racecadotril was also shown to be as effective as loperamide but had fewer adverse effects.^{7,16,18,19,22-25}

The average duration of the acute gastroenteritis in our study was similar between treatment groups. The relevant literature on the effect of racecadotril is varied.²⁶ Although Alam et al did not find a decrease duration of diarrhea in adults with cholera,¹⁵ other authors did find that diarrhea disappeared sooner in patients treated with racecadotril.^{6,13,26} In our population, the percentage of positive bacterial stool cultures or rotavirus antigen detection in faeces was very low. When we restricted the analysis to only patients with positive stool cultures or rotavirus, we observed a tendency toward significance, with a higher percentage of bowel movements at the beginning of treatment and a more pronounced decline after 48 hours in the OR + R group. Other authors have not seen differences in the response to the drug as a function of the agent causing the acute gastroenteritis.^{6,12,13,15}

Our study confirms that racecadotril is a safe drug in children, causing a percentage of adverse effects very similar to that seen with only oral rehydration. All authors agree that the drug is well tolerated in both adults and children, with adverse effects similar to those of the placebo^{4,6,7,12,13,15,20,21,23,26,27} and a lower incidence of constipation and abdominal distension or pain than those seen with loperamide, particularly in the pediatric population.^{6,7,18,19,23-25} The adverse effects described for racecadotril are mild or moderate (constipation, vomiting, fecal blood, itching, dizziness, abdominal distension, and headache).^{6,12,18,19,26,27} One of our patients presented with transient elevation of aminotransferase levels; we could not establish a causal relationship with the drug.

One of the major limitations of this study compared with other similar studies performed previously on children is the lack of monitoring of the administration of the drug.¹⁹ Thus, we based the evaluation of the disease outcome on the answers to a questionnaire, not on direct observation of the number and characteristics of bowel movements. In other studies, the treatment efficacy was evaluated by weighing the diapers.^{12,13} Because our study was performed in ambulatory patients, we could not adopt these measurement methods. Nonetheless, any possible errors in the parent's description of the diarrhea were the same in both groups. One possible bias might have been introduced by the children who left the study, as these might have been children who did not improve or improved very quickly. Although we cannot exclude this possibility, the number of dropouts in both groups was comparable. Despite this concern, the number of patients analyzed was large enough to have yielded differences between the treatment groups.

In previous studies, other authors have proved that racecadotril is effective in the treatment of acute gastroenteritis, and thus more studies in outpatient pediatric population are needed.

We conclude that in children with moderate acute gastroenteritis who do not need hospitalization, racecadotril does not diminish the symptoms of diarrhea more rapidly than oral rehydration therapy alone. ■

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50 Years Ago in THE JOURNAL OF PEDIATRICS

Congenital Leukemia

Brescia MA, Santora E, Sarnataro VF. *J Pediatr* 1959;55:35-41

This classic case report describes an infant who suddenly “refused feeding, rapidly deteriorated, and died in a matter of a few hours.” Striking leukocytosis and organ infiltration by morphologically immature blood cells led to a post-mortem diagnosis of “congenital stem cell leukemia.” Speculation about etiology included intrauterine exposure to a virus or radiation.

Imagine how little was known about leukemia in 1959! Chromosomes and cancer were not linked until the 1960 discovery of the Philadelphia chromosome in chronic myelogenous leukemia (CML). In 1973, the Philadelphia chromosome was shown to be formed by the t(9;22) reciprocal translocation, and a decade later the oncogenic kinase *ABL* was discovered at the t(9;22) breakpoint. But these discoveries did not impact the *treatment* of CML until 1999, when imatinib (an oral *ABL* kinase inhibitor taken once per day) was found to effectively control CML. Imatinib and its successors now stand as shining examples of the promise of *targeted* cancer therapy.

The last 50 years have likewise brought discoveries elucidating the biology of infant leukemia. Because they often coexpress myeloid and lymphoid antigens, these “mixed lineage” leukemias likely originate in a multipotent hematopoietic stem cell. About 80% of cases harbor translocations that fuse the *MLL* (*mixed lineage leukemia*) oncogene at chromosome 11q23 to one of multiple “partner genes.” *MLL* translocations also characterize leukemias caused by previous exposure to chemotherapy drugs that potently inhibit topoisomerase II (e.g., etoposide). Previous studies have suggested that intrauterine exposure to substances in the maternal diet or environment with mild topoisomerase II inhibitory activity (e.g., flavonoids, benzene metabolites, caffeine) increases the risk of infant leukemia, perhaps explaining the “*MLL* link” between infant and treatment-related leukemias. Genome-wide studies have demonstrated that infant leukemias express very high levels of the oncogenic receptor tyrosine kinase *FLT3*, which (like *ABL* in CML) may represent a “druggable” target. Accordingly, the first clinical trial of a drug that targets *FLT3* is currently underway in the Children’s Oncology Group for infants with leukemia.

Although > 90% of leukemic infants now enter remission with standard treatment, most will die of relapsed disease within a few years. Asymmetry between biological understanding and successful treatment is a recurrent theme in medicine, emphasizing the acute need for translational research that bridges bench and bedside.

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