RACECADOTRIL IN THE TREATMENT OF ACUTE WATERY DIARRHEA IN CHILDREN

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ABSTRACT

Background Racecadotril (acetorphan), an enkephalinase inhibitor with antisecretory and antidiarrheal actions, is an effective and safe treatment for acute diarrhea in adults and children. Whether treatment with racecadotril and oral rehydration therapy is more effective than treatment with oral rehydration alone in hospitalized children with acute watery diarrhea is not known.

Methods We treated 135 boys 3 to 35 months of age who had watery diarrhea of five days' duration or less with racecadotril (1.5 mg per kilogram of body weight orally every eight hours) or placebo, in addition to oral rehydration solution. The primary end point was the 48-hour stool output (measured in grams); the total stool output, duration of diarrhea, and total intake of oral rehydration solution were also measured.

Results The mean (±SE) 48-hour stool output was 92±12 g per kilogram in the racecadotril group and 170±15 g per kilogram in the placebo group ($P<0.001$), a 46 percent reduction with racecadotril. The results were similar among the 73 boys with rotavirus infections. The total stool output was 157±27 g per kilogram in the racecadotril group and 331±39 g per kilogram in the placebo group ($P<0.001$). The median duration of diarrhea was significantly less ($P<0.001$) in the racecadotril group (28 hours regardless of rotavirus status) than in the placebo group (72 and 52 hours, respectively, for rotavirus-positive and rotavirus-negative patients). The intake of oral rehydration solution was significantly lower in the racecadotril group than in the placebo group ($P<0.001$). Racecadotril was well tolerated; only seven patients taking racecadotril had adverse effects, which were all mild and transient.

Conclusions In young boys with acute watery diarrhea, racecadotril is an effective and safe treatment. (N Engl J Med 2000;343:463-7.)

DIARRHEAL disease is a leading cause of illness and death in children worldwide.[1,2] Many of the deaths are caused by dehydration resulting from loss of water and electrolytes due to intestinal malabsorption or increased secretion. Replacement of these losses by oral rehydration solution is the mainstay of therapy for children with watery diarrhea.[3]

Racecadotril (acetorphan) is an enkephalinase inhibitor that decreases intestinal hypersecretion but not motility in animals and humans.[4,5] It has proved effective and safe in children and adults with acute watery diarrhea when taken orally.[6-8] It exerts its antidiarrheal effects by preventing the breakdown of endogenous enkephalins in the gastrointestinal tract.[9-11]

A previous study of racecadotril was carried out in children three months to four years old in France.[8] The aim of the current study was to assess the effect of racecadotril as an adjunct to oral rehydration therapy in infants and children in a developing country, who were less well nourished than those in France and had more severe watery diarrhea.

METHODS

Subjects

From 1994 to 1998, we studied 135 boys 3 to 35 months of age who were hospitalized because of dehydration. The boys had had watery diarrhea for five days or less, had passed three or more diarrheic stools in the 24 hours before admission to the hospital, and had passed at least one diarrheic stool within 4 to 6 hours after admission. Boys with blood in the stool, severe dehydration (inability to drink because of drowsiness), or any serious concomitant illness were excluded from the study. We studied only boys to minimize the contamination of stool with urine.

At base line, the child's history was obtained from a parent, and a complete physical examination, hematologic tests, and stool collection were performed. The boys were then observed for four to six hours to confirm the presence of diarrhea. During this time standard oral rehydration solution (111 mmol of glucose, 90 mmol of sodium, 20 mmol of potassium, 80 mmol of chloride, and 10 mmol of citrate per liter) was given as needed to correct dehydration. A second complete physical examination was then carried out, after which the boys were randomly assigned to receive racecadotril or placebo in addition to oral rehydration solution as needed to replace fecal fluid losses.

Study Design

The study was a randomized, double-blind, placebo-controlled comparison and was carried out at a single hospital center. It was conducted in accordance with the Declaration of Helsinki and was approved by the hospital ethics committee. Written informed consent was received from at least one parent of each boy. The boys received racecadotril or placebo orally every eight hours, in addition to oral rehydration solution. Both treatments were administered as saccharose-containing powders of identical appearance and taste, with a small amount of water to facilitate swallowing. The dose of racecadotril was 1.5 mg per kilogram of body weight. This dose was chosen because it was similar to the adult dose in milligrams per kilogram and because a pharmacokinetic study in children found that plasma concentrations of the active metabolite of racecadotril remained higher than the concentration that inhibited 50 percent of enkephalinase activity for up to eight

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hours after oral administration (Olive G: personal communication). Treatment with antibiotics, other antidiarrheal drugs, or aspirin was not permitted during the study.

Boys were withdrawn from the study if blood appeared in their stools during the first 24 hours, if they needed antibiotic treatment for concomitant illness during the first 24 hours, if treatment was judged by the attending physician to be ineffective at any time during the study, if the parent withdrew consent at any point, or if there were severe adverse events at any time. If none of these events occurred, treatment was given for five days or until the diarrhea stopped, whichever came first.

Diarrhea was considered to have stopped after a boy had passed two consecutive formed stools or had not passed a stool for 12 hours. In addition to oral rehydration solution, the boys were given milk or soft foods, as appropriate to their age, to provide a daily calorie intake of 100 to 120 kcal per kilogram (excluding the calories from glucose in the rehydration solution), in accordance with World Health Organization recommendations that diet be maintained during treatment of diarrhea to prevent nutritional disturbance.[3]

Microbiologic Examination of Stool

Fresh stool obtained at admission was tested for bacterial pathogens and rotavirus. The presence of salmonella, shigella, *Campylobacter jejuni,* enteropathogenic *Escherichia coli* (identified by stereotyping), aeromonas, and vibrio was determined by standard microbiologic methods, as described previously.[12] No tests for toxigenicity or pathogenicity were performed on *E. coli,* and no tests for pathogenicity were performed on aeromonas isolates. An enzyme-linked immunosorbent assay (ELISA) was used to test for rotavirus particles in stool (Dakopats commercial kit, Dako, Glostrup, Denmark).

Evaluations

A physical examination was performed each day during the study, and stool weight, intake of oral rehydration solution, and output of vomit were measured every four hours. The primary end point was stool output in the first 48 hours, because both the fluid loss and the risk of dehydration are maximal during this period. During this period, care was taken to ensure that stools were collected separately from urine. Thereafter, stools were collected in preweighed diapers.

Stool output was calculated as the sum of the weights of the watery and loose stools (diarrheic stools) divided by the body weight at base line. The total stool output, duration of diarrhea, and total intake of oral rehydration solution were also measured. These assessments were made at the time of recovery or at the end of five days, if the child had not recovered by this time.

Statistical Analysis

The 48-hour and total stool output and the intake of oral rehydration solution in the two study groups as a whole and in the subgroups of children with and without rotavirus infections were compared by analysis of variance. Square-root transformations were then performed to stabilize the variance and improve the fit of the model; the results were expressed as adjusted means for each treatment group with the 95 percent confidence intervals for the differences between means. Recovery rates were compared by the log-rank test.

Statistical analyses were carried out with two-sided tests according to the intention to treat (including all boys for whom data were available). When a measurement was missing, the last observation was carried forward.

RESULTS

The base-line characteristics of the 68 boys in the racecadotril group and the 67 boys in the placebo group were similar (Table 1). At base line, eight boys in the racecadotril group and one in the placebo group had a respiratory illness, and two boys in the racecadotril group and one in the placebo group had mild hypokalemia. Two boys in the racecadotril group had previously had dysentery. Twenty-three boys were prematurely withdrawn from the study (Table 2).

TABLE 1. BASE-LINE CHARACTERISTICS OF BOYS WITH ACUTE WATERY DIARRHEA.*

CHARACTERISTIC	RACECADOTRIL GROUP (N=68)	PLACEBO GROUP (N=67)
Age — mo		
Mean	13±7	12±7
Range	3–35	3–35
Weight — kg		
Mean	9.0±1.7	8.7±2.1
Range	5.2–12.5	4.4–15.6
Stools in previous 24 hr — no.		
Mean	8.6±4.9	9.7±4.6
Range	3–29	3–20
Stool consistency in previous 24 hr — no. of boys (%)		
Loose	16 (24)	14 (21)
Watery	52 (76)	53 (79)
Duration of diarrhea before hospitalization — hr		
Mean	47.4±30.0	51.5±31.4
Range	9–117	8–118
Pathogens detected in stool — no. of boys (%)		
Bacteria	25 (37)†	28 (42)‡
Rotavirus	34 (50)	39 (58)

*Plus–minus values are means ±SD.

†Two cultures were positive for salmonella species, 3 for *Vibrio cholerae,* 11 for enteropathogenic *Escherichia coli,* 4 for *Campylobacter jejuni,* 7 for aeromonas species, and 1 for shigella species. Some boys had more than one pathogen in the same sample.

‡One culture was positive for salmonella species, 4 for *V. cholerae,* 15 for enteropathogenic *E. coli,* 2 for *C. jejuni,* 11 for aeromonas species, and 3 for shigella species. Some boys had more than one pathogen in the same sample.

Rotavirus status was assessed in all but 3 boys: 34 (50 percent) in the racecadotril group and 39 (58 percent) in the placebo group had positive test results. Bacterial pathogens were identified in 25 boys in the racecadotril group (37 percent) and 28 boys in the placebo group (42 percent). The organisms were salmonella species, *Vibrio cholerae,* enteropathogenic *E. coli, C. jejuni,* aeromonas species, and shigella species.

Forty-Eight-Hour Stool Output

The mean (±SE) 48-hour stool output was 92±12 g per kilogram in the racecadotril group, as compared with 170±15 g per kilogram in the placebo group ($P<0.001$), representing a 46 percent lower output with racecadotril (Fig. 1). Among the boys who were positive for rotavirus, the 48-hour stool output was 105±17 g per kilogram in the racecadotril group and 195±20 g per kilogram in the placebo group ($P<0.001$), also a 46 percent reduction (Fig. 1).

TABLE 2. REASONS FOR WITHDRAWAL FROM THE STUDY.

REASON	RACECADOTRIL GROUP (N=68)	PLACEBO GROUP (N=67)
	no. withdrawn	
Withdrawal of parental consent	3	3*
Treatment considered ineffective by physician	2	3
Adverse event	1	2
Blood in stool during first 24 hr	1	2
Antibiotic treatment required for concomitant illness during first 24 hr	0	1
Protocol violation	2	3*
Total	9	14

*Two of these three boys also received a medication (other than an antibiotic) that was forbidden by the study protocol.

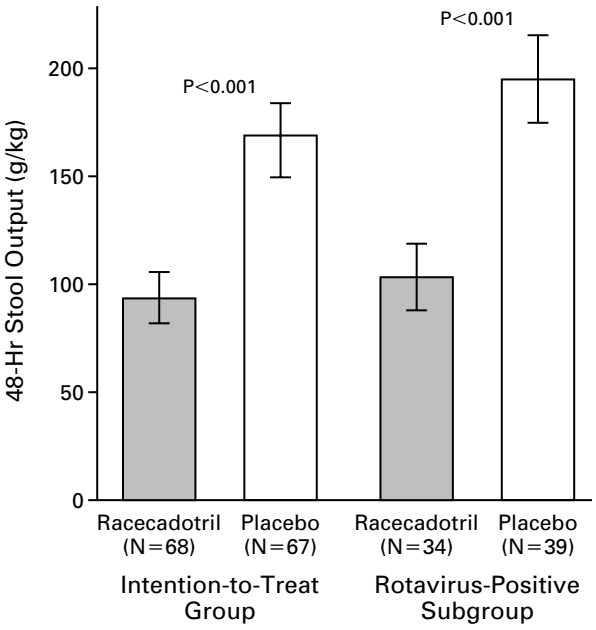

Figure 1. Mean (±SE) 48-Hour Stool Output in All Boys (Intention-to-Treat Group) and in the Rotavirus-Positive Subgroup after Treatment with Racecadotril or Placebo.

After the exclusion of the data from the rotavirus-positive boys, whose stool output was greater, the difference between the racecadotril and placebo groups remained significant (31 percent lower in the racecadotril group; 95 percent confidence interval, 16 to 46 percent; $P<0.001$). The mean hourly rate of stool

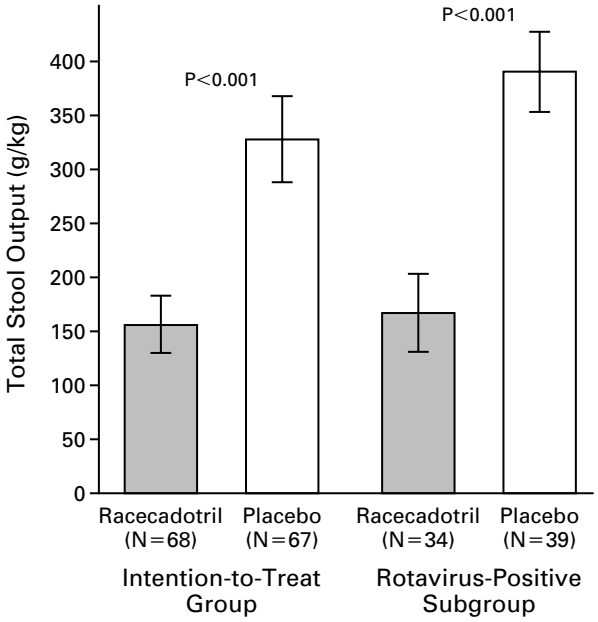

Figure 2. Mean (±SE) Total Stool Output before Recovery in All Boys (Intention-to-Treat Group) and in the Rotavirus-Positive Subgroup after Treatment with Racecadotril or Placebo.

production in the first 48 hours (the total stool weight through hour 48 divided by the number of hours during which the stools were collected) was 1.8±0.2 g per kilogram per hour in the racecadotril group and 3.1±0.3 g per kilogram per hour in the placebo group ($P<0.001$).

Total Stool Output

The mean total stool output before recovery was 157±27 g per kilogram in the racecadotril group and 331±39 g per kilogram in the placebo group, a 53 percent lower output with racecadotril ($P<0.001$) (Fig. 2). In the rotavirus-positive boys, the stool output was 174±36 g per kilogram in the racecadotril group and 397±37 g per kilogram in the placebo group, a 56 percent lower output with racecadotril ($P<0.001$) (Fig. 2). The mean values remained significantly different after exclusion of the rotavirus-positive boys (difference in output, 37 percent; 95 percent confidence interval, 20 to 56 percent; $P<0.001$).

Duration of Diarrhea

The duration of diarrhea in the racecadotril and placebo groups differed according to rotavirus status ($P<0.05$). The rate of recovery of the boys who were rotavirus-positive was more rapid in those who received racecadotril than in those who received placebo (Fig. 3). The median duration of diarrhea in the racecadotril group was 28 hours in both rotavirus-positive and rotavirus-negative boys. The correspond-

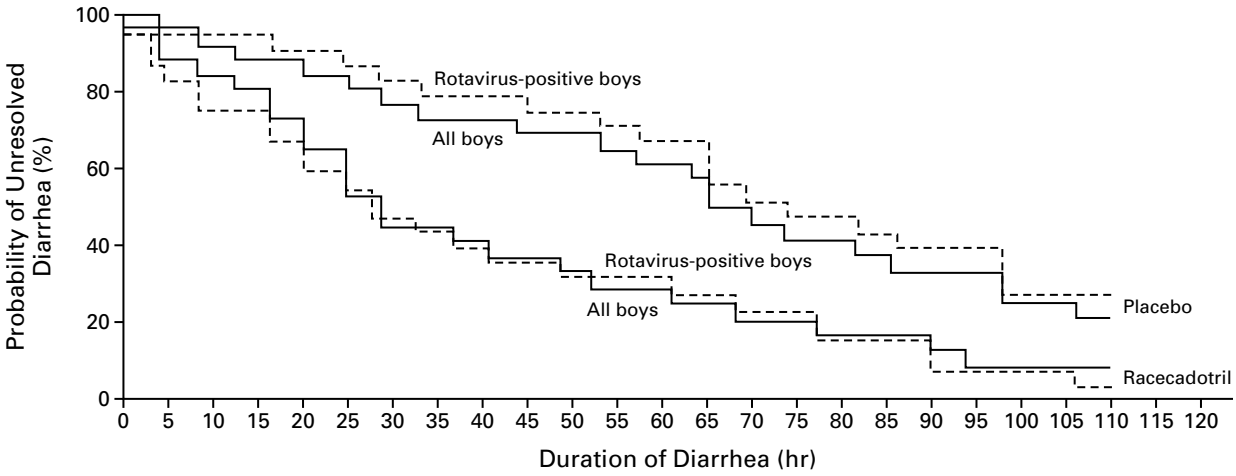

Figure 3. Rates of Unresolved Diarrhea in All Boys and in the Rotavirus-Positive Subgroup during Treatment with Racecadotril or Placebo.

There were 68 boys in the racecadotril group (34 of whom had rotavirus infection) and 67 in the placebo group (39 with rotavirus infection). Nine boys were withdrawn prematurely from the racecadotril group, as were 14 from the placebo group.

ing values in the placebo group were 72 and 52 hours, respectively ($P<0.001$ for the comparisons between treatments and rotavirus-status groups). Hence, the boys in the racecadotril group recovered after about one day, as compared with two days for those in the placebo group who were rotavirus-negative and three days for those in the placebo group who were rotavirus-positive.

The overall five-day rates of cure were 84 percent (57 boys) in the racecadotril group and 66 percent (44 boys) in the placebo group. Moreover, 24 percent of the boys in the racecadotril group, as compared with 8 percent of those in the placebo group, either had no stools or had at least one formed stool within 24 hours after treatment began.

Total Intake of Oral Rehydration Solution

On day 1 the mean intake of oral rehydration solution was 439±49 ml in the racecadotril group and 658±59 ml in the placebo group. The respective values on day 2 were 414±68 ml and 640±68 ml. The total intake of oral rehydration solution was lower in the racecadotril group ($P<0.001$).

Tolerability

Adverse effects of treatment occurred in seven boys (10 percent) in the racecadotril group and five (7 percent) in the placebo group. None were rated as severe. In four boys, all of whom were taking racecadotril, the event was considered by the investigator to be possibly related to treatment. Two boys who had mild hypokalemia at base line continued to have hypokalemia (one of them also had bronchospasm); one had ileus (this boy had passed 29 stools at base line, more than any other subject); and one had a mild fever. Seventy boys vomited at some time during treatment, 35 (51 percent) in the racecadotril group and 35 (52 percent) in the placebo group. Vomiting was not related to rotavirus infection.

DISCUSSION

The results of this study provide strong evidence that racecadotril is an effective treatment for acute watery diarrhea in hospitalized children. As compared with the placebo group, the racecadotril group had a clinically consistent and significant ($P<0.001$) reduction in 48-hour stool output, total stool output before recovery, total intake of oral rehydration solution, and duration of diarrhea. Hence, when used as an adjunct to oral rehydration therapy, racecadotril may reduce both the severity and duration of diarrhea and the duration of hospitalization.

Racecadotril proved effective in both rotavirus-positive and rotavirus-negative boys. Although girls were excluded from the study to avoid contamination of stool with urine, there is no reason to expect they would respond differently.

The efficacy of racecadotril in the treatment of acute diarrhea is thought to be due to its inhibition of enkephalinase.[9,10] By inhibiting this enzyme, racecadotril prevents the inactivation of endogenous enkephalins and prolongs their physiologic action. The enkephalins act as neurotransmitters in the gastrointestinal tract by activating δ-opiate receptors and thus reducing the level of cyclic AMP.[13] The result is reduced secretion of water and electrolytes without any

detectable effect on intestinal motility.[10,14,15] Racecadotril has antisecretory actions only when hypersecretion is present, not in the basal state.[4,5] The opiate drugs currently recommended for the treatment of diarrhea, such as loperamide, seem to act largely by activating μ-opiate receptors, leading to an increase in intestinal transit time as a result of disruption of normal peristaltic motion.[16,17] Side effects associated with the use of these drugs include constipation, bacterial overgrowth, and toxic megacolon.[15,18-20]

Racecadotril was safe in these boys, and the incidence of vomiting did not differ between the racecadotril and placebo groups. Bloody stools were uncommon after the first 24 hours in both the racecadotril and placebo groups. Other adverse events occurred in less than 10 percent of boys, and none were severe. Hypokalemia persisted in two boys who received racecadotril. It may therefore be useful to measure serum potassium regularly in future trials of this drug. However, both hypokalemia and ileus are well known to occur in children with acute diarrhea.

The efficacy and safety of racecadotril as an adjuvant to oral rehydration therapy have also been demonstrated in infants and children with less severe diarrhea.[8] Interestingly, in both our study and that of Cézard et al.,[8] racecadotril was effective in children with rotavirus-associated diarrhea, a condition that is thought to be caused mainly by malabsorption. However, future investigations into the pathophysiologic mechanism of rotavirus diarrhea may reveal the involvement of secretory pathways mediated by enterotoxins[21] or neurotransmitters.[22]

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