Efficacy and Tolerability of Racecadotril in Acute Diarrhea in Children

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Background & Aims: **Oral rehydration therapy is the only treatment recommended by the World Health Organization in acute diarrhea in children. Antisecretory drugs available could not be used because of their side effects, except for racecadotril, which is efficient in acute diarrhea in adults.** ***Methods:*** **The efficacy and tolerability of racecadotril (1.5 mg/kg administered orally 3 times daily) as adjuvant therapy to oral rehydration were compared with those of placebo in 172 infants aged 3 months to 4 years (mean age, 12.8 months) who had acute diarrhea. The treatment groups were comparable in terms of age, duration of diarrhea, number of stools, and causative microorganism at inclusion.** ***Results:*** **During the first 48 hours of treatment, patients receiving racecadotril had a significantly lower stool output (grams per hour) than those receiving placebo. The 95% confidence interval was 43%–88% for the full data set (n = 166; *P* = 0.009) and 33%–75% for the per-protocol population (n = 116; *P* = 0.001). There was no difference between treatments depending on rotavirus status. Significant differences between treatment groups were also found after 24 hours of treatment: full data set (n = 167; *P* = 0.026) and per-protocol population (n = 121; *P* = 0.015). Tolerability was good in both groups of patients.** ***Conclusions:*** **This study demonstrates the efficacy (up to 50% reduction in stool output) and tolerability of racecadotril as adjuvant therapy to oral rehydration solution in the treatment of severe diarrhea in infants and children.**

Oral rehydration therapy is well accepted as the most effective treatment for rehydration of children with acute diarrhea and is recommended by the World Health Organization for prevention and management of dehydration.[1,2] Although the use of oral rehydration therapy has achieved a dramatic reduction in both morbidity and mortality in diarrhea,[3,4] rehydration has little effect on stool volume or frequency. Therefore, the World Health Organization has recommended that drug treatment be added to rehydration therapy, as long as the drug used has proven safety and efficacy in the pediatric population.[1,2]

Racecadotril (acetorphan) is a specific inhibitor of enkephalinase (neprilysin, EC 3.4.24.11), a cell membrane peptidase enzyme located in various tissues, notably the epithelium of the small intestine.[5] This enzyme contributes both to the digestion of exogenous peptides and to the breakdown of endogenous peptides such as enkephalins, neurokinin, and substance P.[6] Studies in animals and humans show that racecadotril, given orally, is effective against the secretory diarrhea caused by cholera toxin and castor oil.[7–9] The effect of racecadotril in these studies was antagonized by the opioid receptor antagonist naloxone, indicating the involvement of endogenous opioid peptides.[10] Moreover, racecadotril does not increase intestinal transit time,[11] implying that the drug has a selective antisecretory mode of action.

In adults, racecadotril has been shown to have better efficacy than placebo in randomized, double-blind clinical trials of patients with acute diarrhea. This efficacy has been combined with a side effects profile similar to that of placebo.[9,12]

The present study was performed to compare the efficacy and tolerability of racecadotril and placebo in hospitalized infants and children (aged 3 months to 4 years) who had severe acute diarrhea necessitating hospitalization.

Abbreviation used in this paper: CI, confidence interval.

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Patients and Methods

Study Population

A randomized, double-blind, placebo-controlled study was carried out in 13 separate centers. A total of 172 children hospitalized for severe acute diarrhea and aged 3 months to 4 years (mean, 12.8 months) of both sexes (71 girls and 101 boys) entered the study. Patients of both genders were included to reflect the actual use of racecadotril in routine clinical practice. The centers included 167 patients (97%). For each of these centers, the number of patients was at least 5 (range, 5–29 patients). Three centers (Nancy, Mairseilles, and Toulouse) included only 1 or 2 patients. Patients were eligible for inclusion if they were suffering from watery diarrhea (3 or more watery stools per day) of less than 72 hours' duration. Before inclusion, each patient had to pass at least 1 watery stool at the hospital. Patients were excluded if they had chronic diarrhea, a weight for age deficit of 20% or more of National Center for Health Statistics standards, or a systemic illness or had received an antibiotic, antidiarrheal drug, or acetylsalicylic acid within the preceding 48 hours.

Informed written consent was obtained from both parents of each child, and the study protocol was approved by the Paris Bichat Faculty Ethical Committee (CCPPRB Paris-Bichat). The size of the patient population was estimated with reference to previous studies, with an assumption of a 33% reduction in stool weight, a type 1 error of 0.05, and a power of 90%. When the actual size of the major endpoint (48-hour stool output), the difference observed between groups, and common variance were taken into account, the actual power was 80%–96% for the intention-to-treat and per-protocol populations, respectively.

Patient Evaluation

Each patient remained in the hospital for at least 48 hours. At the end of this time, patients were followed up either in the hospital or at home via a chart filled in by the parents until recovery took place. Patients who had been discharged from the hospital returned for physician evaluation on the sixth day after the start of treatment.

A complete medical history was obtained and standard physical examination, including assessment of dehydration, was performed on admission to hospital. Rehydration solution (Adiaril; Gallia Villefranche/Saone, France; concentration: 49 mmol/L Na^+, 25 mmol/L K^+, 25 mmol/L Cl^-, 24 mmol/L CO_3, 24 mmol/L H^+, 111 mmol/L glucose, and 58 mmol/L saccharose) was administered ad libitum each hour for the first 24 hours of the study either orally or by a gastric tube; 50% of the total amount was given within the first 6 hours. The amount of oral rehydration solution was estimated by multiplying the child's weight in kg by 100 mL after compensation for weight lost (100 mL/kg + weight lost). Patients with severe dehydration (more than 10% of body weight) received oral solution after intravenous rehydration. These patients were not included in the study until intravenous administration had stopped or if intravenous administration lasted more than 12 hours. No patient was excluded for this reason.

A lactose-containing diet (not diluted) was started within the first 24 hours and normalized (caloric intake) within 48 hours. Breast-fed patients were weighed before and after each breast-feeding.

Stool samples were collected on admission and examined for the presence of *Salmonella*, *Shigella*, and enteropathogenic *Escherichia coli*. Rotavirus antigen was identified by enzyme-linked immunosorbent assay.

Stool weight was measured every 12 hours for the first 48 hours by subtracting the weight of preweighed diapers from that of used diapers. Urine was collected separately in urine bags and weighed. The number of stools and their characteristics (liquid, soft, or normal) were recorded every 4 hours, and body weight and hydration status were assessed at baseline and 12, 24, and 48 hours after entry to the study. Clinical symptoms such as fever, vomiting, or abdominal distention (abdominal circumference) were assessed every 4 hours or less. Intake of oral rehydration solution and food and Na^+/K^+ ratio of urine were measured at 4, 12, 24, 36, and 48 hours to provide an indirect index of dehydration.

The primary efficacy criterion was stool output (grams per hour) during the first 48 hours of the study. Secondary efficacy criteria were stool output during the first 24 hours, Na^+/K^+ ratio of urine, duration of diarrhea, and number and characteristics of stools.

Tolerability was assessed during each clinical evaluation, and all adverse events were recorded.

Drug Treatment

Each patient was randomly assigned to receive oral racecadotril or placebo. Both drug treatments were given as granules of the same appearance and taste. Treatment was given 3 times daily at a dose of 1.5 mg/kg, which was similar, on a body weight basis, to the adult dose of racecadotril.

Patients were not permitted to receive any other antidiarrheal drugs or antibiotics during the study. The only permitted concomitant medication was paracetamol (60 $mg \cdot kg^{-1} \cdot day^{-1}$) if the patient developed a fever.

Treatment was given for 5 days or until the patient recovered if this took place earlier. Patients were considered to have recovered after they had passed 2 formed stools or if they had not passed a stool for 12 hours.

Statistical Analysis

The primary efficacy criterion was stool output during the first 48 hours, divided by the number of hours over which stools were collected during the first 48 hours for patients who were uncured at this time or until recovery in those who recovered sooner. Because the study was stratified according to sex, this parameter was used as a blocking factor in the statistical analysis. Stool output was compared using an analysis of covariance. Potential covariates were age and body weight at baseline. Any term not contributing significantly ($P < 0.05$) was omitted from the final model. The minimal

model comprised terms for sex and treatment. To satisfy normal distribution assumptions, the data were transformed logarithmically to improve the fit of the model. The estimate of treatment difference was expressed as the ratio of the geometric means of the 2 groups with the 95% confidence interval (CI).[13] Analysis of the per-protocol population also included a term for rotavirus status (positive or negative) as a potential covariate.

Two analyses were carried out: a full data set analysis comprising all patients with data available and a per-protocol analysis comprising only fully evaluable patients. In this instance, fully evaluable means that all of the following criteria were satisfied: stool weight data recorded up to 48 hours (or 24 hours) or recovery (end of treatment), whichever occurred earlier; no missing stool weights, unless the patient was withdrawn early because of lack of efficacy; all entry criteria fulfilled as specified in the protocol; no concomitant antidiarrheal medication or antibiotics taken during the 48 hours before and after randomization; and rotavirus status known. Missing values were estimated in the full data set analysis by taking the mean of the 2 weights on either side (chronologically) of the missing value. If the missing value was the last observation for a patient, no estimation was performed, and the last recorded stool weight was used as the study endpoint. If the missing value occurred at the beginning of the study, the total stool weight was calculated for the time between the first and last recordings, and the resulting value was divided by this time interval.

Secondary efficacy criteria were analyzed using the χ^2, Fisher exact test, Student *t* test, analysis of variance, or Wilcoxon test, as appropriate.

Results

Study Population

Of the 172 patients who entered the study (89 in racecadotril group and 83 in placebo group), 4 were excluded because their stool weights were not recorded (3 in racecadotril group and 1 placebo group). Stool weights could not be estimated in 2 other patients receiving racecadotril (1 from 12 to 24 hours and 1 from 24 to 36 hours) because no stools were passed during any other periods. These data were therefore recorded as missing.

The full data set consisted of 86 patients who received racecadotril and 82 who received placebo, but because of the missing data described above, the main efficacy criterion was analyzed for 84 patients receiving racecadotril and 82 receiving placebo. Of these, 121 patients (58 receiving racecadotril and 63 receiving placebo) were fully evaluable and made up the per-protocol population. The reasons patients were not fully evaluable were lack of microbiologic analysis of the stools (14 patients in racecadotril and 10 in placebo group), failure to satisfy the inclusion criteria (12 patients in racecadotril and 4 in placebo group), stool weight not recorded (1 patient in racecadotril and 3 in placebo group), and adverse events (3 patients in racecadotril and 3 in placebo group). The reasons patients did not satisfy inclusion criteria were diarrhea that had already lasted longer than 3 days or was too mild to warrant hospitalization, patient age less than 3 months, signs of undernutrition, and antidiarrheal treatment within the previous 2 days. Three patients (2 in the racecadotril and 1 in the placebo group) were not fully evaluable for 2 reasons (Table 1).

Both groups of patients were similar in terms of baseline characteristics (Table 2), and similar microorganisms were identified in both groups (Table 3). Rotavirus was identified in 32 patients receiving racecadotril and 35 receiving placebo.

A total of 13 patients were withdrawn from the study, 9 of whom received racecadotril and 4 placebo. Ten patients were withdrawn because of adverse events: 4 for vomiting (3 receiving racecadotril and 1 receiving placebo), 2 for dehydration (both receiving racecadotril), 3 for otitis (1 receiving racecadotril and 2 receiving placebo), and 1 for a urinary tract infection (placebo). Three patients were withdrawn because of lack of efficacy, necessitating an intravenous rehydration (2 in the racecadotril group after 16 hours of treatment and 1 in the placebo group after 24 hours of treatment).

Stool Output

The stool output during the first 48 hours of treatment for the full data set analysis and the per-protocol analysis is shown in Figure 1. Stool output was significantly lower in patients receiving racecadotril ($P = 0.009$) in the full data set; the estimate of the treatment difference showed that the stool output on racecadotril was approximately 60% of that on placebo (95% CI, 43%–88%). There was no evidence of any difference in treatment effect between the sexes.

Table 1. Sample Sizes

Population	Racecadotril	Placebo	Total
Full data set	86	82	168
For 48-h stool output	84	82	166
Estimated	5	3	8
Missing	2	0	2
For 24-h stool output	85	82	167
Estimated	4	2	6
Missing	1	0	1
Per-protocol population	58	63	121
For 48-h stool output	53	63	116
Estimated	0	0	0
Missing	5	0	5
For 24-h stool output	58	63	121
Estimated	0	0	0
Missing	0	0	0

Table 2. Clinical Characteristics of the 2 Patient Groups for Full Data Set

Characteristic	Racecadotril (n = 84)	Placebo (n = 82)
Age (*mo*)[a]	12.0 ± 0.9	13.6 ± 1.0
Weight (*kg*)[a]	8.54 ± 0.25	9.27 ± 0.25
Height (*m*)[a]	0.73 ± 0.01	0.75 ± 0.01
Sex (M/F)	51/38	50/33
Duration of diarrhea before inclusion (*days*)[a]	2.0 ± 0.2	1.9 ± 0.1
No. of stools passed in the 24 h before inclusion[a]	6.0 ± 0.3	6.5 ± 0.4
No. of patients rehydrated intravenously before inclusion	26	23
No. of patients receiving antidiarrheal treatment in the 48 h before inclusion	23	22
Abdominal circumference (*cm*)[a]	42.5 ± 0.4	43.0 ± 0.4
Temperature (*°C*)[a]	37.3 ± 0.1	37.4 ± 0.1

[a]Mean ± SEM.

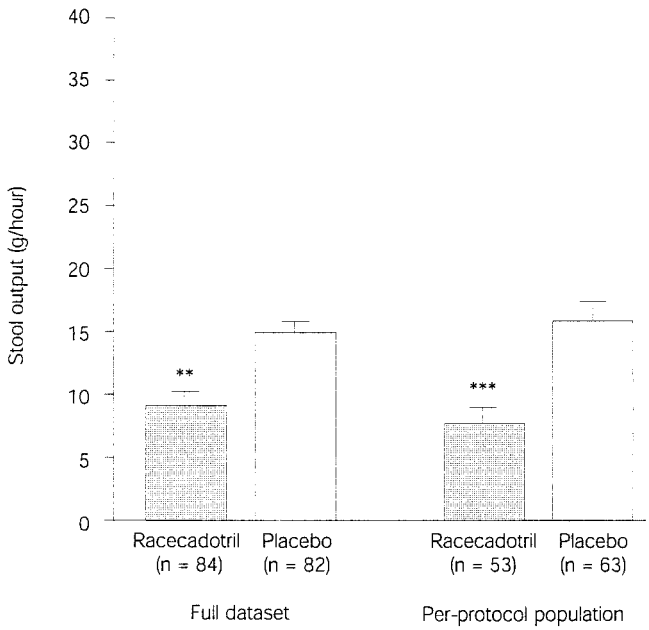

Figure 1. Mean (±SEM) stool output during the first 48 hours of treatment for the full data set and the per-protocol population (covariance analysis). $^{**}P = 0.009$; $^{***}P = 0.001$.

In the per-protocol population, there was no evidence of a difference between treatments depending on rotavirus status (rotavirus × treatment interaction; $P = 0.500$), nor was there evidence of any difference in stool weights according to rotavirus status ($P = 0.130$). This term was therefore not included in the model. Similar results to the analysis of the full data set were seen. Once again, stool output was significantly lower with racecadotril ($P = 0.001$); the estimate of the treatment difference indicated a 50% reduction in stool output (95% CI, 33%–75%). There was no evidence of any difference in treatment effect between sexes.

When patients were further analyzed in terms of rotavirus status for per-protocol analysis (Figure 2), racecadotril was found to be similarly effective in both rotavirus-positive and rotavirus-negative patients.

Secondary Efficacy Criteria

As Figure 3 shows, racecadotril produced a significant reduction in stool output compared with placebo within 24 hours (full data set; $P = 0.026$). Estimate of the treatment difference showed that the stool output with racecadotril for the full data set (n = 167) was approximately 65% of that with placebo during the first 24 hours of treatment (95% CI, 44%–95%). Analysis of the per-protocol population (n = 121) yielded similar results ($P = 0.015$ for racecadotril vs. placebo; 95% CI, 36%–90%).

Recovery rates were similar in both groups and for

Table 3. Microorganisms Identified in Stool Specimens at Inclusion

Microorganism	Racecadotril (n = 86)	Placebo (n = 82)
Rotavirus	32	35
(Missing data)	(14)	(10)
Adenovirus	3	4
Salmonella	4	4
E. coli (enteropathogenic)	4	2
Yersinia	1	—
No enteric pathogens	25	36

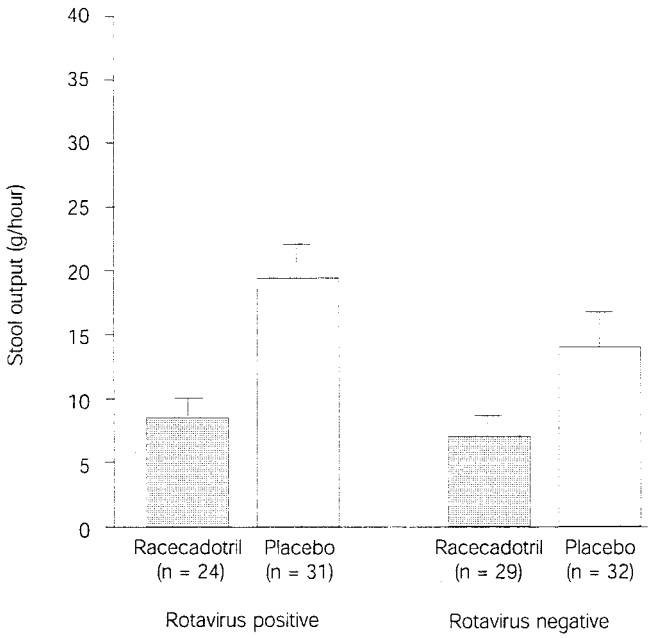

Figure 2. Mean (±SEM) stool output during the first 48 hours of treatment for rotavirus-positive and rotavirus-negative patients (per-protocol population). Treatment effect $P = 0.001$. Interaction rotavirus × treatment, $P = 0.500$.

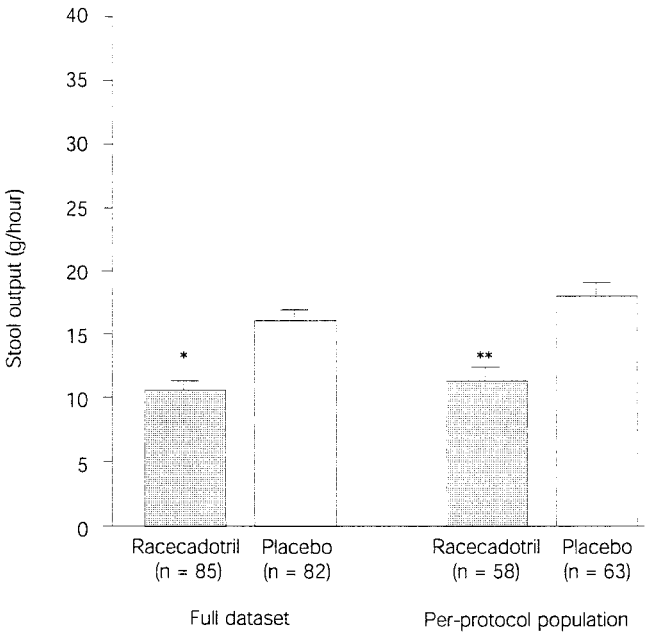

Figure 3. Mean (±SEM) stool output during the first 24 hours of treatment for the full data set and the per-protocol population. *P = 0.025. **P = 0.015.

both sexes. Recovery within 5 days or less was seen in 88% of male and 79% of female patients receiving racecadotril. The corresponding figures for placebo were 90% of male and 82% of female patients. When the time to recovery was analyzed using Kaplan–Meier curves (Figure 4), it was found that most patients recovered considerably earlier. For example, 50% of rotavirus-positive patients had recovered after 6.9 and 36 hours in the racecadotril and placebo groups, respectively (P = 0.02).

Both groups of patients had similar intakes of food and oral rehydration therapy during the study. However, intake of oral rehydration solution decreased more rapidly in patients on racecadotril, and the percentages of patients requiring oral rehydration on the second day of the study were 19% and 35%, respectively, in the racecadotril and placebo groups. An Na^+/K^+ ratio of less than 1 in the urine was found in 24.1% of patients receiving racecadotril and 53.3% of those receiving placebo (P = 0.01), suggesting greater rehydration with racecadotril. The mean (±SEM) Na^+/K^+ values were 2.74 ± 0.56 and 1.27 ± 0.16 in the racecadotril and placebo groups, respectively.

Tolerability

The incidence of adverse events was similar in both groups of patients. Nine patients in each group reported a total of 21 adverse events (10 with racecadotril and 11 with placebo). Most adverse events were classified as mild to moderate, and only 2 were thought by the physician to be possibly related to treatment: 1 case of moderate vomiting in a patient receiving racecadotril and 1 case of moderate facial eczema in a patient receiving placebo. The most common adverse event was vomiting, which was seen in 7 patients receiving racecadotril and 3 receiving placebo.

No differences were seen in abdominal circumference between groups, denoting a lack of abdominal distention with either treatment, in contrast to that commonly observed with the opiate drugs.

Discussion

The results of this study establish the efficacy of racecadotril as an adjunct to oral rehydration therapy and early continued feeding in infants and children with acute diarrhea. Patients who received racecadotril had a statistically significant reduction in stool output compared with those who received placebo; the mean reduction in stool output with racecadotril was 50% in the per-protocol population and 40% in the full data set. The rapidity of effect on stool output was shown by the fact that a significant difference between treatments was seen within the first 24 hours of treatment (P = 0.026). An effect on stool output was the main criterion defined by the World Health Organization to conclude that a drug possesses efficacy in acute diarrhea.[1,2] Indeed, such an effect indicates that treatment with racecadotril reduces hydroelectrolytic losses in children.

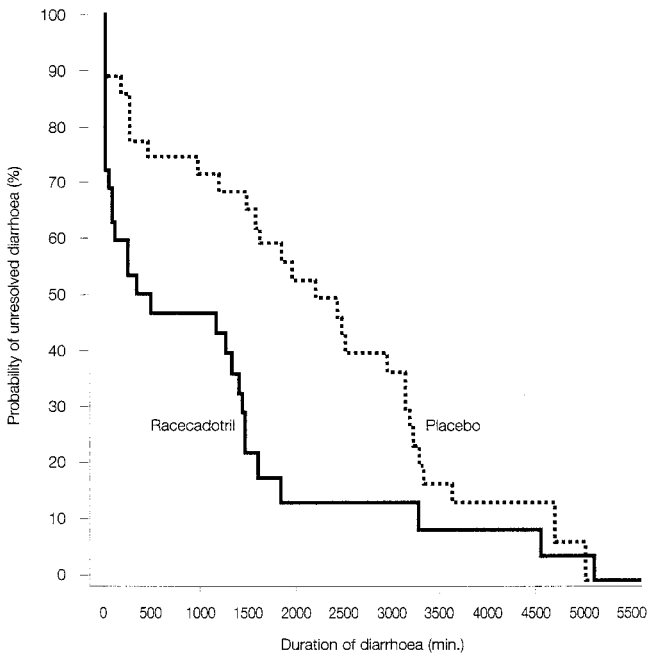

Figure 4. Time to recovery in rotavirus-positive patients receiving racecadotril (n = 32) and placebo (n = 35). P = 0.02.

Loperamide[14] and bismuth subsalicylate[15] have also been shown to reduce stool output in acute diarrhea. However, both drugs are contraindicated in some countries because of their side effects profiles,[16–20] and loperamide is contraindicated in any child younger than 2 years.[17,20] Other drugs have shown some effect on the duration of diarrhea and on stool characteristics and may prove beneficial for children, families, and the community.[21–24]

The efficacy of racecadotril in the current study was demonstrated compared with placebo in boys and girls aged 3 months to 4 years; neither the patients' need for rehydration before inclusion in the study nor the causative microorganism had any effect.

From the full data set, 47 patients were considered inevaluable (28 in the racecadotril and 19 in the placebo group) and were not included in the per-protocol population. The reasons for ineligibility included selective inclusion criteria, lack of microbiologic stool study, inclusion of patients of both sexes (separation of urine from stools is difficult in girls), and possibly the large number of centers. Although a large proportion of the total variance was unexplained, both treatment groups should have been affected equally.

Racecadotril was well tolerated by this pediatric population, and none of the adverse events in the racecadotril group were considered to be definitely related to drug treatment. This result confirms those of other studies in animals and humans that have demonstrated the specificity of action and good tolerability of racecadotril.[9,12,25–28]

Nearly 95% of patients had stool cultures performed; cultures showed the presence of bacteria in 15% and viruses in 63%, with a prevalence of rotavirus. These results confirm the published data. The number of children who presented with rotavirus allowed analysis of a subgroup characterized, as has been well established, by substantial intestinal hypersecretion. This was rapidly (as early as 24 hours) reduced by racecadotril (73%). In these patients, the time to recovery was significantly shorter with racecadotril than with placebo.

Racecadotril does not increase intestinal transit time,[11] suggesting a selective antisecretory action.[29,30] The observation in the present study of a significant enhancement of Na^+/K^+ ratio in the urine is consistent with this view, as is the tendency toward a decrease in intake of oral rehydration solution.

Randomized, placebo-controlled studies in adults have shown that the efficacy of racecadotril on symptoms of diarrhea such as stool consistency and weight and abdominal symptoms is combined with good tolerability and safety.[9,12]

In conclusion, the results of this study are in agreement with those from a study carried out in Peru[31] and indicate that racecadotril is an effective, well-tolerated, and safe adjunct to oral rehydration and nutritional therapy in infants and children with acute diarrhea in developed and developing countries.

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Giovanni Domenico Santorini (1681–1737) was born in Venice, the son of a pharmacist. Tempted, on one hand, to pursue a career in law or, on the other hand, to join the religious order of Jesuits, he chose rather to pursue the study of medicine at Bologna and Padua; from the university at Pisa he obtained his MD degree in 1701. On his return to Venice, he was named professor of medicine, where his duties included instruction in anatomy. He was known as an exacting dissector. His anatomic illustrations, published posthumously in 1765, were regarded as among the masterpieces of that century. In this work, in addition to his delineation of the accessory pancreatic duct, was the first description of the emissary veins that drain the dura mater covering the brain.

—Contributed by WILLIAM S. HAUBRICH, M.D.
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