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RACECADOTRIL IN THE TREATMENT OF ACUTE DIARRHEA IN CHILDREN: A META-ANALYSIS

AUTHORS: Robina Hao, M.D. *, Michelle De Vera, M.D. *, Emily Resurreccion, M.D.*
The Medical City, Ortigas Ave., Pasig City
3rd Place Winner, Poster Research Contest at the 17th Annual PIDSP Convention, 2010

KEYWORDS
diarrhea, racecadotril

ABSTRACT

Diarrhea has been the subject of considerable attention and effort. A variety of anti-secretory agents have been subjected to countless investigations including racecadotril as an adjunct therapy.

Objectives: To assess the effectiveness of racecadotril, along with oral rehydration solution, in the treatment of diarrhea.

Methods: The Cochrane Library and Pubmed were searched for trials; high sensitive search terms were used including "randomized controlled trials", "racecadotril" and "diarrhea". Outcome measures were stool output, duration of diarrhea, and number of bowel movements.

Data Collection and Analysis: Three reviewers assessed the methodological quality. Analysis was implemented with Review Manager 5 using standard mean difference as treatment measure.

Results: The search yielded 21 results; four of which fulfilled selection criteria. A total of 659 participants were given 1.5mg/kg of racecadotril. The meta-analysis showed that racecadotril is effective in reducing stool output in 48 hours compared to the control group. This finding was congruent for those positive for rotavirus and for the duration of the diarrhea. There were lesser children who revisited their doctors after 48 hours of treatment. The chance of cure after day seven of treatment was higher in the racecadotril group when compared to the control group. Racecadotril with ORS was comparable to ORS alone in terms of safety and tolerability.

Conclusion: There is evidence that the drug racecadotril holds promise in terms of reducing stool output, number of bowel movements and duration of diarrhea. However, well-designed randomized control trails with an adequate sample size and absence of any competitive interest in studying the efficacy and safety of racecadotril in acute diarrhea are needed before we reach any conclusion regarding the role of the drug in diarrhea.

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Pediatric acute gastroenteritis remains an important clinical illness commonly encountered by physicians. Its attendant problems of vomiting, diarrhea and dehydration continue to pose significant risks to children and are responsible for considerable health care expenditures. Estimates of the overall incidence of acute gastroenteritis range from 1.3 to 2.3 episodes of diarrhea per year in children under five years of age. Each year, more than 300 U.S. children die from this illness.[1] In the United States alone, gastroenteritis accounts for more than 220,000 hospital admissions per year in children less than five years of age, or approximately 10 percent of hospitalizations in this age group.[1] In the local setting, the Department of Health reported that for the past 20 years, diseases related to diarrhea has been the number one cause of morbidity and mortality. The incidence rate is as high as 1,997 per 100,000 population while the mortality rate is 6.7 percent per 100,000 population.[2]

Through the years, acute gastroenteritis has been the subject of considerable and worldwide attention and effort. Particular emphasis has been given to the development and promotion of inexpensive, easy-to-use oral rehydration solutions (ORS) for the treatment of diarrhea; it is designed to replace and maintain fluid levels combined with appropriate nutrition. However, despite the fact that the American Academy of Pediatrics and Centers for Disease Control and Prevention have published practice parameters for management of acute gastroenteritis, studies have shown ORS continues to be underused globally.[3] The main reason for such is that it does not reduce the frequency of bowel movement and fluid loss nor shorten the duration of diarrhea.[4] Hence, several measures have been investigated as adjunct therapy including a variety of non specific anti-diarrheal agents, anti-motility agents and anti-secretory agents such as racecadotril or acetorphan.

Description of Intervention

Racecadotril represents a promising new approach to the treatment of diarrhea. It is a lipophilic diesterified pro-drug of the enkephalinase inhibitor thiorphan. Racecadotril is rapidly converted to thiorphan, which then interacts specifically with the active site of enkephalinase to produce potent blockade of the enzyme, thus, preventing inactivation of endogenous opioid peptides (enkephalins) released by submucosal and myenteric neurons. Inhibition of enkephalinase by thiorphan increases the availability of opioids, which activate delta (δ) opioid receptors in the gastrointestinal tract.[5] This in turn leads to a reduction in cAMP mucosal levels, resulting in a reduction in the secretion of water and electrolytes into the intestinal lumen.

Data from studies carried out in both adults and children in Europe have provided evidence of the effectiveness of racecadotril in reducing stool output and duration of diarrhea. In the guidelines published in the May 2008 issue of the Journal of Pediatric Gastroenterology and Nutrition, one of the most innovative concepts included in these guidelines is the attention given to racecadotril or acetorphan. However, it was pointed out that there is a need for more trials, especially in the larger outpatient setting.[6]

For this reason, a systematic review of clinical trials is needed to determine the overall effect of racecadotril as an adjuvant therapy in the treatment of diarrhea among children.

OBJECTIVES

The main aim of the study is to assess the effectiveness and safety of racecadotril supplementation, along with oral rehydration solution, in the treatment of diarrhea in children.

This research specifically seeks to determine the efficacy and safety of racecadotril plus oral rehydration versus oral rehydration alone as well as determine the effect of racecadotril in reduction of stool output and the duration of diarrhea, the number of follow up visits to the

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emergency room or primary doctor, and the safety and tolerance of the drug in children .

MATERIALS AND METHODS

Criteria for considering studies for this review

Types of studies

The trials were randomized, placebo-controlled in a hospital setting or out-patient department.

Types of Participants

Participants of this study include pediatric patients of any age who were identified to have acute gastroenteritis or diarrhea and were seen in the hospital setting or as out patients. Diarrhea was defined as three or more loose stools in 24 hours regardless of etiology.

Types of Intervention

Patients for the experimental group received racecadotril at a dosage regimen of 1.5 mg/kg every eight hours as an adjunct to ORS. Patients in the control group received placebo treatment and ORS.

Types of outcome measures

Primary outcome measured were stool output in 48 hours and for the duration of diarrhea. Secondary outcome measures included: (1) number of follow up visits to pediatricians or emergency department after 48 hours of treatment; (2) cure rates defined as percentage of children who no longer exhibit more than three bowel movements in a day or with at least one formed stool in 24 hours; and (3) adverse effects.

Search methods for identification of studies

A highly sensitive search strategy was used for identifying randomized controlled trials. Both electronic and manual means of retrieving relevant studies were performed. PUBMED and COCHRANE Library were searched irrespective of language and publication status. The search strategy combined the search terms “randomized controlled trials”, “racecadotril” and “diarrhea”. The reference lists of all identified papers were searched for further information. Authors for unpublished studies were also contacted. Colleagues and other experts in the field were asked to identify unreported trials.

Data collection and analysis

Data extraction and management

Three reviewers independently assessed the methodological quality of the studies according to criteria used by the Cochrane Infectious Disease Group. Each of the co-authors independently assessed the suitability of each study for inclusion in the meta-analysis; the results of these individual assessments were then compared. In cases in which the original opinions varied, these differences were resolved through consensus by using the pre-established inclusion criteria or further written elaborations of said criteria, when necessary. Studies were assessed as high-quality if they fulfilled the following criteria: (1) treatment allocation was randomized with adequate concealment; (2) the treatment and control groups were balanced in terms of known determinants of outcome; (3) outcome assessment was done in a double-blind manner; (4) outcome detection methods used were similar for both groups; (5) treatment and control groups were treated equally in terms of other therapeutic and co-interventions received, frequency of follow-up and general quality of care; (6) an intention-to-treat analysis was conducted; and (7) drop-out rates between groups were comparable. On the other hand, studies were considered fair-quality if any subtle biases were present, such as: (1) unclear allocation concealment; (2) absence of blinding; and (3) no intent-to-treat analysis. And lastly, studies were considered low-quality if any of the frank biases was seen: (1) significant differences between the treatment and control group in terms of known predictors of outcome; (2) obvious differences in the general quality of care received by subjects in both groups; (3) marked difference in drop-out rates; and (4) outcome detection methods were different for both groups.

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Measures of treatment effect

All the outcome measures were combined and analyzed using a fixed-effect model in Review Manager (RevMan) Version 5. The outcomes were classified as dichotomous or continuous, based on the definition by the Cochrane Handbook of Systematic Reviews. The comparison was classified as dichotomous if the outcome is one of only two possible categorical responses. For dichotomous data, the risk ratio or the probability that an event will occur was determined for each comparison. The number of children who visited the emergency department, the number of children who were cured after seven days were all considered dichotomous in this study. Continuous data are those that can take any value in a specified range. The standardized mean difference (SMD) was used to combine results from studies using different ways of measuring the same concept. The stool output, the number of bowel movements in 48 hours, and the duration of diarrhea were all considered continuous data in this review.

Dealing with missing data

Missing statistics like standard deviation was obtained using the actual p values given in the studies. The Standard deviation was extracted by obtaining the corresponding t value from the table of the t distribution and transforming the t value into the standard deviation [SD = (mean change/ t value) / square root of $(1/n_1 + 1/n_2)$].

Assessment of heterogeneity

Heterogeneity was quantified using the chi square test for heterogeneity with $p < 0.10$ as the cut-off for significant heterogeneity. Heterogeneity can be interpreted as a percentage of total variation between studies that is attributable to heterogeneity rather than to chance. I^2 test was used to assess the degree of heterogeneity, i.e. $I^2 > 50\%$ suggests significant degree of heterogeneity or a value of 0% indicates no observed heterogeneity .

RESULTS

Description of studies

After searching PUBMED and the Cochrane Central Register of Controlled Trials (CENTRAL), a total of 13 studies were identified to be potentially eligible for inclusion in the meta-analysis. After thorough scrutiny, nine articles were excluded due to specific reasons (Figure 1). Four studies were left for more detailed review; however, there was a trial that was excluded because it compared racecadotril with loperamide. Reference lists of articles were reviewed and two more trials were identified. One trial fulfilled the selection criteria and was included in this review. The other study was excluded since it was not a randomized controlled trial. Four articles remained and these were used in this review

Four randomized controlled trials involving 659 participants (racecadotril = 332; control = 327) met our inclusion criteria.[7-10] Two of these studies were placebo-controlled (Salazar –Lindo 2000, Cezard 2001),**Error! Bookmark not defined.** **Error! Bookmark not defined.** and in the other two trials (Cojucaru 2002, Santos 2009), treatment was compared with no intervention. Majority of the trials were conducted in Europe: two trials were performed in France, (Cojucaru 2002, Cezard 2001),**Error! Bookmark not defined.** **Error! Bookmark not defined.** while the other one was in Spain (Santos 2009).**Error! Bookmark not defined.** A lone study was conducted in a third world country (Salazar-Lindo 2001).**Error! Bookmark not defined.** These studies used racecadotril plus ORS, as compared to receiving standard rehydration solution alone as treatment for children with acute gastroenteritis.

Participants of the studies were children aged three-to-48 months. Two studies were exclusively conducted among patients who were hospitalized (Salazar –Lindo 2000, Cezard 2001?),**Error! Bookmark not defined.** **Error! Bookmark not defined.** while the other two were done in an out-patient setting (Cojucaru 2002 , Santos 2009).[9,10] Although in all of the

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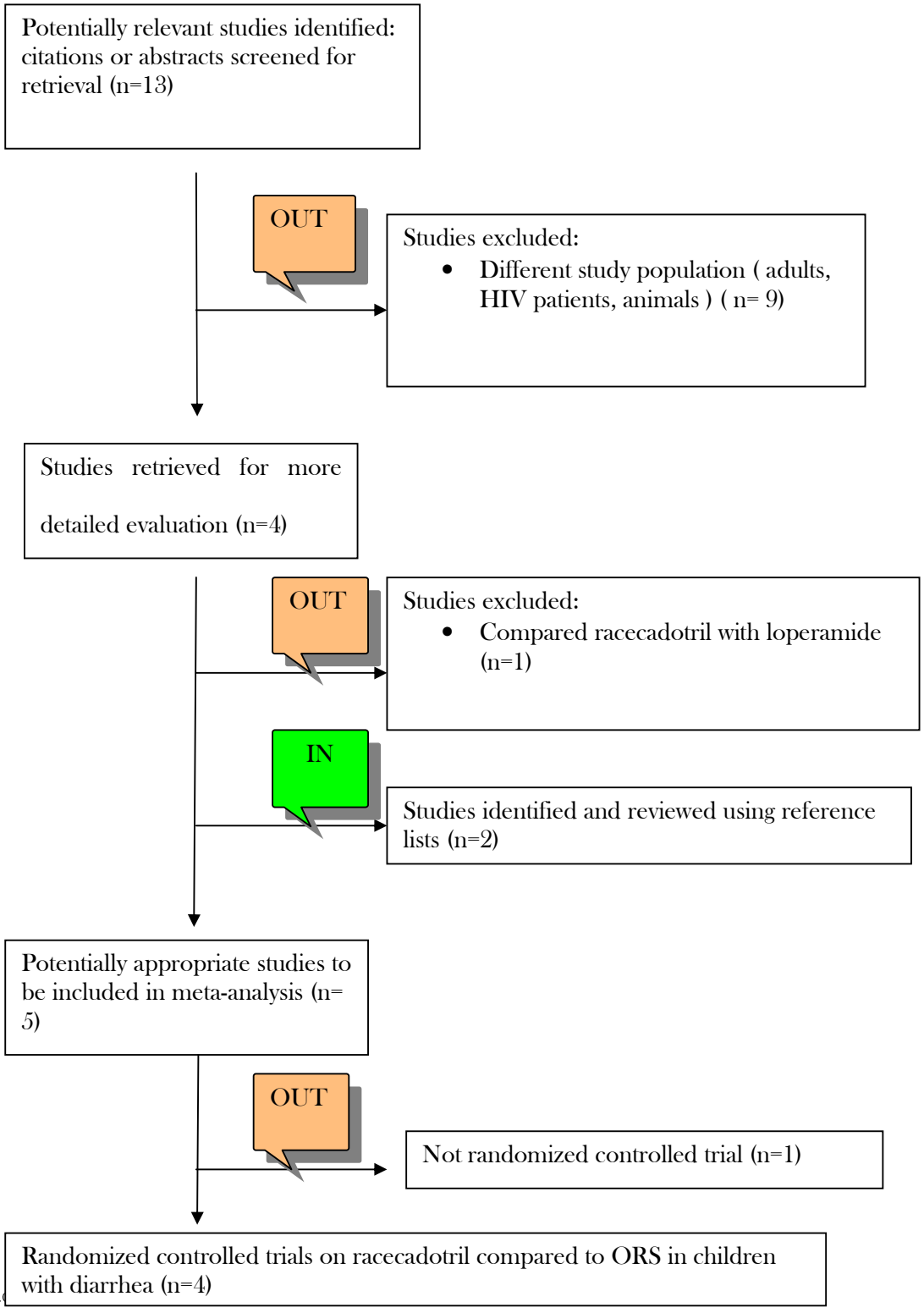
studies conducted the participants recruited had acute gastroenteritis, there were variations in the criteria for diarrhea and its duration before they were enrolled. Excluded subjects from one study were those who had chronic diarrhea or had weight for age deficit of 20% or with

Figure 1. Flow Diagram of Included Studies



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systemic illness or those who received anti-diarrheals or antibiotics (Cezard 2001).

One study (Santos 2009) mentioned specifically that it excluded subjects who had previous exposure to antidiarrheals or antibiotics. Subjects were likewise excluded if they had more than seven days of symptoms and allergy to any component of the drug. Boys with blood and stool, severe dehydration, or any concomitant serious illness were excluded in the study conducted by Salazar-Lindo, et al. The etiology of diarrhea was mentioned in three trials naming rotavirus as the predominant agent (Salazar-Lindo 2000, Cezard 2001, Santos 2009). None of the studies provided data for the hydration status of the subjects. All four studies provided information about adverse events which included mild hypokalemia, ileus, mild fever, respiratory illness (rhinitis, bronchitis, coughing, pneumonia, upper respiratory infection) and exanthem. Outcome measured was stool output using g/kg or g/hr, however only two studies provided data on stool output during the first 48 hours (Salazar–Lindo 2000, Cezard 2001).[7,8] Furthermore, two studies reported stool output in terms of presence of positive culture on rotavirus (Salazar –Lindo 2000, Cezard 2001). All RCT's provided information on the duration of diarrhea, although, reporting of outcomes varied in terms of measurement. Number of follow up visits were reported in two studies (Cojucaru 2002, Santos 2009)[9,10] while cure rates data were given in three trials (Salazar –Lindo 2000, Cojucaru 2002, Santos 2009). [7,8,10]

Excluded Studies

The brief list of excluded studies is presented in the references. It does not contain all articles identified by the comprehensive search as suggested by the Cochrane Handbook version 5. It only covers all studies that may on the surface appear to have met the eligibility criteria, but on further inspection, do not. Also included are studies that do not meet the criteria but are well known and are likely to be thought of by readers.

Risk of bias in included studies

All of the trials included in this study were randomized at level of treatment. However, not all studies described their method of allocation generation concealment. These studies were assessed to have an unclear risk for bias (Salazar-Lindo 2000, Cezard 2001, Cojucaru 2002,). In all four trials, only two (Salazar-Lindo 2000, Cezard 2001) met the criteria for blinding, which suggests low risk for bias for the former and high risk of bias for the other two trials(Cojucaru 2002, Santos 2009). In the criteria for selective outcome reporting and frank bias, all were met; hence, a low risk of bias for these key domains. Incomplete outcome of data were addressed by two trials (Cezard 2001, Santos 2009), one study (Cojucaru 2002) had a potential high risk of bias, while the other study remained uncertain (Salazar-Lindo 2000).

Effects of interventions

Stool output in 48 hours

Two studies assessed the effect of racecadotril on stool output in 48 hours (Salazar-Lindo 2000, Cezard 2001). Standard mean difference (SMD) was taken for the two trials comparing racecadotril with placebo in decreasing the stool output from baseline to that after the treatment with racecadotril. Figure 4.1 shows the comparison of the two groups regardless of the etiology of the gastroenteritis. A significant difference favoring the use of racecadotril in decreasing the stool output was noted (p= 0.000001). Test for heterogeneity was not statistically significant (p=0.86).

Stool volume in rotavirus positive patients

When patients were further analyzed in terms of rotavirus status, the two studies (Salazar-Lindo 2000, Cezard 2001) demonstrated once more a significant difference between racecadotril and placebo treatments favoring the experimental group. SMD for stool output was -0.99 (95% CI -1.36 to -0.62, Z=5.22, p < 0.00001) [Figure 4.2]. The

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Table 1. Included Studies in the Meta Analysis

AUTHOR	SUBJECT (N)	AGE	INCLUSION/	Etiology	TREATMENT REGIMEN	Duration of treatment	OUTCOME
Santos (Spain)	189 children	3-48 months Out patient	3 looses stools within 24 hrs	Viruses (50.5%) Rotavirus 23.6% Bacteria (8.7%)	N= 88 10 mg every 8 hr if less than 9kg; 20 mg every 8 hrs if weight bet 9-13 kg; 30 mg every 8 hrs if more than 13 kg	Until 2 stools of normal consistency, no bowel movement in 12 hrs, maximum of 7 days	Stool volume in rotavirus positive patients Number of bowel movements after 48 hrs, number of children who followed up duration of diarrhea in days
Salazar –Lindo (Peru)	135 children	3-48 months mean age: 13 months; hospitalized	Acute watery diarrhea(3 or more stools in 24 hrs before admission, at least 1 stool within 4-6 hrs after admission	Bacteria (34%) Rotavirus (54%)	N= 68 Racecadotril 1.5 mg/kg every 8 hr	5 days or until cessation of diarrhea	Stool output in 48 hrs in g/kg intake of ORS, stool output in rotavirus positive boys
Cezard (France)	168 children	Mean age: 12.8 months (range 3.5-6.8 mo) hospitalized	Acute watery diarrhea 3 watery stools per day at least 72 hrs	Rotavirus(40 %) Adenovirus(4 %) Salmonella(4 %) E.coli(3%) Negative culture (36%)	N=89 racecadotril 1.5 mg/kg every 8hr	5 days or until cessation of diarrhea	Stool output in g/hr, stool output in rotavirus positive in 48 hrs
Cojucaru (France)	164 children	3-48 months, outpatient	Acute diarrhea more that 3 stools per day	No data	N=81 racecadotril (3-10mg/day if less than 9 kg; 3-20 mg/day if more than 9 kg	Until cessation of diarrhea (no loose stools for 12 hrs, maximum of 7 days	Number of bowel movements in 48 hr, duration of diarrhea in hours, number of children who followed up

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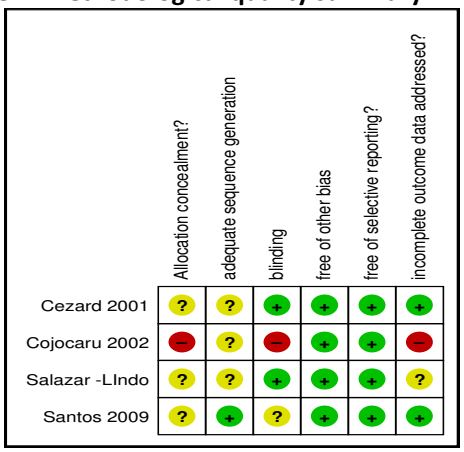
Figure 2. Methodological quality summary



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trials were shown to be homogenous (p = 0.18, I^2 = 44%).

Number of Bowel Movements in 48 hours

Two studies assessed the effects of racecadotril on the number of bowel movements in 48 hours (Cojucaru 2002, Santos 2009). SMD for the two trials comparing racecadotril to placebo in reducing bowel movements from baseline to that after treatment was -0.36 (95% CI -0.57 to -0.14 , Z=3.30, p < 0.0010). However test for heterogeneity was statistically significant (p=01, I^2 = 83%).

Duration of diarrhea

In the trials conducted by Cojucaru and Santos, there was a significant difference between patients who received racecadotril in terms of the duration of diarrhea with an SMD of -0.63 (95% CI -0.85 to -0.41, Z=5.73, p<0.00001) [Figure 4.4]. However, the studies were significantly heterogeneous (p = 0.002, I^2 =90%).

All randomized controlled trials provided data on duration of diarrhea; however, the reporting of outcomes was inconsistent with some missing data so pooling of all studies was not possible.

In the study by Salazar-Lindo, et al, duration of diarrhea differed depending on whether it was caused by rotavirus or not. As compared to placebo, the duration of diarrhea for patients who were negative for rotavirus was 28 hours vs. 52 hours; while the duration for those who were positive for rotavirus was 28 hours vs. 72 hours. Cezard on the other hand reported reduced time to recovery (8 hours) for rotavirus positive patients in the racecadotril group versus the control (26 hours). Cojucaru, et al, reported that duration of diarrhea was shorter for the experimental group versus the control (97 ±35.6 hr vs. 137±42.4). Lastly, Santos calculated an average of four days (± 2.1 SD) of diarrhea in the racecadotril group and 4.7 days (± 2.2 SD) in the hydration group.

Number of children who visited the ER or their pediatricians after 48 hours of treatment

The number of children who visited their pediatricians or the emergency department after treatment was reported in two studies (Cojucaru 2001, Santos 2009). There was a statistical difference noted favoring those who were given racecadotril. (RR=0.62, 95% CI 0.40 to 0.97, Z=2.10 p=0.04). Homogeneity was found in the two studies as well. (p=0.41 I^2 =0%).

Cure rates in 7 days

Three studies assessed recovery of children after treatment (Salazar-Lindo 2000, Cezard 2001, Santos 2009). Pooled relative risk of children who recovered after treatment from three trials was 0.70 (95%CI 0 .49 to 0.99). A significant difference favoring the use of racecadotril was noted (p= 0.05). Test for heterogeneity was not statistically significant (p=0.17 I^2 =43%) (Figure 4. 5).

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Figure 4.1. Stool volume in 48 hours measured in g/hr or g/kg

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cezard 2001	9	9.2	84	15	9.1	82	55.3%	-0.65 [-0.97, -0.34]
Salazar -LIndo 2000	92	99	68	170	122.8	67	44.7%	-0.70 [-1.04, -0.35]
Total (95% CI)			**152**			**149**	**100.0%**	**-0.67 [-0.90, -0.44]**

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 5.67 (P < 0.00001)

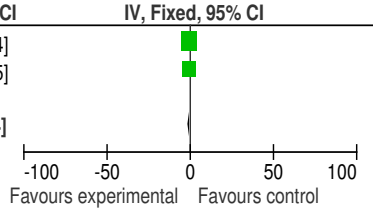

Figure 4.2. Stool volume in g/hr or g/kg in rotavirus- positive patients

Study or Subgroup	Favours experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cezard 2001	8.5	7.3	24	19	8.4	31	39.7%	-1.30 [-1.89, -0.71]
Salazar -LIndo 2000	105	99	34	195	124.9	39	60.3%	-0.78 [-1.26, -0.31]
Total (95% CI)			**58**			**70**	**100.0%**	**-0.99 [-1.36, -0.62]**

Heterogeneity: Chi² = 1.80, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 5.22 (P < 0.00001)

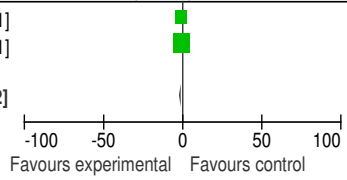

Figure 4.3. Number of bowel movements after 48 hours

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cojocaru 2002	6.8	3.8	81	9.5	4.5	83	45.3%	-0.64 [-0.96, -0.33]
Santos 2009	3.8	2.4	94	4.1	2.7	94	54.7%	-0.12 [-0.40, 0.17]
Total (95% CI)			**175**			**177**	**100.0%**	**-0.36 [-0.57, -0.14]**

Heterogeneity: Chi² = 5.92, df = 1 (P = 0.01); I² = 83%
Test for overall effect: Z = 3.30 (P = 0.0010)

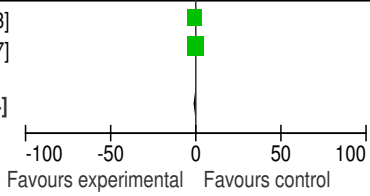

Figure 4.4. Duration of diarrhea in days

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cojocaru 2002	4.05	1.48	81	5.73	1.77	83	43.8%	-1.02 [-1.35, -0.70]
Santos 2009	4	2.1	94	4.7	2.2	94	56.2%	-0.32 [-0.61, -0.04]
Total (95% CI)			**175**			**177**	**100.0%**	**-0.63 [-0.85, -0.41]**

Heterogeneity: Chi² = 9.94, df = 1 (P = 0.002); I² = 90%
Test for overall effect: Z = 5.73 (P < 0.00001)

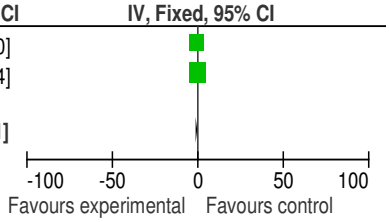

Figure 4.5. Number of children who followed up after treatment

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cojocaru 2002	5	81	8	83	22.9%	0.64 [0.22, 1.88]
Santos 2009	14	76	27	78	77.1%	0.53 [0.30, 0.93]
Total (95% CI)		**157**		**161**	**100.0%**	**0.56 [0.34, 0.92]**
Total events	19		35			

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)

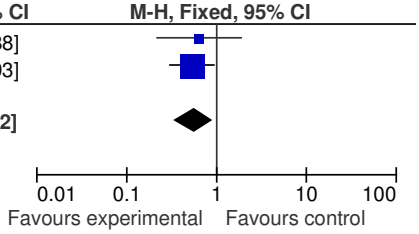

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Figure 4.6. Cure rates of children in 7 days

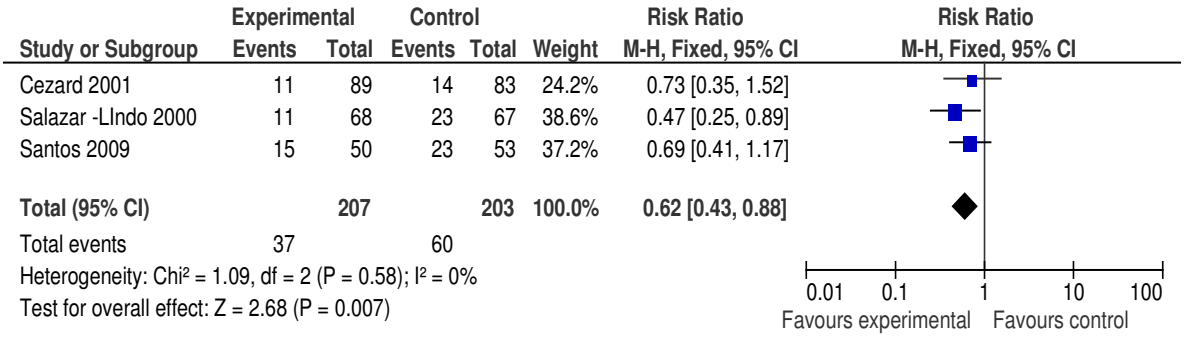
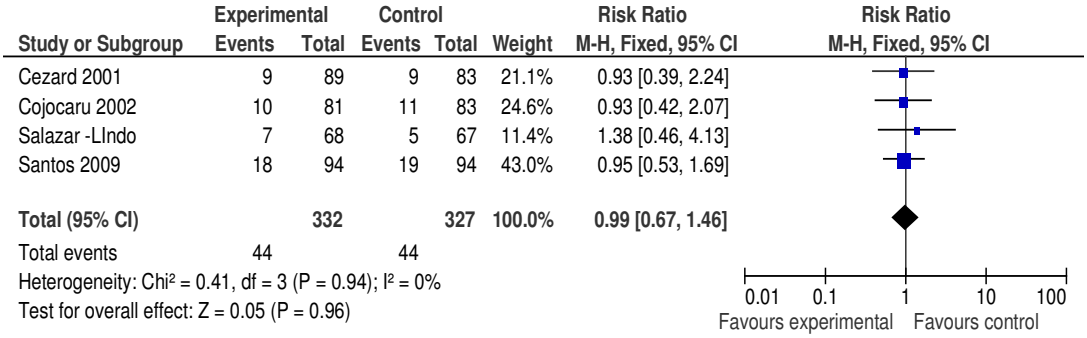


Figure 4.7. Adverse events



Adverse events

All four studies provided information about adverse events. None demonstrated a significant difference in the frequency of adverse events between the experimental group and control group. Reported adverse events for all trials were vomiting, mild fever, ileus, mild hypokalemia, poor taste, exanthem and respiratory problems (Figure 4.6).

DISCUSSION

Summary of main results

The meta-analysis of pooled data from 4 RCTs (racecadotril = 332, control = 327) showed that in children with acute gastroenteritis, whether caused by rotavirus or not, racecadotril significantly reduced stool output in 48 hours and decreased the duration of diarrhea as compared with ORS alone. These were the primary outcomes measured in the studies. For the secondary outcomes measured, racecadotril likewise was significantly better than the control group in reducing the number of children who revisited their doctors after 48 hours of treatment. The chance for cure in seven days was also significantly higher in the racecadotril group. The safety and tolerability was comparable to the control group.

Overall completeness and applicability of evidence

The findings on stool output, number of bowel movements and duration of diarrhea are worth reporting because quantitative diarrhea criteria are recommended by the World Health Organization for the evaluation of therapeutic agents in the management of acute diarrhea.[11]

Unfortunately, the measure on the duration of diarrhea is not considered optimal in our meta-analysis. Because the units of reporting the duration of diarrhea were inconsistent among the studies, there was a need for us to standardize the results to a uniform scale before eventually combining them (standardized mean difference method). This makes the overall treatment effect difficult to interpret as it is in units of standard deviations rather than in any of the units used in the individual trials. It is also unclear as to what constitutes a clinically important change.[12, 13]

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For these reasons, homogenous data were not present as well.

Another important outcome measured was the effect of racecadotril on stool output. Although all four trials suggest benefit of racecadotril therapy as an adjunct in reduction of stool output or number of bowel movements, the authors point out several factors that should be taken into consideration. First, two studies included were in hospital-based settings while the other two were in out-patient settings: this makes it difficult to generalize the results. This difference may be related to severity of diarrhea; those admitted to the hospital may have been more severely dehydrated and thus more responsive to treatment. Evaluation within these subgroups is then warranted. Perhaps more studies from the outpatient department are needed since treatments there are more standardized. Second, most of the studies showed rotavirus as the predominant etiologic agent for the gastroenteritis. Our analysis showed that racecadotril was particularly efficient in rotavirus-positive children. This may be due to two events: the higher stool output in rotavirus-positive patients and pharmacological properties of racecadotril. Rotavirus increases the severity of diarrhea, especially with regard to stool output. The increased efficacy of racecadotril in rotavirus patients could be related to the fact that a pharmacological effect is more likely shown when symptoms are more pronounced. Rotavirus induces a secretory process at the enterocyte level that could be counteracted by racecadotril. After all, racecadotril is a synthetic enkephalinase inhibitor and its anti-diarrheal effects are attributed to its anti-secretory properties mediated by inactivating endogenous opioid peptides, enkephalins, secreted by myenteric and submucus plexus in the digestive tract. Additionally, racecadotril works best when hypersecretion is present.[14] This pharmacologic property of racecadotril may also be the reason why there was also a significant decrease in stool volume among patients who tested positive with rotavirus and received racecadotril. In actuality, there are various agents that can cause acute gastroenteritis. Perhaps a better analysis can be done on specific agents alone or pooling of data on all trials, irrespective of etiology.

Racecadotril was better in terms of cure rate and number of follow up consultations after treatment. It should be pointed yet again, though, that the settings were different for the various trials. Studies done in the outpatient settings lacked monitoring of the administration or response to treatment, hence, no direct observation was made which could provide bias to our analysis.

In general, racecadotril has been reported to have a good safety profile; this was confirmed by our review which showed that the side effects were similar with placebo and no serious events related to study treatment was observed in all trials. This finding then confirms that racecadotril is a safe drug for children. Even in adults, majority of authors agree that the drug is indeed well tolerated.[15, 16]

Quality of evidence and the potential biases in the review process

Meta-analysis techniques are increasingly being used to consolidate results from multiple studies of the same topic and to develop evidence-based policies for clinical practice and public health programming. The reliability of the conclusions derived from meta-analyses depend on the methodological quality of the original studies, the appropriateness of the study, inclusion criteria, and the thoroughness of the review and synthesis of information.**Error! Bookmark not defined.** Given the fact that none of the four trials included in our analysis seemed methodologically sound, this posed a potential problem. For one, all trials had unclear or inadequate allocation concealment which may result in overestimation. Secondly, two trials were not blinded, which can be a source of potential bias. Thirdly, we cannot fully exclude publication bias. According to Bhan, et al, there

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was a drug company that did a multi-center trial on racecadotril which was not published.[17] This raises the issue that the scientific evidence shown to physicians is not the total evidence obtained through clinical trials and may represent selective presentation of trials. While we recognize the hesitation of journals to publish negative trials it is nevertheless an issue of concern. Another source of bias is that two trials were funded by a drug company; given these considerations, some caution must be exercised in interpreting strength of evidence. Lastly, although the included studies were not significantly heterogeneous, given the small number of studies, statistical conclusions on determinants of heterogeneity might be still be flawed.

Agreements and disagreements with other studies of reviews

The result of this review is in agreement with a systematic review done by Szajeweska who concluded that in three relatively small RCT's with some methodological problems, racecadotril was effective in reducing the volume of stool output and in reducing duration of diarrhea. An RCT done in 110 adults with severe cholera reported comparable total stool output, total ORS intake or duration of diarrhea between the racecadotril and loperamide groups.[18] A recent RCT comparing racecadotril and loperamide for stopping acute diarrhea in adults found comparable clinical success rates and mean duration of diarrhea. More patients on loperamide had reactive constipation; itching was notably higher in the racecadotril group.[19] Both studies mentioned though compared racecadotril with loperamide and were carried out in adults. Turk, et al. on the other hand, did a multicentre, parallel-group, double-blind, placebo-controlled study comparing racecadotril with loperamide which found no significant differences in fecal output nor duration of diarrhea. However, there were differences in tolerance, with a lower incidence of constipation and fewer associated treatment modifications in the racecadotril group. It is important to note that racecadotril was compared with loperamide.[20]

CONCLUSIONS/RECOMMENDATIONS

Implications for practice and research

There seems to be evidence that the drug racecadotril holds promise in terms of improving diarrhea quantitatively. However, well-designed RCT's, adequate sample size and absence of any competitive interest in studying the efficacy and safety of racecadotril in acute diarrhea, are needed before we reach a more valid and generalized conclusion regarding the role of the drug in the management of acute diarrhea.

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