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Systematic review: racecadotril in the treatment of acute diarrhoea in children

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SUMMARY

Background
Racecadotril (acetorphan) is an antisecretory drug that exerts its anti-diarrhoeal effects by inhibiting intestinal enkephalinase.

Aim
To summarize studies testing the efficacy and safety of racecadotril for treating children with acute gastroenteritis.

Methods
Reports were gathered by searching electronic databases MEDLINE, EMBASE, the Cochrane Library (all up to April 2007), relevant journals, and bibliographies of reviewed articles. Only randomized-controlled trials were included.

Results
Three randomized-controlled trials (471 participants) met the inclusion criteria. Two trials reported stool output, and data suggested less stool output in the racecadotril group than in the control group. The duration of diarrhoea was significantly reduced in the three trials reporting this outcome. Achievement of a cure by day 5 was similar in both groups. Adverse effects were similar in both groups.

Conclusions
The small number of included trials provided some evidence in favour of the use of racecadotril over placebo or no intervention, to reduce the stool output and duration of diarrhoea in children with acute gastroenteritis. However, more data in out-patients are needed. The safety as well as the cost-effectiveness of the therapy should be explored, before routine therapy with racecadotril is recommended.

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BACKGROUND

Acute gastroenteritis is generally a self-limited illness lasting 5–7 days, and thus the main aim of treatment was to prevent dehydration, metabolic acidosis and electrolyte disturbances. In the vast majority of cases of acute gastroenteritis with mild or moderate dehydration, this can be treated with oral rehydration solutions. Despite the proven efficacy of oral rehydration, it remains underused.[1] The main reason for this is that an oral rehydration solution neither reduces the frequency of bowel movements and fluid loss nor shortens the duration of illness, which decreases its acceptance and prompts interest in adjunctive treatments. Not only parents and carers, but also doctors demand safe, effective and inexpensive agents as an additional treatment that will visibly reduce the frequency and fluidity of stools during gastroenteritis.

Racecadotril (acetorphan) is an antisecretory drug that exerts its antidiarrhoeal effects by inhibiting intestinal enkephalinase; this prevents the breakdown of endogenous opioids (enkephalins) in the gastrointestinal tract and reduces the secretion of water and electrolytes into the gut without interfering with motility.[2] Some randomized-controlled trials (RCTs) have proven its efficacy in adults and in children; however, there is no systematic review of the evidence for its efficacy. Thus, this review was undertaken to assess the overall effectiveness of racecadotril in the treatment of acute gastroenteritis in children and to provide some guidance with respect to future research. This review was initiated as part of the development of the guidelines for the management of acute gastroenteritis in children (submitted).

OBJECTIVE

To systematically evaluate the effectiveness and safety of racecadotril for treating acute gastroenteritis in children.

METHODS

Inclusion and exclusion criteria

We included RCTs in which the intervention was racecadotril compared with a placebo or no intervention for children with acute diarrhoea. While we aimed to include trials in which diarrhoea is defined as three or more loose stools per day, trials in which other definitions of diarrhoea used were also included. The **primary** outcome measures were stool output and the duration of the diarrhoea. The **secondary** outcome measures were stool frequency, the percentage of children with diarrhoea at various time intervals (as specified by the investigators), the percentage of children with diarrhoea lasting longer than 7 days, vomiting and adverse effects. In addition to these outcomes, *a priori* we decided to extract other data reported by the investigators if clinically relevant to the current review. Children could be seen in any setting.

Search strategy

We searched MEDLINE (1966 to April 2007), EMBASE (1980 to April 2007), The Cochrane Database of Systematic Reviews (Issue 2, 2007) and The Cochrane Controlled Trials Register (Issue 2, 2007) for RCTs comparing racecadotril with placebo or no intervention in children with acute diarrhoea (as defined by the investigators). Searches were performed using the following text word terms and MESH headings: diarrhea/diarrhoea, diarrh*, gastroenteritis, racecadotril and acetorphan*. Furthermore, the reference lists from the original studies and review articles were used to identify additional studies.

Data extraction

Each author independently assessed the titles and abstracts of potential papers identified according to the above-described search strategy. All potentially relevant articles were retained, and the full text of these studies was examined to determine which studies satisfied the inclusion criteria. Data extraction were carried out independently by all reviewers, using standard data extraction forms. We compared the extracted data to identify errors. Discrepancies between the reviewers were resolved by discussion.

Study quality

The reviewers independently, but without blinding to the authorship or journal, assessed the included trials for: allocation concealment; blinding of investigators, participants, outcome assessors and data analysis (yes/no/not reported); intention-to-treat analysis (yes/no) and completeness of follow-up.

Table 1. Characteristics of included studies

Study	Allocation concealment	Blinding	IT	FU	Population	Inclusion criteria	Aetiology	Intervention	Comparison	Duration of intervention
Salazar-Lindo *et al.*[4]	Adequate	Double-blind	Yes	83%	N = 112/135 boys 3–35 months (mean age 13 months); hospitalized (Peru)	Watery diarrhoea ≤5 days duration (≥3 diarrhoeal stools within 24 h of admission to the hospital, and ≥1 diarrhoeal stool within 4–6 h after admission)	HRV 54%	N = 68 Racecadotril orally 1.5 mg/kg every 8 h	N = 67 Placebo	For 5 days or until cessation of diarrhoea
Cezard *et al.*[5]	Unclear	Double-blind	Yes	98% (70% per-protocol analysis)	N = 168/172 children 3–48 months (mean age 12.8 months); hospitalized (France)	Acute watery diarrhoea (≥3 watery stools/day for at least 72 h)	HRV 40%; bacteria 9%	N = 89 Racecadotril 1.5 mg/kg every 8 h	N = 83 Placebo	For 5 days or until cessation of diarrhoea
Cojocaru *et al.*[6]	No	No	Yes	99%	N = 164/166 children 3–36 months; out-patients and hospitalized (France)	Acute diarrhoea (>3 loose stools per 12 h)	No data	N = 81 Racecadotril (3 × 10 mg/day if <9 kg; 3 × 20 mg/day if >9 kg)	N = 83 No intervention	Until cessation of diarrhoea (no loose stools for 12 h); maximum for 7 days

FU, completeness to follow-up; ITT, intention-to treat analysis; HRV, human rotavirus.

Statistical analysis

The data were analysed using REVIEW MANAGER 4.2.8 (version date 25 July 2005; The Cochrane Collaboration). The mean difference (MD) between the treatment and control groups was selected to represent the difference in continuous outcomes. The standardized mean difference (SMD) was used to combine results from studies using different ways of measuring the same concept (e.g. in our review, two trials measured stool output, but they used different units). By expressing the effects as a standardized value, the results can be combined since they have no units.[3] The binary measure for individual studies and pooled statistics is reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (CI). The weights given to each study are based on the inverse of the variance. We also estimated outcomes from figures in studies that provided results only in figures but not in numbers.

Heterogeneity was quantified by χ^2 and I^2, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. If there was heterogeneity, we present results of both random effect and fixed effect models for the main analysis. For simplicity, if heterogeneity was not revealed, we present results of only the fixed effects model. Because of the limited data, we did not test for publication bias.

RESULTS

Table 1 summarizes the characteristics of the included trials. Three RCTs involving 471 participants (238 in the experimental group and 233 in the control group) met our predefined inclusion criteria.[4–6] Two studies were placebo controlled,[4, 5] and in one trial, treatment was compared with no intervention.[6] Two trials were performed in France, and the remaining one trial was conducted in a developing country.[4] Excluded trials, including the reasons for exclusion, are summarized in Table 2.[7–12]

Participants were children aged 3–48 months. Two studies were conducted exclusively in hospitalized patients. Although all studies recruited participants with acute diarrhoea, there were variations in the criteria for diarrhoea and for its duration before enrolment. The aetiology of the diarrhoea was determined

Table 2. Characteristics of excluded trials

Study	Reason for exclusion
Alam *et al.*[11]	Review
Cezard *et al.*[10]	Letter
Nagpal *et al.*[9]	Review
Bhan *et al.*[8]	Editorial
Rao *et al.*[7]	Letter
Turck *et al.*[12]	RCT comparing racecadotril with loperamide

in two RCTs;[4, 5] in those two studies, rotavirus was a predominant aetiological agent (see Table 1). None of the studies provided data on the hydration status of participants before inclusion. The treatment was administered in similar doses for 5–7 days.

Methodological quality

The methodological quality of the studies is reported in Table 1. Two studies received pharmaceutical company sponsorship;[4, 5] the source of funding is not clear in one trial.[6] The investigators in two studies failed to report on the generation of an allocation sequence, and the generation of allocation concealment was inadequate in one study. Except for one trial,[4] concealment of allocation was unclear. Three studies conducted an intention-to-treat analysis. Only two studies were double-blind,[4, 5] and one study was open.[6]

Data synthesis

48 h stool output

Two RCTs provided data on stool output during rehydration (Figure 1).[4, 5] These trials measured stool output in various ways using different units (g/kg vs. g/h). We therefore used the SMD to analyse these data (after conversion of the documented standard errors into the standard deviations). The pooled SMD for all patients is −0.67 (95% CI: −0.9 to −0.44), which indicates that those in the racecadotril group had significantly less stool output than those in the control group. We also found a statistically significant difference in the stool volume in a subgroup of rotavirus-positive patients (two RCTs, n = 128, SMD −1.01, 95% CI: −1.52 to −0.51, random effect model). We detected statistical heterogeneity between the trials (χ^2 = 1.8, d.f. = 1, P = 0.018; I^2 = 44.5%).

Total stool output

One RCT provided data on total stool output.[4] The mean total stool output at 5 days was lower in the racecadotril group than in the placebo group (n = 135, MD −174 g/kg, 95% CI: −185 to −163, relative risk reduction 53%, $P < 0.001$). The same effect was found in rotavirus-positive boys (n = 73, MD −223 g/kg, 95% CI: −240 to −206).

Duration of diarrhoea

All RCTs provided data on the duration of the diarrhoea; however, the reporting of outcomes was inconsistent, and therefore, formal pooling of data was not possible. In the study by Salazar-Lindo *et al.*,[4] the median duration of diarrhoea was significantly reduced in the racecadotril group compared with controls, both in the rotavirus-positive boys (28 h vs. 72 h, $P < 0.001$) and in the rotavirus-negative boys (28 h vs. 52 h, $P < 0.001$). Cezard *et al.*[5] reported a significantly reduced time until recovery in rotavirus-positive patients receiving racecadotril (n = 32) compared to placebo (n = 35; P = 0.02). Cojocaru *et al.*[6] found a significantly reduced duration of diarrhoea in those treated with racecadotril compared with controls who received no intervention (n = 164, 97.2 ± 36 h vs. 138 ± 42; MD −40.5 h, 95% CI: −52.5 to −28.5).

Cure ≤5 days

This outcome was estimated in two RCTs (n = 307).[4, 5] The pooled results showed no significant difference between the racecadotril group and the control group (RR 1.1, 95% CI: 0.97–1.21, in fixed effect model, and 1.1, 95% CI: 0.83–1.46, in random effect model; Figure 2).

Other outcomes

Based on the results of the study by Salazar-Lindo *et al.*,[4] the mean oral rehydration intake was reduced in the racecadotril group compared with the control group on day 1 (439 ± 49 vs. 658 ± 69 mL; P-value not reported) and day 2 (414 ± 68 vs. 640 ± 48 mL, P-value not reported). Also, the total intake of oral rehydration solution was significantly lower in the racecadotril group ($P < 0.001$). In another RCT, racecadotril compared to the control group significantly

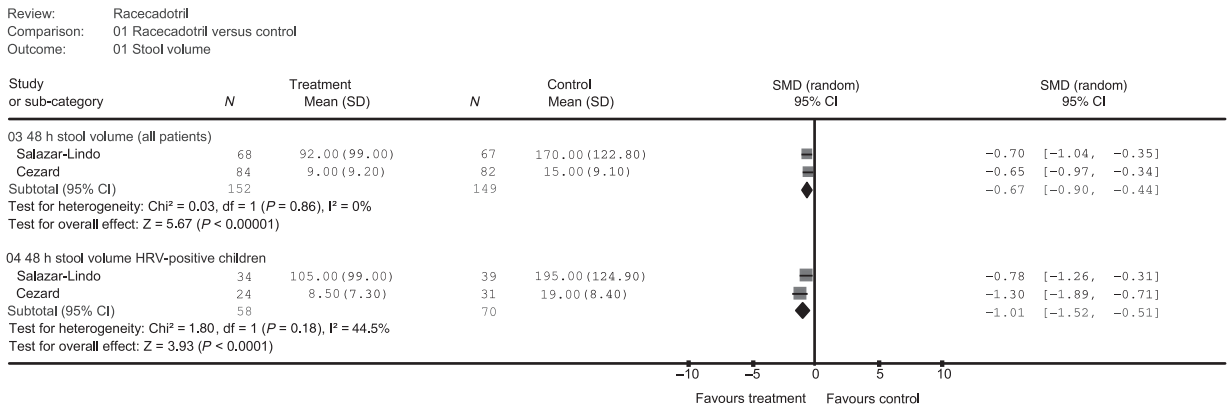

Figure 1. Forest plot showing effect of racecadotril compared with control on stool volume at 48 h.

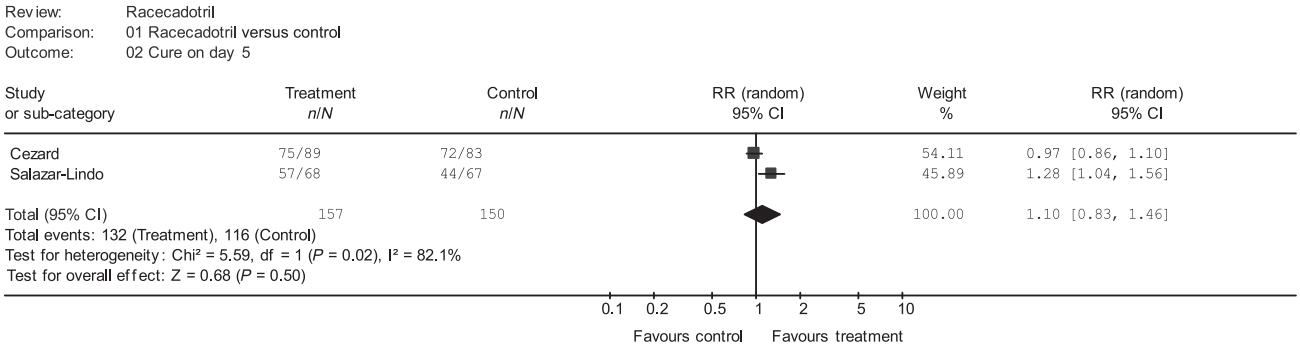

Figure 2. Forest plot showing effect of racecadotril compared with placebo on cure on day 5.

reduced the number of stools during the first 48 h (one RCT,[6] $n = 164$, 6.8 ± 3.8 vs. 9.5 ± 4.5, $P < 0.001$). This RCT[6] demonstrated a reduced need for additional emergency department visits for the same episode in those receiving racecadotril compared to the control group (eight of 76 vs. 21 of 78, RR 0.39, 95% CI: 0.19–0.8, NNT 7, 95% CI: 4–24).

Adverse effects

All three studies provided information about adverse events. None demonstrated a significant difference in the frequency of adverse effects between the racecadotril group and the control group. Reported adverse effects in the racecadotril group were mild hypokalemia (but also at baseline), ileus, mild fever and vomiting. Pooled dropout rates, i.e. the percentage of patients who stopped taking racecadotril compared to placebo during the clinical trials, were similar.

Sensitivity analysis

As there were only three studies, we did not perform sensitivity analysis or construct a funnel plot.

DISCUSSION

Principal findings

The objective of this study was to provide some resolution to the uncertainty regarding the use of racecadotril in the treatment of acute gastroenteritis in children. With the limited evidence available, we found that racecadotril, as an adjunct to oral rehydration therapy, reduced duration of acute diarrhoea and stool volume in children aged 3–48 months. The latter outcome is particularly important as quantitative diarrhea criteria are recommended by the World Health Organization for the evaluation of therapeutic agents

in the management of acute diarrhea.[13] None of the studies revealed any significant adverse effects resulting from the administration of racecadotril, although some minor adverse effects were observed. The results apply primarily to hospitalized children, while the efficacy of the racecadotril may be different for various subgroups (e.g. out-patients compared with in-patients). The subgrouping of out-patients vs. in-patients may be related to the severity of the gastroenteritis; those admitted to the hospital may be more severely affected, later in the course of the disease, or more dehydrated, and thus more responsive to treatment. Evaluation within these subgroups is warranted.

Study limitations

This systematic review has several limitations. Only a limited number of trials were available for this review. The methodological quality varied. For example, one of the important limitations of the included trials was unclear or inappropriate allocation concealment which may result in overestimation of the intervention effect.[14] An additional limitation is inadequate blinding in one of the trials. Again, this can overestimate the effect and skew the results in favour of either treatment, depending on the biases of the investigators. Other concerns apart from methodology may come from the fact that at least two RCTs were supported by the developer of the drug; it is not clear if all steps necessary to avoid bias were taken. Given these considerations, some caution must be exercised in interpreting the strength of evidence.

As studies provided results on the stool volume using different measurements, we used the method of standardized effects, as recommended by the Cochrane Handbook.[3] However, sceptics argue that this method cannot reliably meet the goals of a meta-analysis.[15] In that respect, it is noteworthy that two trials[4, 5] were consistent in their results showing a reduction in the stool volume supporting the pooled results.

Safety

There was no evidence that the racecadotril differs from placebo in terms of safety. However, trials were powered for effectiveness and were short-term. Given that adverse events from either drug or placebo were rare in the included trials, a large-scale randomized trial (or its equivalent as several smaller studies) would be required to detect any small but real differences in safety. Vomiting was one of the adverse events reported in one study. Because vomiting is common in children with acute gastroenteritis and it occurred equally often in the control group, it is unlikely to have been caused by the treatment. Similarly, while vomiting was the cause of the withdrawal of participants from one trial,[5] it appears not to be related to the treatment. Based on the results of our review and the available literature, there does not appear to be any evidence that the use of racecadotril results in major harmful events. However, in light of some other reported adverse effects of racecadotril (e.g. nausea, thirst, vertigo, constipation, headache, vomiting and hypersensitivity to racecadotril)[16] more research is required to draw firm conclusions on the safety of racecadotril in children.

CONCLUSIONS AND FUTURE RESEARCH

In conclusion, in three relatively small RCTs with some methodological problems, racecadotril was effective in reducing the volume and frequency of stool output and in reducing the duration of diarrhoea (particularly in children with rotavirus). However, more data are needed. The safety of racecadotril, as well as the cost-effectiveness of this therapy, needs to be defined. Further investigations comparing racecadotril with other treatment options (e.g. smectite[17] and probiotics[18–21]) would be worthwhile. As two trials were company funded, independent trials are needed.

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REFERENCES

1 Guarino A, Albano F, Guandalini S, for the ESPGHAN Working Group on Acute Diarrhea. Oral rehydration solution: toward a real solution. *J Pediatr Gastroenterol Nutr* 2001; **33**: S2–12.

2 Primi MP, Bueno L, Baumer P, *et al.* Racecadotril demonstrates intestinal antisecretory activity in vivo. *Aliment Pharmacol Ther* 1999; **13**: 3–7.

3 Higgins JPT, Green S (eds) Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In: *The Cochrane Library*, Issue 4, Chichester, UK: John Wiley & Sons, Ltd, 2006: 106–7.

4 Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E, *et al.* Racecadotril in the treatment of acute watery diarrhea in children. *N Engl J Med* 2000; **343**: 463–7.

5 Cézard JP, Duhamel JF, Meyer M, *et al.* Efficacy and tolerability of racecadotril in acute diarrhea in children. *Gastroenterology* 2001; **120**: 799–805.

6 Cojocaru B, Bocquet N, Timsit S, *et al.* Effect of racecadotril in the management of acute diarrhea in infants and children. *Arch Pediatr* 2002; **9**: 774–9.

7 Rao SG. Racecadotril (acetorphan) in the treatment of acute watery diarrhoea in children. *J Indian Med Assoc* 2002; **100**: 530.

8 Bhan MK, Bhatnagar S. Racecadotril-is there enough evidence to recommend it for treatment of acute diarrhea? *Indian Pediatr* 2004; **41**: 1203–4.

9 Nagpal J, Gogia S. Racecadotril. *Indian Pediatr* 2004; **41**: 1218–24.

10 Cezard JP, Salazar-Lindo E. Racecadotril in acute diarrhea. *Indian Pediatr* 2005; **42**: 502–3.

11 Alam S, Bhatnagar S. Current status of anti-diarrheal and anti-secretory drugs in the management of acute childhood diarrhea. *Indian J Pediatr* 2006; **73**: 693–6.

12 Turck D, Berard H, Fretault N, Lecomte JM. Comparison of racecadotril and loperamide in children with acute diarrhoea. *Aliment Pharmacol Ther* 1999; **13** (Suppl. 6): 27–32.

13 World Health Organization. *The Rational Use of Drugs in the Management of Acute Diarrhoea in Children.* Geneva, Switzerland: World Health Organization, 1990.

14 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273**: 408–12.

15 Cummings P. Meta-analysis based on standardized effects is unreliable. *Arch Pediatr Adolesc Med* 2004; **158**: 595–7.

16 Nucera E, Schiavino D, Altomonte G, Buonomo A, Sabato V, Patriarca G. Hypersensitivity to racecadotril: a case report. *Eur J Pediatr* 2006; **165**: 418–9.

17 Szajewska H, Dziechciarz P, Mrukowicz J. Meta-analysis: Smectite in the treatment of acute infectious diarrhoea in children. *Aliment Pharmacol Ther* 2006; **23**: 217–27.

18 Szajewska H, Mrukowicz J. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebo controlled trials. *J Pediatr Gastroenterol Nutr* 2001; **33**: S17–25.

19 Van Niel C, Feudtner C, Garrison MM, Christakis DA. *Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* 2002; **109**: 678–84.

20 Huang JS, Bousvaros A, Lee JW, Diaz A, Davidson EJ. Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. *Dig Dis Sci* 2002; **47**: 2625–34.

21 Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF. Probiotics for treating infectious diarrhoea. *Cochrane Database Syst Rev* 2004; **2**: CD003048.