Systematic review: racecadotril in the treatment of acute diarrhoea in children
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CRD summary
This review concluded that there was limited evidence in favour of using racecadotril compared with placebo or no intervention for the reduction of stool output and duration of diarrhoea in children with acute gastroenteritis. The authors' cautious conclusions appear to reflect the limitations of the evidence presented.

Authors' objectives
This review concluded that there was limited evidence in favour of using racecadotril compared with placebo or no intervention for the reduction of stool output and duration of diarrhoea in children with acute gastroenteritis. The authors' cautious conclusions appear to reflect the limitations of the evidence presented.

Searching
MEDLINE (1966 to April 2007), EMBASE (1980 to April 2007), the Cochrane Database of Systematic Reviews (2007) and the Cochrane Controlled Trials Register (2007) were searched; the search terms were reported. The bibliographies of retrieved articles and review articles were also screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies evaluating racecadotril compared with placebo or no intervention were eligible for inclusion. Two studies compared 1.5 mg/kg racecadotril every 8 hours with placebo, and one compared three doses of 10 to 20 mg/day racecadotril with no intervention. The duration of treatment was 5 to 7 days.

Participants included in the review
Studies of children in any setting with acute diarrhoea were eligible for inclusion. Diarrhoea was primarily defined as three or more loose stools per day. The participants in the included trials were aged from 3 to 48 months. Various definitions of acute diarrhoea were used, but rotavirus infection was identified as the primary cause of infection in 2 studies. The included studies were conducted in France and Peru. Two studies were conducted in hospitalised patients.

Outcomes assessed in the review
Studies assessing stool output, duration of diarrhoea, stool frequency, the percentage of children with diarrhoea lasting longer than 7 days, vomiting and adverse events were eligible for inclusion.

How were decisions on the relevance of primary studies made?
All reviewers independently assessed studies for inclusion.

Assessment of study quality
All reviewers independently assessed the included studies for: allocation concealment; blinding of the investigators, participants, outcome assessors and data analysis; intention-to-treat analysis; and completeness of follow-up.

Data extraction
All reviewers independently extracted the data using a standardised form. Any discrepancies were resolved by discussion. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes and mean differences (MDs) for continuous outcomes. Reviewers estimated missing data in the studies.

Methods of synthesis
How were the studies combined?
The results were combined in a meta-analysis using both random-effects and fixed-effect models. Only fixed-effect
data were reported where there was no evidence of statistical heterogeneity, and only the results of random-effects models were reported for other outcomes. The pooled standardised mean difference (SMD) and 95% CIs were reported for continuous outcomes, and pooled RRs with 95% CIs for dichotomous outcomes. Publication bias was not assessed.

**How were differences between studies investigated?**
Statistical heterogeneity was assessed using the chi-squared and I-squared tests. Subgroup analyses were reported for patients with rotavirus infection.

**Results of the review**
Three RCTs (n=471) were included.

Random allocation methods and concealment of allocation were clear in only one study. Two studies were reported as double-blind. All 3 studies conducted an intention-to-treat analysis. The follow-up rates ranged from 70 to 99%.

Participants in the racecadotril group had significantly less stool output at 48 hours than those in the control group (2 studies, n=301); the SMD was -0.67 (95% CI: -0.9, -0.44, p<0.00001). A similar reduction was found for a subgroup of rotavirus-positive patients (2 studies, n=128), but there was evidence of significant statistical heterogeneity. The mean total stool output at 5 days was also lower for participants in the racecadotril group than for those in the placebo group (1 study, n=135); the MD was -174 g/kg (95% CI: -185, -163; RR reduction 53%, p<0.001). A similar effect was found for a subgroup of rotavirus-positive boys (1 study, n=73); the MD was -233 g/kg (95% CI: -240, -206).

The duration of diarrhoea was significantly reduced in the racecadotril group compared with the control group (3 studies, n=471). However, owing to inconsistent reporting of the outcomes, it was not possible to pool the data (further details were reported).

There were no significant differences between the racecadotril and control groups for a ‘cure’ in 5 days or less (2 studies, n=307).

There were no significant differences in the frequency of adverse effects between the racecadotril and control groups. The percentages of participants who stopped taking racecadotril during the trial compared with placebo were similar.

**Authors’ conclusions**
There was limited evidence in favour of using racecadotril compared with placebo or no intervention for the reduction of stool output and duration of diarrhoea in children with acute gastroenteritis. However, the safety and cost-effectiveness of racecadotril should be explored before routine therapy using racecadotril is recommended.

**CRD commentary**
Inclusion criteria were clearly defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched, although a formal assessment of publication bias was not conducted because of the small number of included studies. Several reviewers independently selected studies, assessed validity and extracted the data, thus reducing the potential for reviewer bias and error. The analyses seemed appropriate and statistical heterogeneity was assessed. However, there is the potential for clinical heterogeneity given the variation in participants, settings and administration of the intervention, as well as differences in the assessment of outcomes. The results also primarily apply to hospitalised patients; the authors advise caution when extending their findings to other patient groups. The authors also noted that at least 2 studies were funded by pharmaceutical company sponsorship. Overall, the authors’ cautious conclusions appear to reflect the limitations of the evidence presented.

**Implications of the review for practice and research**
Practice: The authors stated that further research is needed before routine therapy using racecadotril is recommended.

Research: The authors stated that further independent studies are needed to determine the safety and cost-effectiveness of racecadotril. Additional studies comparing racecadotril with other treatment options should be carried out.
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