Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis

CRD summary
This individual patient data meta-analysis of nine trials found that racecadotril as an adjunct to oral rehydration solution had a clinically relevant effect in reducing diarrhoea (duration, stool output and number) in children with acute gastroenteritis. Despite some shortcomings regarding the available evidence and model uncertainty, this conclusion is likely to be reliable.

Authors' objectives
To assess racecadotril efficacy as an adjunct to oral rehydration solution against oral rehydration alone or with placebo for reducing diarrhoea incidence and severity in children with acute gastroenteritis

Searching
Cochrane databases, EMBASE, Google and MEDLINE were searched with specified search terms from January 1985 to December 2010. Selected Journals and conference abstracts were handsearched and bibliographies were checked for additional studies. Authors and manufacturers were contacted to provide unpublished data and to identify any further eligible studies.

Study selection
Randomised controlled trials that compared racecadotril as an adjunct against oral rehydration or placebo in children from one month to 15 years old with acute gastroenteritis were eligible provided methodological quality was sufficient to achieve a score above 50 on the Chalmers' scale. Outcomes were duration of diarrhoea and number of stools between first drug intake and the last unformed stool before recovery (defined as two consecutive formed stools or no stools for 12 hours). Stool output during the first 48 hours (inpatients) and total number of stools until recovery (outpatients) were secondary outcomes.

Patient characteristics were reported and generally did not exhibit noteworthy variation with the exceptions of the proportion of children with rotavirus at baseline (range of trials means 0.1 to 0.68 based on a WHO classification) and the mean number of stools produced per day (range five to ten).

The number of reviewers determining study eligibility was not stated.

Assessment of study quality
The risk of bias for each study was assessed using the Chalmers' scale which considered known sources of bias in the conduct of randomised trials. Individual patient data was checked for reliability with the original trialists.

The number of reviewers determining study quality was not stated.

Data extraction
Individual patient data was collected to allow calculation of Hazard ratios (HR) for duration of diarrhoea. The number of diarrhoeic stools and stool output were collated as continuous metrics.

Methods of synthesis
An unspecified multilevel model with a random treatment effect was used to examine treatment effectiveness after adjusting for baseline predictors (study centre, country, treatment, age, gender, height, weight, body mass index, diarrhoea duration before inclusion, body temperature, dehydration level, rotavirus presence, number of stools in the 24 and four hours prior to treatment) which were selected using a backwards stepwise strategy. Hazard ratios for diarrhoea duration were synthesised using Cox Proportional Hazards models stratified by study.

Results of the review
Individual patient data was available for all nine eligible trials (1,384 patients). Trial quality was reasonable, but allocation concealment and blinding were not always optimal and attrition bias was a possible issue in one trial.
Diarrhoea duration was reduced with racecadotril compared to placebo (HR 2.04, 95% CI 1.85 to 2.32) which also reduced mean stool output (ratio 0.59, 95% CI 0.51 to 0.74) and number of diarrhoeic stools (ratio 0.63, 95% CI 0.47 to 0.85 in text, 95% CI 0.51 to 0.74 in table). Heterogeneity was small to moderate for these analyses with $I^2$ that ranged from 26% to 31%. Model fit was reasonable for duration of diarrhoea ($r^2=0.55$), but poor for stool output ($r^2=0.23$) and number ($r^2=0.31$). Catalogued adverse events were not differentiated by treatment.

**Authors’ conclusions**
Racecadotril as an adjunct to oral rehydration solution had a clinically relevant effect in reducing diarrhoea (duration, stool output and number) in children with acute gastroenteritis.

**CRD commentary**
This review of nine trials based on individual patient data utilised appropriate methods to minimise sources of bias, while searching, selecting and appraising studies. The appropriateness of the analytical approach was hard to judge in the absence of full model specification. The adjustment of treatment effects for statistically significant baseline confounders was atypical of analysis in a randomised setting but was judged as unlikely to have had a profound impact on results. Poor model fit for stool output and number suggest that some uncertainty surrounds these results, but the author’s conclusions are consistent with the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors mentioned the need for network meta-analysis that compared racecadotril with other symptomatic treatments in combination.

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