

Racecadotril was effective for severe watery diarrhoea in children

Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E, Gutierrez M. *Racecadotril in the treatment of acute watery diarrhea in children*. *N Engl J Med* 2000 Aug 17;343:463-7.

QUESTION: In children with severe watery diarrhoea, is racecadotril (acetorphan, an enkephalinase inhibitor), as an adjunct to oral rehydration therapy, more effective than oral rehydration alone?

Design

Randomised [allocation concealed*]†, blinded [patients, clinicians, outcome assessors, and statisticians]‡,* placebo controlled trial with 5 days follow up.

Setting

Hospital in Lima, Peru.

Patients

135 boys who were 3–35 months of age (mean age 13 mo) and had watery diarrhoea for ≥ 5 days, had passed ≥ 3 diarrhoeic stools within 24 hours of admission to the hospital, and had passed ≥ 1 diarrhoeic stool within 4–6 hours after admission. Exclusion criteria were blood in the stool, inability to drink, or any serious concomitant illness. 112 boys (83%) completed the study.

Intervention

Patients were allocated to racecadotril, 1.5 mg/kg of body weight orally every 8 hours ($n = 68$), or to placebo ($n = 67$). All patients received standard oral rehydration solution (ORS). Other antidiarrhoeal drugs, antibiotics, or aspirin were not permitted during the study.

Main outcome measures

The primary outcome was 48 hour stool output. Secondary outcomes were total stool output, duration of diarrhoea, and total intake of ORS.

Main results

Analysis was by intention to treat. Patients who received racecadotril had a lower mean 48 hour stool output than patients who received placebo ($p < 0.001$) (table). The mean total stool output was lower in the racecadotril group than in the placebo group ($p < 0.001$) (table). More patients who received racecadotril were cured by 5 days than were patients who received placebo ($p = 0.015$)‡. The total intake of ORS was lower in the racecadotril group ($p < 0.001$). The groups did not differ for adverse effects (10% *v* 7%), none of which was severe.

Conclusion

In children with severe watery diarrhoea, racecadotril as an adjunct to oral rehydration therapy reduced stool output, duration of diarrhoea, and intake of oral rehydration solution.

*See glossary.

†Information provided by author.

‡p Value calculated from data in article.

Racecadotril *v* placebo for severe watery diarrhoea in children§

Outcomes	Racecadotril	Placebo	Mean difference (95% CI)	Relative rate reduction
48 hour stool output (g/kg)	92	170	78 (40 to 116)	46%
Total stool output at 5 days (g/kg)	157	331	174 (80 to 268)	53%
			RBI (CI)	NNT (CI)
5 day cure rate	84%	66%	28% (4.9 to 59)	6 (4 to 29)

§Abbreviations defined in glossary; mean difference, RBI, NNT, and CI calculated from data in article.

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COMMENTARY

Diarrhoeal dehydration is the most common killer of children. Dehydration is caused by secretion of fluids into the gut, particularly in infective diarrhoeas. Antimotility agents are not recommended because of the danger of colonisation leading to chronicity. Against this background, the promising efficacy of racecadotril, shown in the study by Salazar-Lindo *et al*, is welcome.

Racecadotril is an acetorphan, which acts by inhibiting intestinal enkephalinase, thus preventing the inactivation of endogenous enkephalins and reducing the secretion of water and electrolytes into the gut.¹ Intestinal transit times are not altered in healthy people.²

In their elegant, simple, randomised trial, Salazar-Lindo *et al* have shown that racecadotril is effective in reducing the volume and frequency of stool output and in reducing the duration of diarrhoea without causing adverse reactions. These results were more marked in children with rotavirus or *Escherichia coli* diarrhoea, conditions known to increase secretion into the gut.

Despite the reduction in morbidity by ORS, diarrhoea accounts for 24% of disability adjusted life years.³ Racecadotril, by controlling diarrhoea within 24–48 hours, promises to reduce this percentage further. Other studies have shown that racecadotril is better than octreotide and is effective in patients with AIDS.⁴

It has long been held that ORS is sufficient to treat watery diarrhoea in children. The results of the study by Salazar-Lindo *et al* suggest that antisecretory agents should be routinely used in acute watery diarrhoea in addition to ORS.

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

2 Bergmann JF, Chaussade S, Couturier D, *et al*. Effects of acetorphan, an antidiarrhoeal enkephalinase inhibitor, on oro-caecal and colonic transit times in healthy volunteers. *Aliment Pharmacol Ther* 1992;6:305-13.

3 World Health Organisation. The World Health Report 1999. Making a difference. Geneva: World Health Organisation, 1999:41. (<http://www.who.int/whr/1999/en/pdf/whr99.pdf>)

4 Beaugerie L, Baumer P, Chaussade S, *et al*. Treatment of refractory diarrhoea in AIDS with acetorphan and octreotide: a randomized crossover study. *Eur J Gastroenterol Hepatol* 1996;8:485-9.