

Racecadotril was effective for severe watery diarrhea 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 diarrhea, is racecadotril (acetorphan, an enkephalinase inhibitor) as an adjunct to oral rehydration therapy more effective than oral rehydration alone?

DESIGN

Randomized {allocation concealed*}†, blinded {patients, clinicians, outcome assessors, and statisticians}‡,* placebo-controlled trial with 5-day follow-up.

SETTING

Hospital in Lima, Peru.

PATIENTS

135 boys who were 3 to 35 months of age (mean age 13 mo) and had watery diarrhea for ≤ 5 days, had passed ≥ 3 diarrheic stools within 24 hours of admission to the hospital, and had passed ≥ 1 diarrheic stool within 4 to 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 antidiarrheal drugs, anti-

biotics, 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 diarrhea, 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 did 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% vs 7%), none of which was severe.

CONCLUSION

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

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*See Glossary.

†Information provided by author.

‡ P value calculated from data in article.

Racecadotril vs placebo for severe watery diarrhea in children§

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

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

COMMENTARY

Diarrheal dehydration is the most common killer of children. Dehydration is caused by secretion of fluids into the gut, particularly in infective diarrheas. Antimotility agents are not recommended because of the danger of colonization leading to chronicity. Against this background, the promising efficacy of racecadotril, shown in the study by Salazar-Lindo and colleagues, 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 persons (2).

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

Despite the reduction in morbidity by ORS, diarrhea accounts for 24% of disability-adjusted life-years (3). Racecadotril, by controlling diarrhea within 24 to 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 diarrhea in children. The results of the study by Salazar-Lindo and colleagues suggest that antisecretory agents should be routinely used in acute watery diarrhea in addition to ORS.

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