Aliment Pharmacol Ther 1999; 13 (Suppl. 6), 27–32.

Comparison of racecadotril and loperamide in children with acute diarrhoea

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SUMMARY

Methods A multicentre, parallel-group, double-blind, double-placebo study was carried out to compare the efficacy, tolerability, and safety of racecadotril and loperamide in children aged 2 to 10 years who were suffering from acute diarrhoea. Patients received racecadotril (1.5 mg/kg) or loperamide (0.03 mg/kg) three times daily plus matching placebo until recovery. Fifty-two children received racecadotril and 50 loperamide.

Results Patients on racecadotril passed a mean ($\pm$ S.E.M.) of 2.7 $\pm$ 0.4 stools before recovery compared with 2.1 $\pm$ 0.4 stools for loperamide. The duration of diarrhoea was similar with both treatments. The incidence of adverse events was lower with racecadotril than with loperamide (11.5% vs. 22%), and significantly more patients on loperamide suffered from constipation (58% vs. 36.5%; $P = 0.03$). Moreover, significantly more children receiving loperamide required concomitant medication during the study (38% *v* 19.2%; $P = 0.047$). Measurement of abdominal circumference at the final consultation, 6 days after entry to the study, revealed no significant differences between treatments.

Conclusions Racecadotril and loperamide were equally effective in treating acute diarrhoea in these children, and racecadotril had a superior tolerability and safety profile.

INTRODUCTION

Although the μ-receptor agonist loperamide is an effective antidiarrhoeal drug, its use is often accompanied by adverse effects such as constipation,[1] abdominal distension,[2] and bacterial overgrowth in the intestine.[3] It has therefore been proposed that the use of μ-receptor agonists should be avoided in young children and in patients with fever, dysentery, or inflammatory bowel disease.[4] Indeed, the use of loperamide is not indicated in children aged less than 2 years.[5]

Research has therefore concentrated on developing drugs that inhibit hypersecretion by the intestinal mucosa but do not increase intestinal transit time.

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Racecadotril [racecadotril is the official international nonproprietary name (INN); the drug was known as acetorphan in early studies] is a potent inhibitor of enkephalinase, and therefore prevents the breakdown of the endogenous enkephalins, thus prolonging their antisecretory activity.[6] Because racecadotril is a pure antisecretory agent, its antidiarrhoeal effect is not accompanied by an increase in gastrointestinal transit time,[6] and its administration in adults has been associated with an incidence of constipation similar to that of placebo[7] and significantly lower ($P < 0.02$) than that of loperamide.[8] Racecadotril has also been shown to be devoid of central neurotoxicity.[9]

The present study was carried out to compare the efficacy, tolerability, and safety of racecadotril and loperamide in children aged 2 to 10 years who were suffering from acute diarrhoea. The lower age limit of 2 years was applied as the use of loperamide is not indicated in children younger than this.[5]

MATERIALS AND METHODS

Patient population

Male or female children aged between 2 and 10 years were eligible for participation in the study. All patients were suffering from acute diarrhoea, which was defined as production of at least three liquid or loose stools for a minimum of 24 h and a maximum of 5 days. All children were treated as out-patients.

Exclusion criteria were chronic, purulent, or bloody diarrhoea. In addition, patients were excluded if their symptoms suggested functional intestinal disorder, they were febrile, or were known to have renal or hepatic insufficiency. Treatment with an antidiarrhoeal agent in the 48 h prior to inclusion, antibiotic treatment up to 30 days before entering the study, and a current need for antibiotic treatment also excluded patients from participating in the study. A number of the above criteria were set up because treatment with loperamide is contraindicated if the clinician considers that the diarrhoea may have been caused by an invasive microorganism.

Study design

The study was a multicentre, parallel-group, double-blind, double-placebo, comparative design. A total of 102 children entered the study, 52 of whom were randomly allocated to receive racecadotril and 50 loperamide. As the formulations of racecadotril and loperamide differ, each patient received their allocated active drug plus a matched placebo to ensure that the trial remained double-blind. Patients received either 1.5 mg/kg of racecadotril powder or 0.03 mg/kg of loperamide (four drops of a solution containing 0.2 mg/mL loperamide) three times a day before meals until recovery. The definition of recovery was the production of two consecutive normal stools, production of one normal stool followed by 12 h with no stool production, or no stool production for a period of 12 h.

Treatment with aspirin or antidiarrhoeal, antibiotic, or antitussive drugs was not permitted during the study; administration of concomitant medications such as oral rehydration solution, analgesics, or antiemetics was recorded.

Evaluations

Efficacy was recorded by the physician and by a self-assessment form filled in by the child's parents. Patients visited the physician for formal evaluation on entry to the study and 6 days after entering the study. In addition, a telephone check was carried out 24 h after the study had started.

The primary efficacy criterion was the number of diarrhoeic stools until recovery, as recorded by the child's parent on their self-assessment sheet. Secondary efficacy criteria consisted of the duration of the diarrhoea (the time between the start of treatment and production of the final diarrhoeal stool) and the recurrence rate (recurrence was defined as production of at least three diarrhoeic stools within a 24-h period in a patient who had previously recovered).

Tolerability and safety were evaluated by recording the adverse events experienced during treatment, measurement of the change in abdominal circumference, and assessment of constipation (at least 1 day without stool production).

The study was approved by the Consultative Committee for the Protection of Persons in Biomedical Research of Lille, and at least one parent provided written consent in each case.

Statistical analysis

With a sample size of 50 patients per group, the minimal detectable difference between the racecadotril and loperamide groups for the mean number of stools passed over the previous 24 h was 1.5 with a standard deviation of 2.7, a power of at least 80%, and a type I error of 5% using a two-sided test.

Analysis of efficacy was carried out on the intent to treat population.

The duration of diarrhoea and the total number of diarrhoeic stools were analysed using the Wilcoxon nonparametric test; all other quantitative variables were analysed using Student's *t*-test. All qualitative variables were analysed by the chi-squared test; if any group contained less than five values, Fisher's exact test was used to compare the two groups.

RESULTS

The mean ($\pm$ S.E.M.) age of children in both groups was 4.7 ± 0.3 years. Twenty-nine children were male and 33 female in the racecadotril-treated group compared with 28 and 22, respectively, for loperamide. Patients were also comparable for other demographic variables.

The mean (± S.E.M.) duration of diarrhoea on entry to the study was 1.7 ± 0.1 days for patients receiving racecadotril and 1.4 ± 0.1 for those on loperamide. In addition, 88.8% of racecadotril-treated children and 76.0% of loperamide-treated children had liquid stools.

Of the children who received racecadotril, four were assessed as positive for rotavirus and one as positive for adenovirus; *Salmonella enteritidis* was identified in two children, *Campylobacter jejuni* in one, and *Escherichia coli* in one. Of those receiving loperamide, seven were identified as positive for rotavirus and four as positive for adenovirus; *Salmonella enteritidis* was identified in one child and *Staphylococcus* β-lactamase + in one.

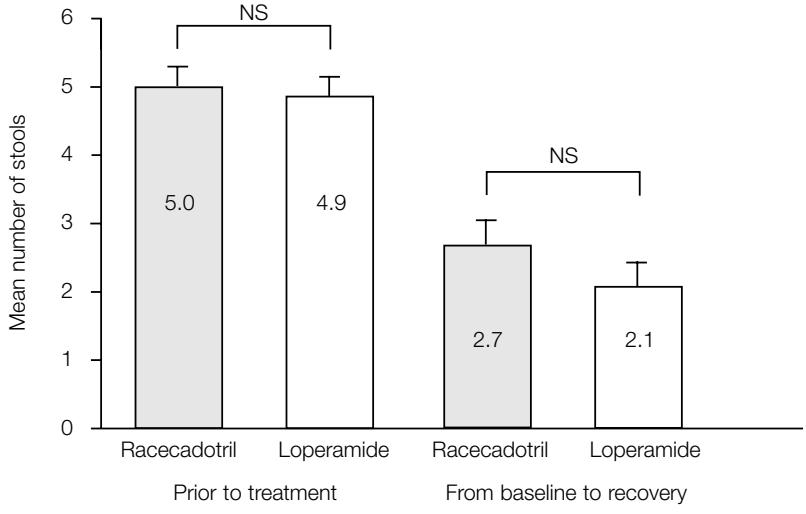

Figure 1. Mean (± S.E.M.) number of stools passed by patients receiving racecadotril (n = 51) or loperamide (n = 47) during the 24 h before treatment commenced and from the start of treatment until recovery.

Number of diarrhoeic stools until recovery

Four children, one on racecadotril and three on loperamide, could not be evaluated for this criterion as the times of the stools were not recorded by the parents on their assessment sheets. Hence, 51 children on racecadotril and 47 on loperamide were evaluated.

At baseline, patients on racecadotril had passed a mean (± S.E.M.) of 5.0 ± 0.3 stools over the previous 24 h; patients who received loperamide had passed 4.9 ± 0.3 stools (Figure 1).

Patients on racecadotril passed a mean (± S.E.M.) of 2.7 ± 0.4 stools before recovery, while patients receiving loperamide passed a mean of 2.1 ± 0.4 stools (Figure 1). The differences between treatments were not statistically significant.

Duration of diarrhoea

In addition to the above four patients, one further patient on racecadotril could not be evaluated for this variable due to lack of recovery. This patient had been identified as positive for *Campylobacter jejuni* on entry to the study. Thus, 50 patients on racecadotril and 47 on loperamide were assessed.

The mean (± S.E.M.) duration of diarrhoea was 10.7 ± 1.7 h in patients receiving racecadotril and 8.8 ± 2.3 h for loperamide (Figure 2). No statistically significant differences were noted between the two groups.

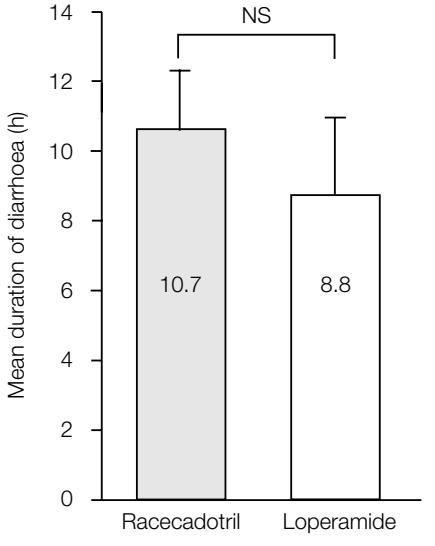

Figure 2. Mean (± S.E.M.) duration of diarrhoea in children treated with racecadotril (n = 50) or loperamide (n = 47).

The mean (± S.E.M.) duration of treatment was similar for both groups: 1.9 ± 0.2 days with racecadotril and 1.8 ± 0.2 days for loperamide.

Recurrence of diarrhoea

Fifty children on racecadotril and 47 on loperamide were evaluated for the recurrence of diarrhoea. Diarrhoea was found to recur in 11 (22%) patients who received racecadotril and nine (19%) receiving loperamide. No statistically significant differences were found between the treatments.

Tolerability and safety

Adverse events were noted in six patients (11.5%) receiving racecadotril and in 11 patients (22%) on loperamide. The most frequent adverse event was vomiting (four patients on racecadotril and five on loperamide); two patients on loperamide suffered from abdominal pain. Only one serious adverse event occurred; one loperamide-treated patient developed a fever which necessitated emergency admission to hospital.

Measurement of abdominal circumference during the final consultation with the physician showed no significant difference between treatments. The mean (± S.E.M.) circumference was 51.7 ± 0.8 cm after treatment with racecadotril and 50.7 ± 0.9 cm for loperamide. As the final consultation took place 6 days after the patient had entered the study, measurement of abdominal circumference was carried out an average of 3.9 days after patients had ceased drug treatment.

The incidence of constipation was significantly greater with loperamide ($P = 0.03$); 29 patients (58%) on loperamide had constipation (defined as at least 1 day without a stool) compared with 19 on racecadotril (36.5%; Figure 3). However, the average duration of constipation was comparable between the two treatments (1.8 and 1.6 days, respectively, for racecadotril and loperamide).

More patients on loperamide required concomitant medication during the study than those receiving racecadotril ($P = 0.047$; Figure 4). Patients in both groups were given antiemetic drugs (eight loperamide- and five racecadotril-treated patients) during the study for vomiting, the most frequent adverse event encountered. In addition, patients on loperamide required

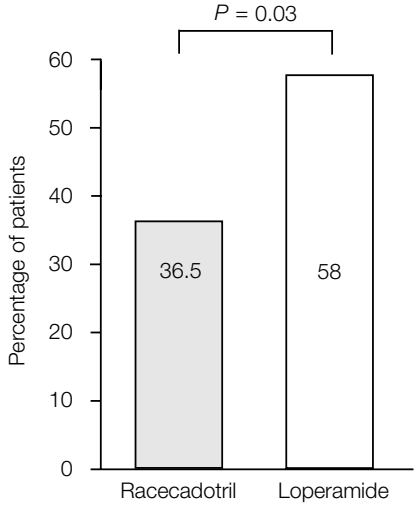

Figure 3. Percentage of patients treated with racecadotril ($n = 52$) or loperamide ($n = 50$) who suffered from constipation during the study.

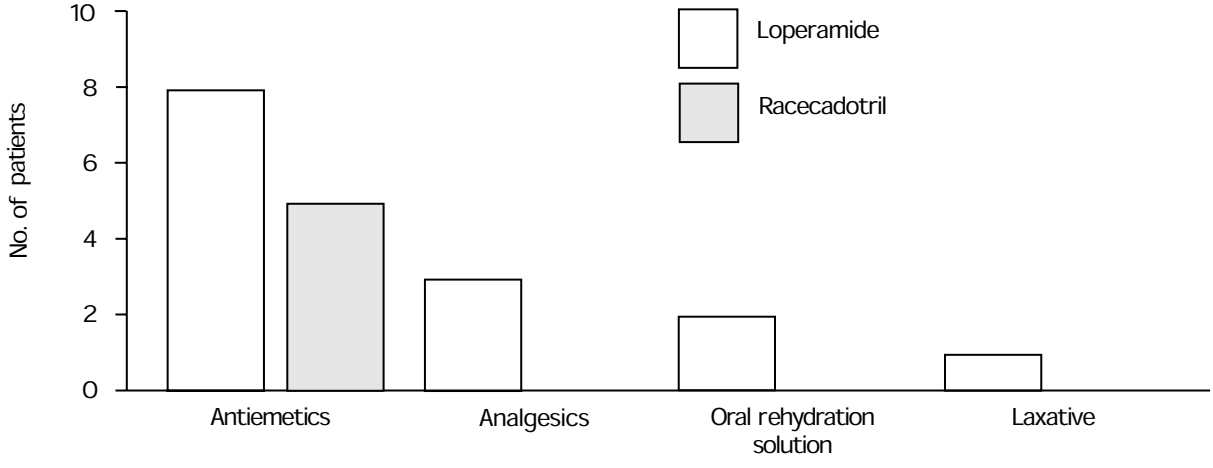

Figure 4. Number of patients receiving racecadotril ($n = 52$) or loperamide ($n = 50$) who required concomitant medication during the study. $P = 0.047$ for loperamide vs. racecadotril.

analgesic (three patients), oral rehydration (two patients), and laxative (one patient) treatment during the study.

DISCUSSION

The results of this study demonstrate that racecadotril and loperamide are equally effective in treating acute diarrhoea in children aged 2 to 10 years. However, the tolerability and safety profile of racecadotril was significantly superior to that of loperamide. In particular, constipation was significantly more frequent with loperamide than with racecadotril. In addition, the only child who required laxative treatment for secondary constipation during the study was found to be receiving loperamide.

Overall, racecadotril was well tolerated in these children, and the only concomitant treatment needed during the study was antiemetic therapy for vomiting.

These results also confirm those from studies carried out in both healthy adults and adult patients suffering from acute diarrhoea. Bergmann *et al.*[6] compared the effects of racecadotril and placebo on oro-caecal and colonic transit times in 12 healthy subjects, and found no increase in intestinal transit time with either treatment. In addition, two studies have been carried out to compare racecadotril and loperamide in acute diarrhoea in adults.[8,10] Both studies concluded that, although the two drugs were equally effective in treating acute diarrhoea, racecadotril was associated with considerably less constipation than loperamide.

Loperamide is a μ-receptor opioid agonist and hence acts by disrupting intestinal peristalsis, thereby enhancing intestinal capacitance, delaying the passage of fluid through the intestine, and allowing more time for net absorption of fluid to occur.[1,11] In contrast, racecadotril, by inhibiting enkephalinase, prolongs the intestinal antisecretory activity of the endogenous enkephalins (δ-receptor opioid agonists).[6,12] The antisecretory action of racecadotril has been demonstrated in both animal models of hypersecretory diarrhoea and in hypersecretory diarrhoea in humans.[7,13,14]

The disruption of intestinal peristalsis caused by loperamide is also thought to account for the pooling of fluid in the distended lumen of the bowel, promotion of bacterial overgrowth in the intestine, invasion by *Shigella*, and precipitation of megacolon.[2,15–17] In an experimental study[9] specifically designed to evaluate the effect of therapeutic doses of racecadotril on bacterial overgrowth, the drug did not cause proliferation of a nonenterotoxigenic strain of *E. coli* in the jejunum of the gnotobiotic piglet.

In addition to the above adverse effects, loperamide has been associated with central neurotoxicity in children in the form of lethargy, coma, and respiratory depression. For this reason, the use of loperamide is not indicated in children under 2 years of age.[5] In contrast, racecadotril does not cross the blood–brain barrier in humans after oral administration, even at high doses,[18] and does not cause physical dependence.[19] Moreover, a study[9] carried out in gnotobiotic newborn piglets, which have the same blood–brain barrier immaturity as human infants, demonstrated that racecadotril, given at 60 times the recommended dose for children (260 mg/kg/day), did not induce central nervous system toxicity. Loperamide, given at an equivalent high dose (10 mg/kg/day), was associated with neurotoxicity, followed by death, in three out of four gnotobiotic piglets.

Two placebo-controlled studies have been carried out to examine the effects of racecadotril in infants and children suffering from acute diarrhoea.[20,21] Patients ranged in age from 1 month to 4 years. Both studies demonstrated racecadotril to be effective and well tolerated over this age range.

In conclusion, racecadotril was demonstrated to be as effective as loperamide in treating acute diarrhoea in children aged from 2 to 10 years. This efficacy was combined with a superior tolerability and safety profile compared with loperamide. In addition, fewer children on racecadotril required concomitant medication during the study. The good efficacy, tolerability, and safety of racecadotril demonstrated in this and other studies in infants and children illustrate the potential for the use of this drug in the paediatric population.

ACKNOWLEDGEMENTS

Financial support for this study was provided by Bioprojet (France).

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