Aliment Pharmacol Ther 1999; 13 (Suppl. 6), 21–26.

Comparison of racecadotril and loperamide in adults with acute diarrhoea

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SUMMARY

Methods A multicentre, randomized, double-blind, double-placebo, parallel-group study was carried out to compare the efficacy, tolerability, and safety of racecadotril (100 mg three times daily) and loperamide (2 mg after each diarrhoeic stool) in 157 adults with acute diarrhoea. Patients were treated for 7 days or until recovery, if this took place earlier.
Results Both groups of patients passed similar numbers (mean ± S.E.M.) of stools before recovery (3.5 ± 0.5 for racecadotril vs. 2.9 ± 0.4 for loperamide), and the duration of diarrhoea (mean ± S.E.M.) was similar in both groups (14.9 ± 2.0 h for racecadotril and 13.7 ± 2.2 h for loperamide). Both treatments reduced the incidence of associated symptoms and signs during the study, and both were similarly well tolerated. However, more patients on loperamide reported rebound constipation during treatment (18.7% vs. 9.8% with racecadotril).
Conclusions The enkephalinase inhibitor, racecadotril, and the intestinal transit inhibitor, loperamide, were similarly and rapidly effective in resolving the symptoms and associated signs of diarrhoea.

INTRODUCTION

Treatment of patients with acute diarrhoea is usually based on rehydration with replacement of electrolytes. Opiate drugs (μ-receptor agonists) are also often given to patients to shorten the duration of the diarrhoea, relieve symptoms, and reduce the patient's discomfort. Such drugs increase oro-caecal and colonic transit times, and increase the capacitance of the gut. They also delay the passage of fluid through the intestine, which provides more time for water and electrolytes to be absorbed from the gut.[1–6]

The deleterious effect of the μ-receptor agonists on gut motility is thought to be responsible for the main gastrointestinal side-effects of these drugs, such as pooling of fluid in the distended bowel lumen and enhancement of bacterial colonization.[7–10] Hence, research has concentrated on developing drugs that exert an antisecretory effect but do not increase intestinal transit time.

Inhibitors of the membrane metalloendopeptidase enzyme, enkephalinase, prevent the breakdown of endogenous enkephalins, thereby prolonging their intestinal antisecretory activity. Racecadotril [racecadotril is the official international nonproprietary name (INN); the drug was known as acetorphan in early studies] is an orally active, potent inhibitor of enkephalinase,[11] and has been shown to exert naloxone-reversible antidiarrhoeal effects in rodents which arise from the protection of endogenous enkephalins.[11,12] Moreover, racecadotril did not increase intestinal transit time in these animals.[11] The lack of effect of racecadotril on oro-caecal and colonic transit times has been confirmed in healthy adult subjects.[13]

Studies in humans have demonstrated that the efficacy of racecadotril in treating acute diarrhoea is accompanied by a tolerability profile similar to that of placebo.[14,15] Moreover, a double-blind study against the intestinal transit inhibitor, loperamide, showed that

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racecadotril was as effective as loperamide in treating acute diarrhoea but was associated with significantly less rebound constipation and abdominal distension.[16] However, this study did not employ a double-placebo design, and the dosage schedule for loperamide did not adhere strictly to the recommended one.[17] The current study was therefore carried out to compare the efficacy and tolerability of racecadotril with those of loperamide using a double-placebo design and the recommended dosage regimen for loperamide.

MATERIALS AND METHODS

Patient population

Male and female out-patients aged over 18 years took part in this study. All patients were suffering from acute diarrhoea, defined as the production of at least three soft or liquid stools for a minimum of 24 h and a maximum of 5 days.

Patients were excluded from the study if they were suffering from bloody, purulent, or chronic diarrhoea or exhibited symptoms of functional intestinal disorder. In addition, any patient who had started on a new medication less than 7 days before the onset of the diarrhoea, or had received antibiotic treatment in the 15 days before entering the study, was excluded. Other criteria that prevented a patient from entering the study were renal or hepatic insufficiency, HIV positivity, diabetes, or a progressive concomitant infection.

A number of the above exclusion criteria were necessary because loperamide cannot be given to a patient if the clinician considers that the diarrhoea may have been caused by an invasive microorganism.

Patients were withdrawn from treatment if a serious adverse event occurred, if treatment was assessed as ineffective at any time, or if concomitant drug treatment was required. The only drug that could be administered during the study was paracetamol, if the patient developed a fever.

Study design

This study was a randomized, double-blind, double-placebo, parallel-group study, carried out in 34 separate general practice centres. Patients were examined on entry to the study and 7 days after inclusion. In addition, a telephone check was carried out after 72 h of treatment.

A double-placebo design was used, as racecadotril and loperamide were administered via different dosing schedules. At inclusion, patients received three capsules: either two capsules of loperamide (2 mg) plus one placebo capsule (in the loperamide group) or one racecadotril capsule (100 mg) plus two placebo capsules (in the racecadotril group) and thereafter: one loperamide capsule or one placebo capsule after each diarrhoeic stool and one racecadotril capsule or one placebo capsule before each meal.

Patients were treated for 7 days, or until their recovery from diarrhoea if this took place earlier. Recovery was defined as the production of two consecutive normal stools or lack of production of stools for a period of 12 h.

Evaluations

The primary efficacy criterion was the number of diarrhoeic (soft or liquid) stools passed by the patient until recovery took place. In addition, the duration of the diarrhoea and the change in associated symptoms and signs (for example, abdominal pain or distension, anal burning, asthenia, anorexia) during treatment were assessed. The physician also made a global evaluation of efficacy using an analogue scale from 0 (no efficacy) to 100 (excellent efficacy). In addition to the physician's evaluation, each patient was asked to complete an auto-evaluation sheet.

Tolerability and safety were evaluated by the incidence and severity of adverse events reported by the patient and the occurrence of rebound constipation. Once again, the physician made a global evaluation of tolerability using an analogue scale.

All patients gave written informed consent, and the study was approved by the Consultative Committee for the Protection of Persons in Biomedical Research of Nantes.

Statistical analysis

The sample size was calculated in order to detect a difference between the racecadotril and loperamide groups for the number of stools passed until recovery (the primary efficacy criterion) using a two-sided test and a type I error of 5%. With a standard error of 1.3, 73 patients per group were needed to detect a difference of at least 0.7 between the racecadotril and loperamide groups with a minimal power of 90%.

The efficacy of treatment was analysed using the intent to treat population. Quantitative variables were examined to see whether they followed a normal distribution; those that did were compared by the Student's *t*-test,

while those that did not were compared by the nonparametric Wilcoxon test. In addition, Kaplan–Meier curves were drawn for the duration of diarrhoea with racecadotril and loperamide. These curves were then compared using a log rank test.

Qualitative variables were analysed by the chi-squared test or the Fisher's exact test.

RESULTS

A total of 157 male and female patients entered the study; 82 were randomized to receive racecadotril and 75 to receive loperamide. The average age (mean ± S.E.M.) was 40.9 ± 1.8 years for patients receiving racecadotril and 41.5 ± 2.2 years for patients on loperamide. Patients were also comparable for other demographic variables and physical characteristics, the frequency of associated symptoms and signs, their medical histories were similar, and they were taking similar types of medications (mainly hormonal therapy). Almost twice as many women as men entered the study.

At inclusion, the mean (± S.E.M.) duration of diarrhoea was similar in both groups (39.4 ± 1.7 h for the racecadotril group and 41.4 ± 2.0 h for the loperamide group), as was the mean (± S.E.M.) number of stools passed during the previous 24 h (5.9 ± 0.2 for the racecadotril group and 5.3 ± 0.2 for the loperamide group).

Causative microorganisms were identified in four patients who received racecadotril: *Salmonella* in two patients, *Pseudomonas aeruginosa* in one, and *Yersinia frederiksenii* in one. In the group that received loperamide, *Staphylococcus aureus* was identified in two patients, *Pseudomonas aeruginosa* in two, and *Clostridium difficile* in one.

Of the 157 patients who entered the study, six on racecadotril and two on loperamide withdrew before the end of the treatment period. The reasons for patient withdrawal are given in Table 1.

Table 1. Reasons for patient withdrawal from treatment.

	Number of patients withdrawn	
Reason for withdrawal	Racecadotril	Loperamide
Withdrawal of consent	1	1
Lack of efficacy	2	1
Lost to follow-up	1	
Concomitant treatment with aspirin	1	
Concomitant antibiotic treatment	1	
Total	6	2

Ten patients (five in each group) failed to complete their evaluation sheets correctly, and could not be evaluated for efficacy. Hence, results were available for 77 patients on racecadotril and 70 on loperamide.

Number of diarrhoeic stools passed until recovery

The mean (± S.E.M.) number of stools passed until recovery were similar for both patient groups at 3.5 ± 0.5 for racecadotril and 2.9 ± 0.4 for loperamide (Figure 1).

The definition of recovery used for analysis was as defined in the study protocol: the production of two consecutive normal stools or lack of production of stools for a period of 12 h.

Other efficacy criteria

The mean (± S.E.M.) duration of diarrhoea was 14.9 ± 2.0 h with racecadotril and 13.7 ± 2.2 h with loperamide. Figure 2 shows the Kaplan–Meier curves for both patient groups.

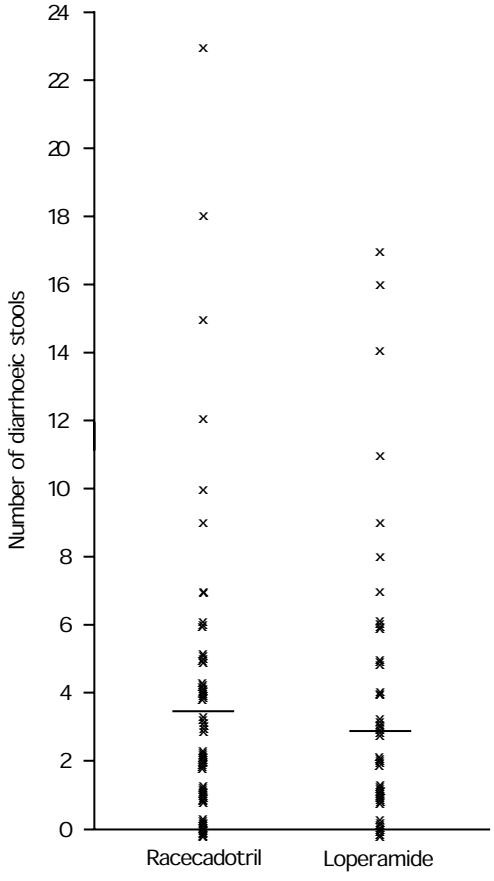

Figure 1. Number of stools passed by each patient during treatment with racecadotril ($n = 77$) or loperamide ($n = 70$) until recovery from diarrhoea. Mean numbers of stools are indicated by horizontal bars.

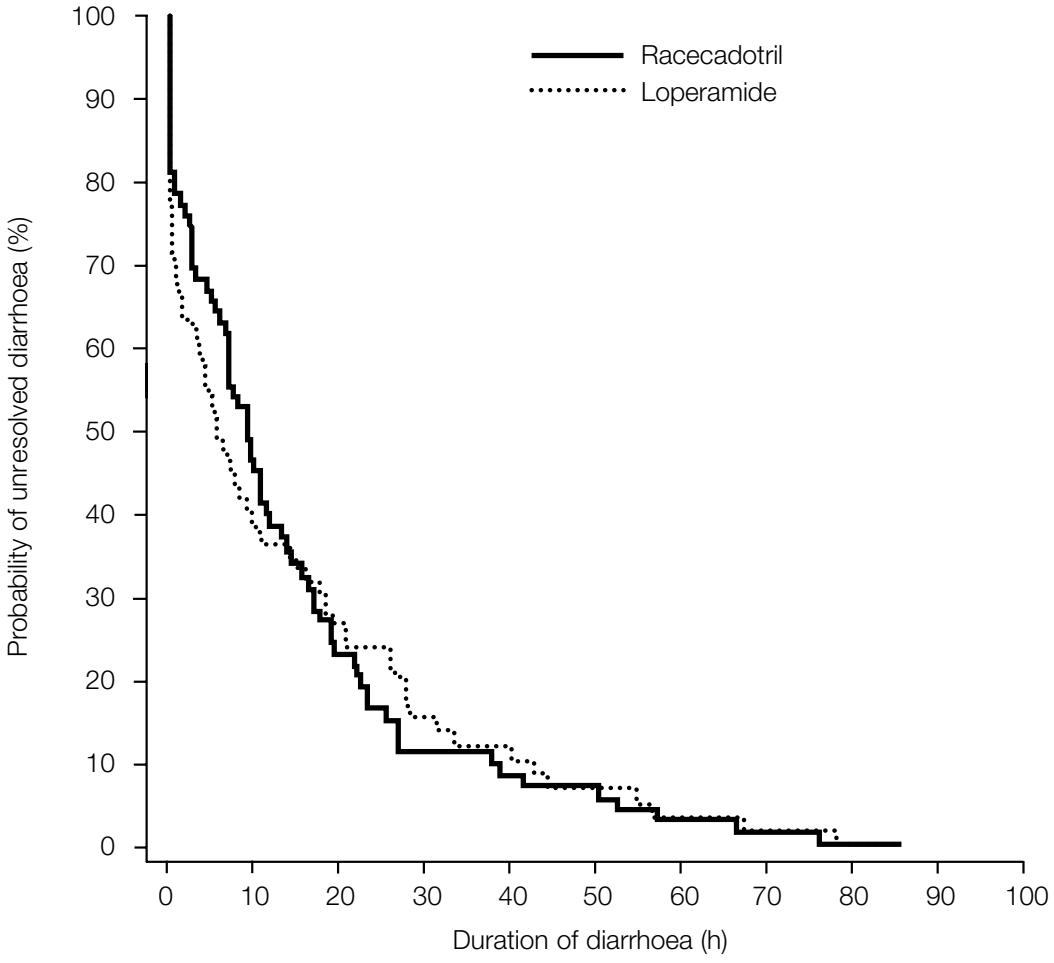

Figure 2. Kaplan–Meier curves showing the duration of diarrhoea in patients receiving racecadotril ($n = 77$) or loperamide ($n = 70$).

The physician's global evaluation demonstrated that both treatments were of similar efficacy (efficacy on the visual analogue scale was assessed as 83.7 ± 2.1 for racecadotril and 82.2 ± 2.3 for loperamide).

Both groups of patients were comparable in terms of the incidence of associated symptoms and signs at the beginning of treatment. In particular, a high incidence of asthenia, spontaneous abdominal pain, pain on palpation of the abdomen, and abdominal distension were found (over 80% of patients in each treatment group). At the end of the study, the incidence of asociated symptoms and signs was low in both racecadotril-and loperamide-treated patients (Figure 3).

Tolerability and safety

The incidence of adverse events was similar with both racecadotril and loperamide: 7.4% of patients reported adverse events during treatment with racecadotril compared with 12% during loperamide treatment. The majority of adverse events were considered to be mild to moderate.

Rebound constipation was defined as the percentage of patients who did not pass a stool for at least 2 days during treatment. The results showed that 18.7% of patients receiving loperamide suffered from rebound constipation during the study compared with 9.8% of patients on racecadotril. The mean ($\pm$ S.E.M.) duration of constipation was 1.3 ± 0.1 days for racecadotril and 1.6 ± 0.1 days for loperamide, and severe constipation was seen only with loperamide.

DISCUSSION

The results of this multicentre, randomized, double-blind, double-placebo, parallel-group study confirm that racecadotril is as effective as loperamide in treating acute diarrhoea, but is less likely to be associated with adverse events such as rebound constipation. The

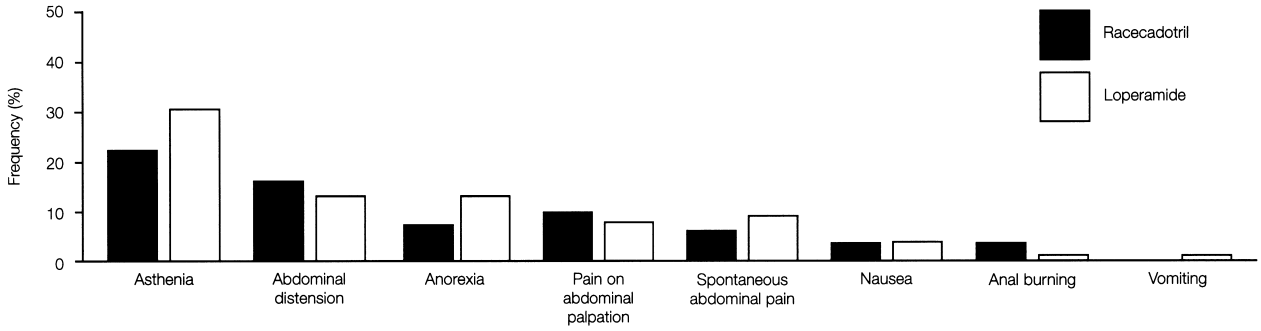

Figure 3. Incidence of associated symptoms and signs after treatment with racecadotril ($n = 80$) or loperamide ($n = 75$).

duration of diarrhoea was similar with both racecadotril and loperamide, and patients receiving either treatment passed similar numbers of stools until recovery from their diarrhoea. Although the results did not reach statistical significance, twice as many patients suffered from rebound constipation during treatment with loperamide (18.7%) compared with racecadotril (9.8%).

Racecadotril acts by inhibiting enkephalinase, thus prolonging the antisecretory action of endogenous enkephalins. Studies in both animals and humans have shown that racecadotril is active in models of hypersecretory diarrhoea: after administration of cholera enterotoxin in dogs and humans,[18,19] and in castor oil-induced diarrhoea in rodents and humans.[11,12,14] Further evidence for the pure antisecretory action of racecadotril was obtained from the cholera infusion study, where racecadotril had no effect on basal secretion and acted only in the hypersecretory state.[18]

The effect of racecadotril in rodents was inhibited by naloxone, an opioid receptor antagonist, showing that racecadotril acts by protecting endogenous enkephalins.[12]

A further experimental study in newborn gnotobiotic piglets compared the effects of racecadotril and loperamide on the intestinal growth of a nonpathogenic strain of *Escherichia coli* (E 404).[20] These authors found that the ratio of *E. coli* content between the stomach and the proximal jejunum was similar for both the control and racecadotril groups. In contrast, this ratio was significantly higher with loperamide compared with both the control ($P < 0.005$) and the racecadotril groups ($P < 0.04$). It was therefore concluded that racecadotril did not promote bacterial overgrowth in the small intestine.

In clinical trials, the efficacy of racecadotril in treating acute diarrhoea has been demonstrated against both placebo and loperamide. The adverse events profile was found to be similar to that of placebo and more favourable than that of loperamide.

Baumer *et al.*[14] reported that racecadotril was significantly ($P < 0.001$) more effective than placebo in 194 patients with acute diarrhoea. In addition, the incidence of constipation was similar in both groups of patients (4.2% with racecadotril vs. 2% with placebo), and racecadotril was associated with significantly less abdominal distension and abdominal pain than placebo ($P < 0.05$). Hamza *et al.*[15] also compared racecadotril and placebo, and reported that racecadotril acted quickly to resolve acute diarrhoea without inducing secondary constipation.

The effects of racecadotril and loperamide in acute diarrhoea have previously been compared by Rogé *et al.*,[16] who concluded that racecadotril and loperamide were similarly and rapidly effective, but that loperamide was associated with significantly more rebound constipation (31.3% compared with 8.1% on racecadotril; $P < 0.02$) and abdominal distension (50.0% compared with 27.0% on racecadotril; $P < 0.05$). This study used identical capsules for racecadotril and loperamide, but did not employ a double placebo. In addition, both drugs were given three times daily to maintain the blinding of the study, whereas the FDA recommends that loperamide be taken after each diarrhoeic stool for a maximum of four times a day.[17] Hence, the protocol for the present study was designed to comply with the recommended dosage regimen for loperamide.

In conclusion, the results of this study confirm that racecadotril was similar in efficacy to loperamide in terms of the number of stools passed until recovery, duration of diarrhoea, and physician's global evaluation. Racecadotril was well tolerated, and was effective in resolving the symptoms and signs associated with diarrhoea.

ACKNOWLEDGEMENTS

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

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