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Racecadotril versus placebo in the treatment of acute diarrhoea in adults

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SUMMARY

Methods A two-centre, double-blind, parallel-group, randomized study was carried out to compare the efficacy and tolerability of racecadotril (100 mg three times daily) and placebo in 70 adult patients with acute diarrhoea. An objective criterion of antisecretory activity, stool weight, was used.
Results Racecadotril produced a significant ($P = 0.025$) decrease in stool weight during the first day of treatment compared with placebo, and was also associated with significantly fewer diarrhoeic stools than placebo after 1 day of treatment ($P = 0.027$). Racecadotril and placebo were equally well tolerated, and the frequency of symptoms and signs was similar in both groups after 4 days of treatment. Fewer patients on racecadotril suffered from abdominal distension following treatment (5.6% vs. 18.2% on placebo).
Conclusions Racecadotril acts rapidly to resolve acute diarrhoea and has an incidence of adverse events similar to that of placebo.

INTRODUCTION

In a patient who is suffering from acute diarrhoea, hypersecretion is generally the underlying pathophysiological problem. Indeed, when Edelman[1] speculated on the future treatment of diarrhoea in 1985, he commented that the ideal drug for the treatment of diarrhoea should act rapidly to inhibit hypersecretion by the intestinal mucosa without inducing constipation.

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,[2] the enzyme responsible for the inactivation of enkephalins. Thus, racecadotril acts by prolonging the antisecretory activity of enkephalins in the gastrointestinal tract.[3,4] The antisecretory action of racecadotril has been demonstrated not only in animal models,[5,6] but also in hypersecretory diarrhoea in humans.[7,8]

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The antidiarrhoeal activity of racecadotril has not been associated with an increase in intestinal transit time,[2,3] and racecadotril did not induce bacterial overgrowth in a validated experimental model of bacterial proliferation, the gnotobiotic piglet.[9]

In a double-blind clinical study in adult patients with acute diarrhoea, racecadotril proved more effective than placebo, and had a similar level of side-effects.[7] The present study was therefore carried out to confirm the efficacy and tolerability of racecadotril compared with placebo in acute diarrhoea in adults using an objective criterion, namely stool weight.

MATERIALS AND METHODS

Patient population

Male or female patients over 18 years of age who were suffering from acute diarrhoea of presumed infectious origin were eligible for inclusion in the study. Acute diarrhoea was defined as the passing of at least three liquid or soft stools per day for no more than 5 days.

Patients were excluded if they had chronic diarrhoea, a concomitant illness likely to cause diarrhoea, iatrogenic diarrhoea, symptoms of functional intestinal disorder, or a severe concomitant illness. Patients who had started on a new treatment less than 7 days before the onset of diarrhoea were also excluded, as were pregnant women or any women who might become pregnant. Treatment was discontinued in any patient who started taking a new drug for any reason during the study.

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group study, carried out in two separate centres in Tunisia. Patients were randomly allocated to receive racecadotril (100 mg three times daily) or placebo capsules. Each capsule was taken 30 min before meals.

Patients were treated for a maximum of 6 days, the exact duration of treatment depending on the duration of the diarrhoeal episode. Treatment was stopped when no liquid or soft stools had been passed for a period of at least 12 h.

Treatment with adsorbent, spasmolytic, antibiotic, or sulphonamide agents was not permitted during the study.

Evaluations

The primary efficacy criterion was the stool weight during the first day of treatment. The number of diarrhoeic stools (liquid and/or soft stools) on day 1 and the presence of associated signs and symptoms such as abdominal pain or distension, anal burning, painful anal contractions, nausea, vomiting, or loss of appetite were also evaluated.

Tolerability was determined by questioning patients about any adverse events experienced during treatment; in addition, the physician carried out a global evaluation on a visual analogue scale (0 mm = zero tolerability to 100 mm = excellent tolerability). Safety was examined by comparison of haematological and urine analyses before and after treatment.

The evaluation criteria were assessed by both the physician and the patients themselves, using self-assessment sheets in which they entered the number and characteristics of their stools. The formal physician evaluations took place on inclusion and on day 4; if the patient was not assessed as cured on day 4, a further consultation was scheduled for day 6.

The study was approved by the Ethics Committee of the Association for Ethical Assistance in Therapeutic Trials; informed consent was obtained from all patients.

Statistical analysis

A sample size of 70 patients was necessary in order to detect a difference of at least 25% with a minimum power of 90% and a type I error of 5%, and using a two-sided procedure, between the racecadotril and placebo groups for stool weight during the first day of treatment (the primary efficacy criterion).

Statistical analyses were carried out on the intent to treat population. The primary efficacy criterion, stool weight, was analysed using the nonparametric, bilateral Wilcoxon rank-sum test. Other variables were compared using the chi-squared test for qualitative variables and the one- or two-sided Student's *t*-test for quantitative variables.

RESULTS

Of the 71 patients who entered the study, one was lost to follow-up, one patient on placebo stopped treatment on day 2 due to lack of efficacy, and one patient did not attend for evaluation on day 4. Hence 70 patients were available for inclusion in the intent to treat analysis.

Thirty-two patients received racecadotril (16 males and 16 females) and 38 placebo (26 males and 12 females). Their mean ages ($\pm$ S.D.) were 35.0 ± 10.0 years for racecadotril and 36.2 ± 11.5 years for placebo. Patients in both groups were comparable in terms of height, weight, blood pressure, and heart rate.

The two groups had a similar duration and severity of diarrhoea, and a similar number of diarrhoeic stools at inclusion. Associated symptoms were similar at the start of treatment, but there was a higher incidence of abdominal distension at baseline in patients receiving racecadotril ($P = 0.02$).

Causative microorganisms were identified in five patients: *Pseudomonas aeruginosa*, *Proteus*, *Shigella*, and enterotoxigenic *Escherichia coli* (racecadotril), while one patient receiving placebo tested positive for enterotoxigenic *E. coli*.

Stool weight

The stool weight during the first day of treatment was the primary efficacy criterion (Figure 1). When the two groups of patients were compared, the mean (± S.E.M.) stool weight in the racecadotril group was 355 ± 35 g, while the stool weight in placebo-treated patients was 499 ± 46 g ($P = 0.025$). Hence, a significant decrease in stool weight of 28.9% was achieved with racecadotril.

Other efficacy criteria

At entry, patients who received racecadotril had passed a mean (± S.E.M.) of 6.4 ± 0.5 diarrhoeic stools in the previous 24 h, while those who received placebo had passed 6.3 ± 0.4 stools (Figure 2).

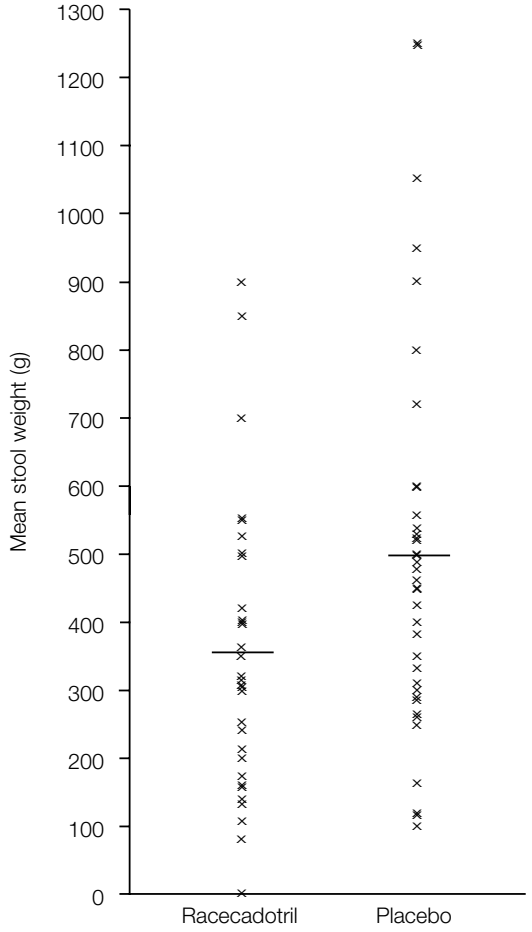

Figure 1. Individual stool weights in adult patients with acute diarrhoea after 1 day of treatment with racecadotril ($n = 32$) or placebo ($n = 38$). Mean stool weights are indicated by horizontal bars. $P = 0.025$ for the difference in mean stool weight between racecadotril and placebo.

After one day's treatment, patients on racecadotril had passed a mean (± S.E.M.) of 4.3 ± 0.4 diarrhoeic stools compared with 5.4 ± 0.4 in patients who received placebo ($P = 0.027$; Figure 2).

A total of 15.6% of patients on racecadotril passed at least one formed stool on day 2 of treatment compared with 5.3% of patients on placebo.

Tolerability and safety

Both racecadotril and placebo were equally well tolerated, with 3.1% of patients in the racecadotril group reporting adverse events on day 4 compared with 5.3% who received placebo. One patient in the racecadotril group reported dizziness and malaise, which were scored as moderate. Two patients on placebo reported adverse events: one had a moderate backache and one had abdominal distension which required hospitalization.

The physician's global evaluation confirmed that both treatments were well tolerated (the tolerability on the visual analogue scale was 96.1 ± 4.2 mm for racecadotril and 94.2 ± 16.5 mm for placebo).

The frequency of symptoms and signs on day 4 (second patient consultation) was similar for both patient groups (Table 1). However, it is noteworthy that fewer patients receiving racecadotril were suffering from abdominal distension on day 4 (5.6% of patients vs. 18.2% on placebo).

There were no significant differences between groups in terms of haematological or urine analyses.

DISCUSSION

The results of this study confirm the efficacy and tolerability of racecadotril compared with placebo in acute diarrhoea using measurement of stool weight, an objective criterion that directly reflects the loss of fluid and electrolytes.

It was not possible, for ethical reasons, to measure the stool weight in these patients in the 24 h before treatment commenced. However, the homogeneity of the two patient groups was confirmed by other criteria of the severity of diarrhoea including number of stools, duration of diarrhoea, and severity of symptoms. In addition, any missing data were estimated by carrying over the last recorded observation to ensure that no values were missed.

The results demonstrated that stool weight was significantly decreased by 28.9% with racecadotril

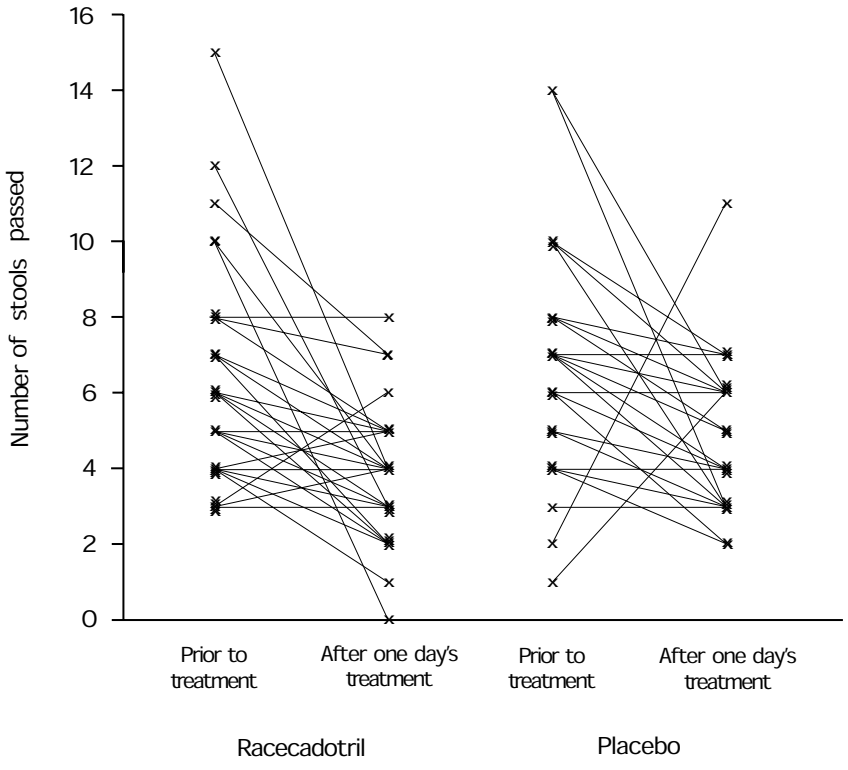

Figure 2. Number of stools passed by each patient during the 24 h before treatment and after 1 day of treatment with racecadotril ($n = 32$) or placebo ($n = 38$). The mean number of stools passed was 6.4 ± 0.5 with racecadotril and 6.3 ± 0.4 with placebo before treatment, and 4.3 ± 0.4 with racecadotril and 5.4 ± 0.4 with placebo after 1 day of treatment. $P = 0.027$ for the difference in mean stool number between racecadotril and placebo after 1 day of treatment.

Table 1. Percentage of patients with symptoms or signs on day 4 of treatment with racecadotril ($n = 31$) or placebo ($n = 37$)

Symptom or sign	Racecadotril (% patients)	Placebo (% patients)
Anal burning	18.2	25
Painful anal contraction	0	12.5
Spontaneous abdominal pain	22.6	27.3
Pain on abdominal palpation	10.7	9.7
Abdominal distension	5.6	18.2
Nausea	4.8	16.7
Vomiting	0	12.5
Loss of appetite	15.4	18.8

($P = 0.025$) compared with placebo during the first day of treatment, demonstrating the drug's rapid onset of effect. These results are in agreement with those of Baumer *et al.*[7] who assessed the efficacy of racecadotril in a model of hypersecretory diarrhoea (castor oil-induced diarrhoea) in healthy subjects. These authors also used measurement of stool weight as an objective criterion of antisecretory activity, and obtained a reduction in 24-h stool weight of 37%.

The number of stools was used as a secondary efficacy criterion in this study. This variable is easily recorded, and is often used to assess the efficacy of a drug against diarrhoea as it provides a good indication of the discomfort suffered by the patient. Racecadotril produced a significant reduction in the number of diarrhoeic stools ($P = 0.027$) after 1 day of treatment compared with placebo. Moreover, although the results did not achieve statistical significance, three times as many patients on racecadotril passed at least one formed stool on day 2 of treatment than those on placebo (15.6 and 5.3%, respectively).

Both racecadotril and placebo were well tolerated in these patients with acute diarrhoea. In particular, the incidence of gastrointestinal side-effects was equally low in both groups and abdominal distension was found to be threefold lower on day 4 of treatment with racecadotril than with placebo (5.6% vs. 18.2%). These results confirm those of previous studies, which have demonstrated the good tolerability of racecadotril. Baumer *et al.*[7] carried out a comparative, double-blind, placebo-controlled study in patients with acute diarrhoea and found that racecadotril and placebo were associated with a similar low incidence of adverse events. In particular, the incidence of constipation was similar in both groups.

Rogé *et al.*[10] carried out a double-blind study to compare racecadotril with the antimotility agent, loper-

amide. They reported that, although racecadotril and loperamide were equally effective in resolving diarrhoea rapidly, racecadotril was associated with a significantly lower incidence of constipation ($P < 0.02$) than loperamide. The duration of abdominal distension was also significantly lower ($P < 0.05$) with racecadotril. These authors ascribed the lower occurrence of constipation and the more rapid resolution of symptoms related to fluid accumulation in the distended bowel to the lack of effect of racecadotril on gastrointestinal motility.

In conclusion, the results of this study confirm the rapid efficacy of racecadotril in acute diarrhoea in adults using an objective measure of antisecretory activity: stool weight. The good tolerability of racecadotril vs. placebo was also demonstrated.

ACKNOWLEDGEMENTS

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