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An overview of clinical studies with racecadotril in adults

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Abstract

Since preclinical studies had indicated the potential efficacy and tolerability of racecadotril for the treatment of diarrhoea in man, a series of studies was carried out to assess the clinical effects of racecadotril. These studies were also designed to evaluate whether racecadotril possessed the clinical properties that had been previously identified for an ideal agent to treat infectious diarrhoea. The pure antisecretory action of racecadotril was confirmed in these clinical studies, as was the drug's rapid onset of action. The high therapeutic index of racecadotril was combined with a lack of effect on the central nervous system. Finally, racecadotril was found to be effective in treating acute diarrhoea in double-blind studies against both placebo and the μ opiate receptor agonist, loperamide. The efficacy of racecadotril in acute diarrhoea was not associated with adverse gastrointestinal effects, and its adverse events profile was similar to that of placebo. It was concluded that racecadotril offers a new approach to the treatment of diarrhoea via its mechanism of action as a true antisecretory agent.

Keywords: Acute diarrhoea; Adult diarrhoea; Antisecretory agents; Drug therapy; Racecadotril

1. Introduction

Because of their adverse effects, many traditional drugs are of limited use in the treatment of diarrhoea. For example, the opiate drugs (μ opiate receptor agonists) work by increasing oro-caecal and colonic transit times, increasing the capacitance of the gut, and delaying the passage of fluids through the intestine [1–3]. However, the increase in intestinal transit time brought about by these drugs is also thought to underlie their adverse effects on the gastrointestinal system, which include pooling of fluid in the distended bowel lumen and enhancement of bacterial colonization [4–6].

In 1985, a paper published in the *American Journal of Medicine* [7] set out the characteristics that, ideally, should be possessed by a drug for the treatment of infectious diarrhoea, upon which the clinical properties in Table 1 are based. At that time, the author commented, no drug was available that met these high standards. Hence, racecadotril (acetorphan was the name given to the drug in early studies; racecadotril is the official INN) was developed specifically with these characteristics in mind.

Racecadotril is a specific inhibitor of enkephalinase, and therefore prolongs the antisecretory effect of the endogenous enkephalins. Preclinical studies have shown that racecadotril is active in experimental models of hypersecretory diarrhoea [8,9]. These studies also indicated that racecadotril does not prolong gastrointestinal transit time [9] or promote bacterial overgrowth in the small intestine [10]. In addition, racecadotril did not cross the blood–brain barrier after oral administration [11]. The results of these studies indicated potential efficacy for the treatment of acute diarrhoea in man, combined with good tolerability. The studies described in this paper were carried out to confirm the efficacy and tolerability of racecadotril in man, and also to determine how well the drug met the high standards required of an ideal treatment for diarrhoea.

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Table 1
Clinical properties that should be possessed by the ideal agent for the treatment of infectious diarrhoea (after Edelman, 1985 [7])

Inhibits fluid secretion or stimulates fluid absorption by intestinal mucosa
Onset of action within minutes
Limited constipating effects to avoid:
Pooling of fluid in the distended bowel lumen
Enhancement of bacterial colonization of the upper bowel
Invasion by *Shigella*
Does not interfere with recovery of local bowel function
High therapeutic index
Minimal central nervous system effects
Low abuse potential

2. Racecadotril inhibits intestinal fluid secretion

The first property is that a drug should inhibit fluid secretion or stimulate fluid absorption by the intestinal mucosa since hydroelectrolytic fluid loss in the form of hypersecretion represents the major danger in acute diarrhoea. The antisecretory activity of racecadotril previously demonstrated in animal models [8,9] was confirmed in studies carried out in man.

In the first study, the effect of racecadotril on cholera-induced hypersecretion in the human jejunum of six healthy subjects was examined [12]. A 30 cm segment of the jejunum was perfused with a plasma-like electrolyte solution, and the effect of cholera toxin (a 6.25 μg intrajejunal bolus) was examined with and without prior oral administration of racecadotril (3 × 100 mg capsules). As shown in Fig. 1, cholera toxin alone produced net secretion of water. However, prior administration of racecadotril significantly ($P < 0.05$) inhibited the effect of cholera toxin, changing the net effect to absorption of water. Intestinal electrolyte transport was also significantly changed towards absorption.

A second study evaluated the effect of racecadotril in diarrhoea induced by castor oil, a model of hypersecretory diarrhoea [13]. Six healthy adult subjects were pretreated with racecadotril (10 mg/kg) or placebo 45 min prior to receiving castor oil (30 g). All subjects received both treatments. The cumulative stool weight was significantly lower ($P < 0.001$) with racecadotril than with placebo, and racecadotril also delayed the onset of the diarrhoea (Fig. 2).

3. Racecadotril has a rapid onset of action

The second property is that a drug for the treatment of diarrhoea should have a rapid onset of action. The rapid onset of action of racecadotril has been demonstrated in both healthy adult subjects and in patients suffering from diarrhoea.

Plasma enkephalinase activity was measured in eight healthy adult subjects after a single oral dose of 100 mg racecadotril. As Fig. 3 shows, racecadotril produced significant inhibition of plasma enkephalinase ($P < 0.01$) within the first 30 min of administration. Maximum inhibition was seen after 60 min.

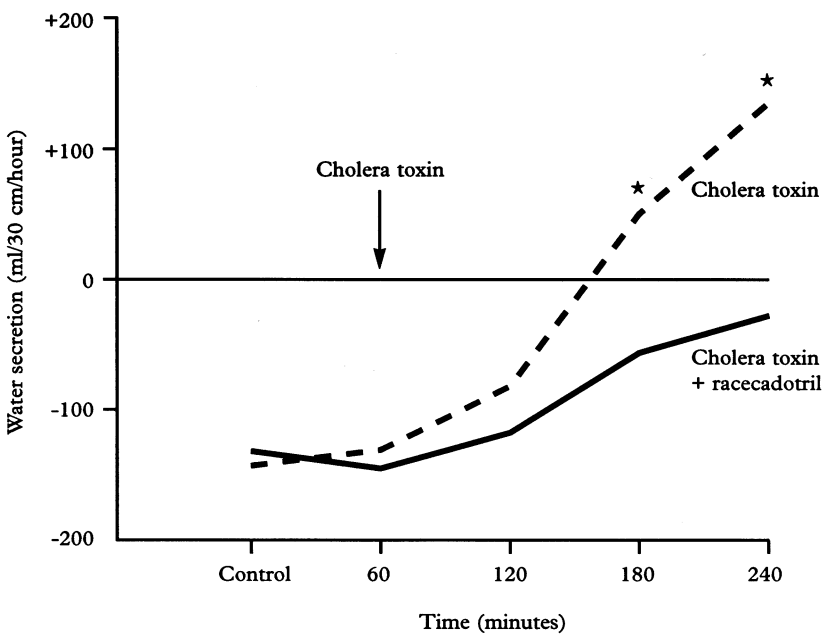

Fig. 1. Effect of racecadotril (a single oral dose of 300 mg) on cholera toxin-induced water secretion in the jejunum of six healthy adult subjects. Positive values represent secretion and negative values absorption. *$P < 0.05$ (after Hinterleitner et al., 1997 [12]).

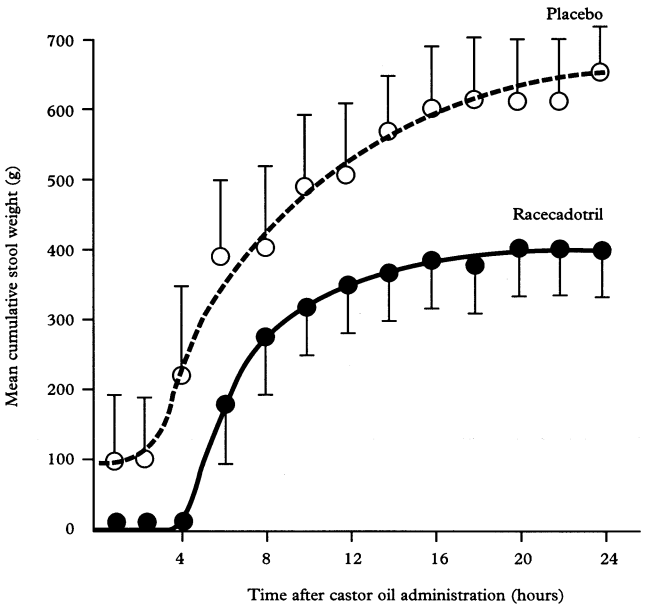

Fig. 2. Mean (±SEM) cumulative stool weights in six healthy adult subjects with castor oil-induced diarrhoea after pre-treatment with racecadotril (10 mg/kg) or placebo. The difference between treatments was statistically significant ($P < 0.001$) (after Baumer et al., 1992 [13]).

A double-blind, parallel-group, randomized study in which adult patients with acute diarrhoea received 100 mg racecadotril three times daily (32 patients) or placebo (38 patients) for up to 7 days confirmed the rapidity of action of racecadotril [14]. Stool weight was used in this study to provide an objective criterion of antisecretory activity. Compared with placebo, racecadotril produced a significant, 28.9% decrease ($P = 0.025$) in stool weight within the first 24 h of treatment (Fig. 4). Racecadotril was also associated with significantly fewer diarrhoeic stools than placebo ($P = 0.027$).

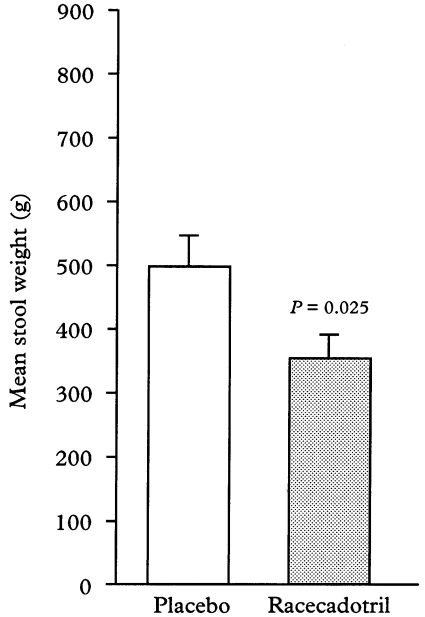

Fig. 4. Mean (±SD) stool weight in adult patients with acute diarrhoea after 24 h of treatment with racecadotril ($n = 32$) or placebo ($n = 38$) (adapted from Hamza et al., 1999 [14]).

4. Racecadotril is not associated with adverse gastrointestinal effects

The third property is that a drug for the treatment of diarrhoea should have limited constipating effects to avoid pooling of fluid in the distended bowel lumen, enhancement of bacterial colonization, and invasion by *Shigella*. The fourth property is that the drug should not interfere with recovery of local bowel function.

In clinical practice, the antimotility mechanism of action of many of the traditional drugs used to treat diarrhoea can lead to adverse effects such as constipation, abdominal pain, and abdominal distension, which has limited the potential use of these drugs [4–6].

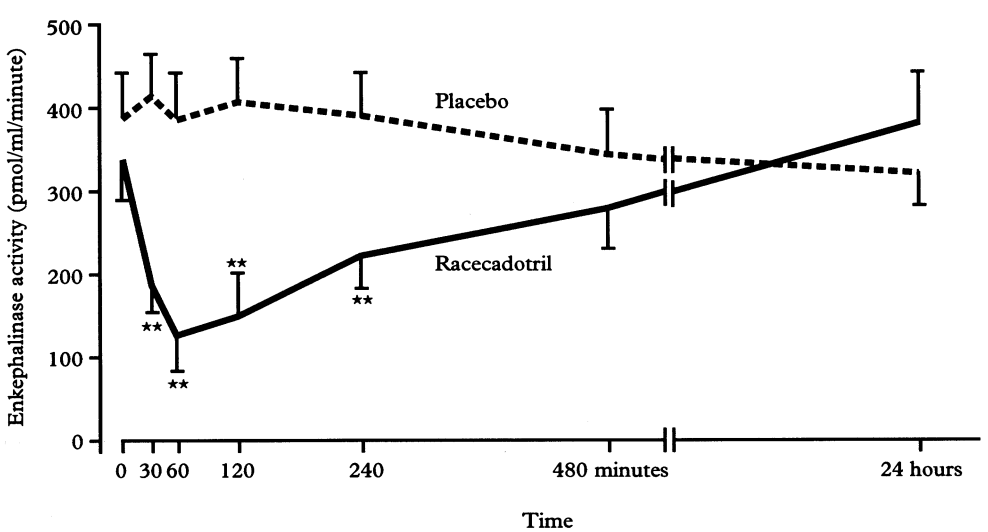

Fig. 3. Plasma enkephalinase activity in eight healthy adult subjects after a single oral dose of racecadotril (100 mg); $^{**}P < 0.01$.

The effect of racecadotril on gastrointestinal transit time was studied in 12 healthy adult subjects in a randomized, double-blind, crossover, placebo-controlled study [15]. Oro-caecal transit time was assessed by following the transformation of sulphasalazine into its metabolite sulphapyridine. Subjects took 100 mg racecadotril or placebo three times daily for 7 days. On day 7, each subject received 2 g sulphasalazine with a standardized breakfast and blood samples were then drawn every 30 min over an 8-h period. The oro-caecal time was quantified by the first appearance of sulphapyridine in the plasma.

As shown in Fig. 5, racecadotril had no significant effect on mean ($\pm$SEM) oro-caecal transit time. The respective values were 282 ± 27 min with racecadotril and 303 ± 32 min with placebo.

Colonic transit times were measured in the same experiment following oral ingestion of radio-opaque markers during the first 5 days of drug treatment. The number of markers in the colon was then counted by X-ray on day 6. Once again, racecadotril had no significant effect on mean ($\pm$SEM) colonic transit time (31.3 ± 5.6 h with racecadotril vs. 25.8 ± 5.8 h with placebo; Fig. 5).

The implications of the lack of effect of racecadotril on gastrointestinal transit time have been confirmed in patients suffering from acute diarrhoea. Clinical studies have been carried out to compare the incidence of constipation during treatment with racecadotril with that of placebo and the μ opiate receptor agonist loperamide.

Baumer et al. [13] treated 193 patients who had acute diarrhoea with racecadotril ($n = 95$) or placebo ($n = 98$) for a maximum of 10 days. The incidence of constipation was similarly low in both groups; only four patients receiving racecadotril suffered from constipation and two on placebo. The incidence of both abdominal pain and abdominal distension was significantly ($P < 0.05$) lower with racecadotril; eight patients (9.6%) had abdominal pain at the end of the study compared with 18 (20.5%) on placebo, and 13 (18.3%) had abdominal distension at the end of the study compared with 26 (34.7%) on placebo.

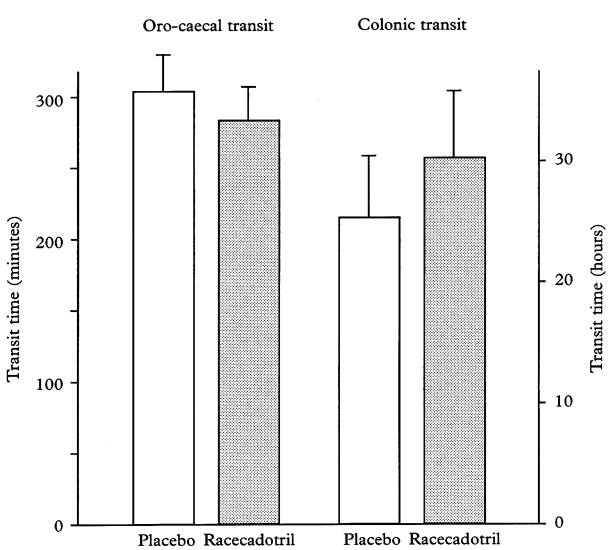

Fig. 5. Mean ($\pm$SEM) oro-caecal and colonic transit times in 12 healthy adult subjects receiving racecadotril (100 mg) or placebo three times daily for 7 days (adapted from Bergmann et al., 1992 [15]).

In their double-blind study comparing the effects of racecadotril and placebo in adults with acute diarrhoea, Hamza et al. [14] reported no significant difference in stool weights between the two groups of patients after the diarrhoea had resolved, again showing the lack of constipation with racecadotril. The frequency of abdominal distension at the second patient consultation on day 4 was 5.6% on racecadotril compared with 18.2% on placebo.

Rogé et al. [16] carried out a double-blind trial to compare the effects of racecadotril (100 mg three times daily; $n = 37$) and loperamide (1.33 mg three times daily; $n = 32$) in patients with acute diarrhoea. Treatment was continued for a maximum of 7 days. After the diarrhoea had resolved, 8.1% of patients receiving racecadotril reported rebound constipation compared with 31.3% receiving loperamide ($P < 0.02$). In addition, 50% of patients on loperamide reported abdominal distension for more than one day compared with 27% on racecadotril ($P < 0.05$), while 59.4 and 40.5% of patients on loperamide and racecadotril, respectively, complained of abdominal pain for more than 1 day during treatment. These results are shown in Fig. 6.

Similarly, Vetel et al. [17] found the incidence of rebound constipation (defined as the percentage of patients who did not pass a stool for at least 2 days during treatment) to be lower with racecadotril (9.8% vs. 18.7% on loperamide).

5. Racecadotril has a high therapeutic index

The fifth property is that a suitable drug for the treatment of diarrhoea should have a high therapeutic index. The therapeutic index of a drug is based on its safety profile. Pharmacological studies have demonstrated that racecadotril does not produce any toxic effects when given at doses of up to 100 times the therapeutic dose for up to 12 months in primates. In man, a single oral dose of 2 g, equivalent to more than 20 times the therapeutic dose has been given to healthy subjects without ill effects.

Overall, 1883 adult patients have been treated with racecadotril in clinical trials, 100 of whom received the drug for at least three months. Regardless of the characteristics of the patients studied, this clinical experience has demonstrated that the tolerability and safety

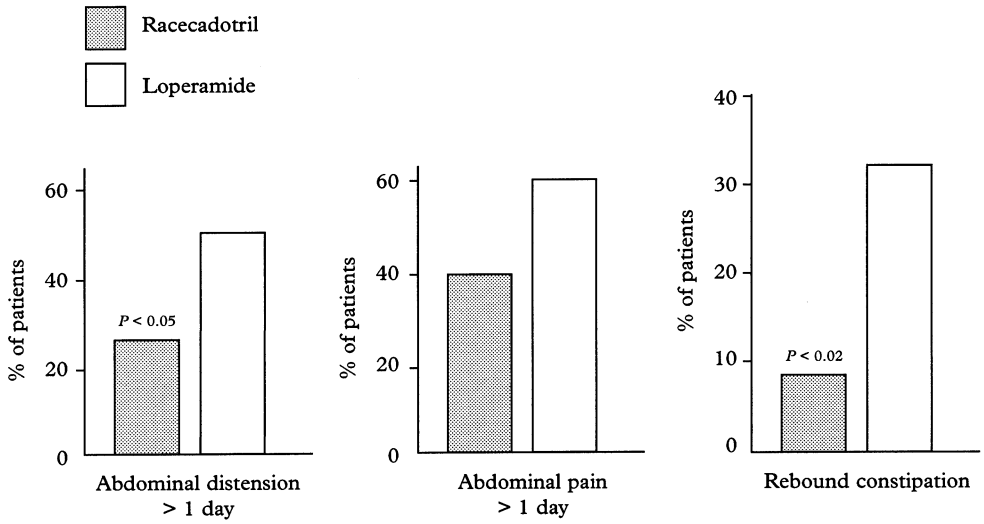

Fig. 6. Percentage of patients reporting abdominal distension for more than 1 day, abdominal pain for more than 1 day, or rebound constipation during treatment with racecadotril (100 mg; $n = 37$) or loperamide (1.33 mg; $n = 32$) three times daily for a maximum of 7 days (adapted from Rogé et al., 1993 [16]).

profile of racecadotril is similar to that of placebo and more favourable than that of the μ opiate receptor agonist loperamide. Moreover, almost 4 million doses of racecadotril have been taken to date without any major side-effects.

Individual clinical studies have confirmed the favourable tolerability and safety profile of racecadotril. Baumer et al. [13], in their study of 193 patients with acute diarrhoea, reported that the incidence, nature, and severity of adverse events were similar for both racecadotril and placebo. Global evaluation by both physician and patient confirmed the good tolerability of racecadotril. Similarly, Hamza et al. [14] found that 3.1% of patients taking racecadotril reported adverse events at the second physician consultation on day 4 compared with 5.3% of those receiving placebo.

The two double-blind comparative studies against loperamide also demonstrated that racecadotril was well tolerated [16,17].

6. Racecadotril does not affect the central nervous system

The final properties are that a drug should have minimal central nervous system effects and a low abuse potential.

The ability of racecadotril to enter the brain was assessed by comparing the enkephalinase activity in cerebrospinal fluid and plasma following oral administration. Two patients who had been hospitalized to undergo myelography were given a single, high, oral dose of racecadotril (20 mg/kg). The activity of enkephalinase in the plasma had decreased to a minimum within 30 min, demonstrating maximal enzyme inhibition by racecadotril. In contrast, the activity of the enzyme in the cerebrospinal fluid remained unchanged, indicating that racecadotril does not cross the blood–brain barrier.

The lack of effect of racecadotril on the central nervous system was confirmed by the results of a double-blind, randomized, crossover study carried out in 12 healthy subjects. Each subject received placebo or racecadotril (300 mg/day) for 3 days, and a battery of psychometric tests was carried out to assess vigilance before and after treatment. Subjects were also asked to complete a number of visual analogue scales designed to evaluate their degree of alertness. All subjects received both treatments. The results showed that racecadotril did not impair vigilance.

The lack of potential for abuse with racecadotril has been demonstrated in studies carried out in monkeys and rats [18]. Rats who had been trained to discriminate morphine from saline did not generalize to racecadotril after administration of doses ranging from 5–50 mg/kg. In addition, monkeys who had been trained to self-administer cocaine did not do so when racecadotril was substituted for cocaine. Racecadotril did not suppress withdrawal in morphine-dependent monkeys and rats, nor were any signs of withdrawal observed after termination of chronic infusion in the rat. Hence these results confirm that racecadotril has minimal potential for abuse.

7. Racecadotril is effective in treating acute diarrhoea

The clinical efficacy of racecadotril has been confirmed in four double-blind, randomized, comparative trials in patients suffering from acute diarrhoea of

presumed infectious origin. Two studies compared racecadotril with placebo and two compared the drug with loperamide.

As mentioned previously, the study carried out by Hamza et al. [14] demonstrated the rapidity of action of racecadotril in acute diarrhoea together with its lack of constipating effect.

The second placebo-controlled study was carried out in Paris during a 5-month winter epidemic [13]. A total of 193 adult outpatients with severe acute diarrhoea received racecadotril ($n = 95$) or placebo ($n = 98$) until recovery (defined as the disappearance of any unformed stools) or for a maximum of 10 days. Patients were examined by the physician at the beginning and end of the study. In addition, each patient completed an auto-evaluation sheet.

Table 2
Efficacy results (mean ± SEM) in adult patients with acute diarrhoea who were treated with racecadotril or placebo for up to 10 days (After Baumer et al., 1992 [13])

Efficacy criterion	Racecadotril ($n = 95$)	Placebo ($n = 98$)
Duration of diarrhoea (days)	3.0 ± 0.2	4.4 ± 0.3***
Total number of capsules administered	11.6 ± 0.9	15.5 ± 1.2**
Probability of recovery on day 4 (%)	75 ± 5	37 ± 5***
Global evaluation of efficacy (analogue scale of 0 to 100)		
Physician's rating	83 ± 2	61 ± 3***
Patient's rating	82 ± 2	62 ± 3***

** $P < 0.01$.
*** $P < 0.001$.

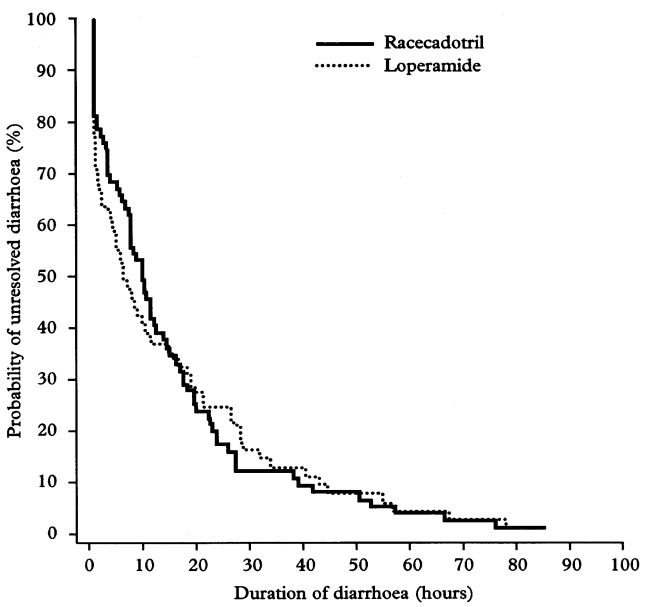

Fig. 7. Kaplan-Meier curves showing the duration of diarrhoea in patients receiving racecadotril (100 mg three times daily; $n = 77$) or loperamide (2 mg after each diarrhoeic stool; $n = 70$) for a maximum of 7 days (after Vetel et al., 1999 [17]).

As shown in Table 2, racecadotril was significantly superior to placebo in terms of all efficacy criteria assessed.

Rogé et al [16] treated 69 adult outpatients with racecadotril (100 mg; $n = 37$) or loperamide (1.33 mg; $n = 32$) three times daily until recovery (defined as the disappearance of any unformed stools), or for a maximum of 7 days. Patients were examined by the physician at the beginning and end of the study, and each patient also completed an auto-evaluation sheet.

Physicians rated the efficacy of treatment to be excellent or good in 91.9% of patients receiving racecadotril and 87.5% of patients on loperamide. In addition, the mean (± SEM) duration of diarrhoea was 2.2 ± 0.2 days with racecadotril and 2.3 ± 0.2 days with loperamide.

The second study against loperamide was carried out in 157 adult patients with acute diarrhoea, and was of randomized, multicentre, double-blind, double-placebo, parallel-group design [17]. Patients received one 100 mg capsule of racecadotril plus one placebo capsule three times daily, or one 2 mg capsule of loperamide plus one placebo capsule after each diarrhoeic stool. Treatment was continued until recovery (defined as the production of two normal stools or lack of production of stools for a period of 12 h), or for a maximum of 7 days. In addition to the physician's assessment, patients completed an auto-evaluation sheet.

Fig. 7 shows the actuarial curves for both groups. The mean (± SEM) duration of diarrhoea was 14.9 ± 2.0 h for racecadotril and 13.7 ± 2.2 h for loperamide. The mean (± SEM) number of stools passed until recovery was 3.5 ± 0.5 with racecadotril and 2.9 ± 0.4 with loperamide.

The results of these studies demonstrate that racecadotril is rapidly effective in treating acute diarrhoea. As described above, this efficacy is accompanied by a lack of undesirable effects such as constipation, abdominal distension, and abdominal pain, and racecadotril is generally well tolerated by patients.

8. Conclusions

Clinical pharmacology studies and clinical trials in patients have confirmed the validity of the innovative concept of prevention of water and electrolyte losses (the major pathogenetic mechanism underlying acute diarrhoea) by protection of endogenous enkephalins from inactivation. Racecadotril therefore offers a new approach to the treatment of diarrhoea via its mechanism of action as the first true antisecretory agent available for clinical use.

References

[1] Basilisco G, Camboni G, Bozzani A, Paravicini M, Bianchi PA. Oral naloxone antagonizes loperamide-induced delay of oro-caecal transit. Dig Dis Sci 1987;32:829–32.

[2] Heel RC, Brogden RN, Speight TM, Avery GS. Loperamide: a review of its pharmacological properties and therapeutic efficacy in diarrhoea. Drugs 1978;15:33–52.

[3] Kachel G, Ruppin H, Hagel J, Barma W, Meinhardt M, Domschke W. Human intestinal motor activity and transport: effects of a synthetic opiate. Gastroenterology 1986;90:85–93.

[4] Ruppin H. Review: loperamide — a potent anti diarrhoeal drug with actions along the alimentary tract. Aliment Pharmacol Ther 1987;1:179–90.

[5] Du Pont HL, Hornick RB. Adverse effect of lomotil therapy in shigellosis. J Am Med Assoc 1973;226:1525–8.

[6] Brown JW. Toxic megacolon associated with loperamide therapy. J Am Med Assoc 1979;241:301–2.

[7] Edelman R. Prevention and treatment of infectious diarrhoea. Speculations on the next 10 years. Am J Med 1985;78:99–106.

[8] Primi MP, Bueno L, Baumer Ph, Bérard H, Lecomte JM. Racecadotril demonstrates intestinal antisecretory activity in vivo, Aliment Pharmacol Ther 1999;13(Suppl. 6):3–7.

[9] Marçais-Collado H, Uchida G, Costentin J, Schwartz JC, Lecomte JM. Naloxone reversible antidiarrheal effect of enkephalinase inhibitors. Eur J Pharmacol 1987;144:125–32.

[10] Duval-Iflah Y, Bérard H, Baumer Ph, et al. Effects of racecadotril and loperamide on bacterial proliferation and on the central nervous system of the newborn gnotobiotic piglet, Aliment Pharmacol Ther 1999;13(Suppl. 6):9–14.

[11] Schwartz J-C. Racecadotril: a new approach to the treatment of diarrhoea. Int J Antimicrob Agents 2000;14:73–77.

[12] Hinterleitner TA, Petritsch W, Dimsity G, Bérard H, Lecomte JM, Krejs GJ. Acetorphan prevents cholera-toxin induced water and electrolyte secretion in the human jejunum. Eur J Gastroenterol Hepatol 1997;9:887–91.

[13] Baumer P, Danquechin-Dorval E, Bertrand J, Vetel JM, Schwartz JC, Lecomte JM. Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhoea. Gut 1992;33:753–8.

[14] Hamza H, Ben Khalifa H, Baumer Ph, Bérard H, Lecomte JM. Racecadotril versus placebo in the treatment of acute diarrhoea in adults, Aliment Pharmacol Ther 1999;13(Suppl. 6):15–19.

[15] Bergmann JF, Chaussade S, Couturier D, Baumer P, Schwartz JC, Lecomte JM. Effects of acetorphan, an antidiarrhoeal enkephalinase inhibitor, on oro-caecal and colonic transit times in healthy volunteers. Aliment Pharmacol Ther 1992;6:305–13.

[16] Rogé J, Baumer Ph, Bérard H, Schwartz JC, Lecomte JM. The enkephalinase inhibitor, acetorphan, in acute diarrhea: a double-blind controlled clinical trial versus loperamide. Scand J Gastroenterol 1993;28:352–4.

[17] Vetel JM, Bérard H, Frétault N, Lecomte JM. Comparison of racecadotril and loperamide in adults with acute diarrhoea, Aliment Pharmacol Ther 1999;13(Suppl. 6):21–26.

[18] Knisely JS, Beardsley PM, Aceto MD, Balster RL, Harris LS. Assessment of the abuse potential of acetorphan, an enkephalinase inhibitor. Drug Alcohol Depend 1989;23:143–51.