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Racecadotril

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Contents

Abstract

▲ Racecadotril is an oral enkephalinase inhibitor used in the treatment of acute diarrhoea. It prevents the degradation of endogenous opioids (enkephalins), thereby reducing hypersecretion of water and electrolytes into the intestinal lumen.

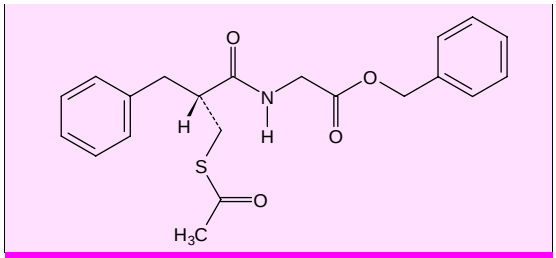
▲ In a randomised double-blind study in 6 adult volunteers with castor oil-induced diarrhoea, racecadotril significantly reduced stool weight and stool number in comparison with placebo. Similar results have been obtained in treating castor oil-induced diarrhoea in rats.

▲ Racecadotril was significantly more effective than placebo in randomised double-blind studies in adults or children with diarrhoea (of infectious origin or in adults with HIV infection).

▲ In well controlled trials, racecadotril had efficacy similar to that of loperamide and was generally as effective as loperamide-oxide.

▲ Racecadotril had a similar tolerability profile to placebo, and was better tolerated than loperamide, in adults and children with diarrhoea. It caused significantly less constipation after resolution of diarrhoea than loperamide.

Features and properties of racecadotril (acetorphan)	
Indications	
Treatment of acute diarrhoea	
Mechanism of action	
Antidiarrhoeal (prodrug of thiorphan)	Enkephalinase inhibitor
Dosage and administration	
Usual dosage in clinical trials	100-300mg (adults) 1.5mg/kg (children)
Route of administration	Oral
Frequency of administration	3 times daily
Pharmacokinetic profile of thiorphan (after oral administration of racecadotril 300mg in 10 healthy volunteers)	
Peak plasma concentration	805-1055 nmol/L
Time to peak plasma concentration	1h
Elimination half life	3h
Adverse events	Similar to placebo



Racecadotril (acetorphan)

Racecadotril (acetorphan) is a lipophilic diesterified prodrug of the enkephalinase inhibitor thiorphan.[1] It is the first and only enkephalinase inhibitor in its class.

1. Pharmacodynamic Profile

Mechanism of Action and Binding Profile

• In peripheral tissues, orally administered racecadotril is rapidly hydrolysed to the more potent enkephalinase inhibitor thiorphan.[1-3] Within these tissues, membrane-bound enkephalinase enzymes degrade endogenous opioids (enkephalins). Inhibition of enkephalinase by thiorphan increases the availability of opioids, which activate delta (δ) opioid receptors in the gastrointestinal tract.[4] This in turn leads to a reduction in cAMP mucosal levels, resulting in a reduction in the secretion of water and electrolytes into the intestinal lumen (i.e. an antisecretory mechanism in contrast to loperamide which slows gastrointestinal transit).[5-9]

• *In vitro* tissue binding of [^{3}H]thiorphan varies according to tissue type [maximum amount bound (B_{max}) of 63 pmol/mg protein in the striatum, 860 pmol/mg protein in the kidney].[2] This binding is correlated with the catalytic activity of enkephalinase in these tissues. *In vivo* B_{max} values for binding of [^{3}H]racecadotril were 65 fmol/mg protein in the striatum and 1305 fmol/mg protein in the kidney after intravenous administration in mice.

Effects on Enzyme Activity

• The concentration of racecadotril required to inhibit purified enkephalinase enzyme by 50% (IC_{50}) was 4500 nmol/L, compared with 6.1 nmol/L for thiorphan.[1] When racecadotril (100 μmol/L) was preincubated in the presence of mouse whole brain membranes, the subsequent IC_{50} was 8.6 nmol/L. Preincubation of racecadotril in the absence of cerebral membranes had no significant effect on the IC_{50} value.

• Maximum enkephalinase inhibition increased with racecadotril dose (59, 76 and 89% inhibition with single 30, 100 and 300mg doses, respectively) in a placebo-controlled double-blind crossover study in 8 healthy human volunteers.[10]

• Intravenous administration of racecadotril 1 mg/kg in mice significantly reduced enkephalinase activity in striatal membrane fractions for approximately 8 hours. At 24 hours enkephalinase activity matched that seen in control mice.[1] Enkephalinase activity in hypothalamic membranes was reduced by 55, 68 and 70% 1 hour after administration of racecadotril 10, 25 and 50 mg/kg (intraperitoneally) in comparison with activity in rats receiving vehicle.[1]

Models of Diarrhoea

• Racecadotril significantly reduced castor oil-induced diarrhoea in 6 adult volunteers. In a randomised, double-blind placebo-controlled crossover study, participants received either a single dose of racecadotril (mean 11.1 mg/kg, dosage chosen to approximate 10 mg/kg) or placebo (200mg lactose per capsule) with a 1-week gap between treatments. At the beginning of each treatment participants took 5 capsules after 1 spontaneous stool, and 45 minutes later they ingested 30g of castor oil. Racecadotril significantly reduced stool weight during the following 24-hour period by 37% and stool number by 49% ($p = 0.009$ and $p < 0.002$, respectively) compared with placebo.[5]

• Racecadotril reduced castor oil-induced diarrhoea in rats in a dose-dependent manner.[1] Treatments were administered 15 minutes before a 1ml dose of castor oil and total cumulative stool weight was calculated at 90 minutes. Intravenous racecadotril (5, 10 and 20 mg/kg) significantly reduced

stool weight by 61, 79 and 100%, respectively, compared with that in rats receiving vehicle.

2. Pharmacokinetic Profile

Data in this section are primarily derived from a product monograph from the manufacturer.[10]

- After intravenous administration in mice racecadotril is rapidly metabolised to its active metabolite thiorphan. High performance liquid chromatography of mouse kidney membranes 30 minutes after administration of [^{3}H]racecadotril (500 μCi/kg) indicated that the bound radioactivity corresponded to [^{3}H]thiorphan; unchanged [^{3}H]racecadotril was not detectable.[2]

- In a placebo-controlled double-blind crossover study in 8 healthy volunteers, the peak plasma concentration (C_{max}) of thiorphan was reached 60 minutes after administration of a single oral dose of racecadotril (30, 100 or 300mg). Biological half-life of enkephalinase activity ($t_{½}$) was 3 hours.[10] Area under the concentration time curve (AUC) values of 1285 and 1049 (arbitrary units) for 100 and 300mg doses of racecadotril were associated with significant inhibition of enkephalinase activity compared with placebo.

- The pharmacokinetic parameters of repeated doses of racecadotril (30, 100 or 300mg 3 times daily for 7 days) were the same on days 1 and 7 as those observed for a single oral dose, in a placebo-controlled double-blind study in 16 healthy volunteers.[10]

- C_{max} of thiorphan 1 hour after administration of racecadotril to 10 healthy volunteers with cholera toxin-induced diarrhoea ranged from 805 to 1055 nmol/L. A therapeutic plasma level was observed throughout the study with plasma levels at 4 hours ranging from 92 to 240 nmol/L.[6]

- The pharmacokinetics of a single oral 100mg dose of racecadotril were evaluated in 7 healthy elderly volunteers. The time to C_{max} (90 minutes), maximum enkephalinase inhibition (73%) and AUC [155 (arbitrary units)] of thiorphan were comparable to those in young adults [nature of the comparison (direct or historical) not reported].[10]

- 92% of radioactively labelled racecadotril (10 mg/kg) was eliminated within 24 hours of single-dose administration in rats.[10]

3. Therapeutic Trials

Racecadotril has been studied primarily in children and adults with acute diarrhoea of presumed infectious origin and in patients with HIV-related chronic diarrhoea. All trials in this section are randomised double-blind design unless stated otherwise. Diarrhoea duration and frequency at inclusion in these trials was typically 1.5 days and ≥3 stools per day for acute diarrhoea, and approximately 9 months and 5 stools per day in participants with chronic diarrhoea. Efficacy criteria were duration of diarrhoea from treatment onset and stool number or stool weight at the end of the trial.

Comparisons with Placebo

Children

- Racecadotril (1.5 mg/kg 3 times daily) given as adjuvant therapy to oral rehydration solution was effective in a multicentre study in 172 infants (aged 2 months to 4 years) with severe acute diarrhoea.[11] Mean stool output during the first 48 hours of racecadotril treatment was significantly reduced by approximately 50% after 24 hours of treatment ($p = 0.004$) and approximately 70% at 48 hours ($p = 0.002$) compared with that in the placebo group. Racecadotril was effective in children who were rotavirus positive and negative.[11]

Adults

- In 193 adult patients with acute diarrhoea, racecadotril significantly decreased the incidence of diarrhoea by 30% ($p < 0.01$) when compared with placebo.[5] The mean duration of diarrhoea was also significantly decreased by 1 day when compared with placebo (3.4 *vs* 4.4 days, $p = 0.001$). Patients taking racecadotril (figure 1 legend for regimen) had a significant reduction in symptoms associated with diarrhoea (e.g. anal burning, spontaneous abdominal pain, nausea and anorexia) compared with placebo recipients [fig. 1].[5]

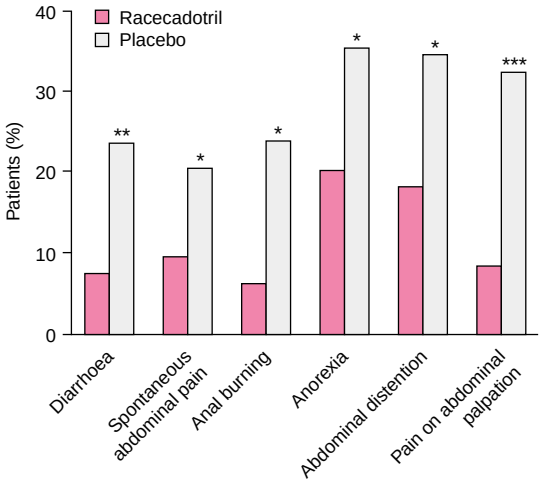


Fig. 1. Symptoms and clinical signs in patients with diarrhoea of infectious origin after 10-day treatment with racecadotril (n = 95) or placebo (n = 98).[5] In a randomised double-blind study, patients received two 100mg capsules of racecadotril (or placebo) on day 1, and 1 capsule after each unformed bowel movement until diarrhoea resolution or for a maximum of 10 days. * $p < 0.05$, ** $p < 0.01$,*** $p < 0.001$ vs placebo.

• Racecadotril provided a greater reduction in stool number than placebo in 174 patients with HIV infection and chronic diarrhoea.[12] Patients received racecadotril (100 to 200mg 3 times daily) or placebo for 2 to 4 weeks. Response was defined as a reduction of more than one third in stool number. Response rates for racecadotril and placebo were 36% and 23%, respectively. On day 30 there was a significant reduction in mean stool number with racecadotril (2.4 vs 3.7 with placebo, $p = 0.02$, n = 41). Racecadotril showed greater efficacy in HIV patients without cryptosporidium infection than in those with this infection ($p = 0.045$).[12]

Comparisons with Other Antidiarrhoeal Agents

• Several randomised placebo-controlled double-blind clinical trials have shown that racecadotril generally has similar efficacy to loperamide in the treatment of acute diarrhoea in adults and children.[13-16]

• Racecadotril and loperamide showed similar efficacy in the treatment of acute diarrhoea in a multicentre trial in 102 children (aged 2 to 10 years) [fig. 2].[15,17] Children received either racecadotril (1.5 mg/kg 3 times daily, n = 52) or loperamide (0.03 mg/kg 3 times daily, n = 50) until recovery (2 consecutive formed stools, 1 formed stool followed by 12 hours without stool production or no stool production for a period of 12 hours). The mean number of loose stools in the 24 hours preceding inclusion and during treatment until recovery was similar for both groups (5.0 *vs* 4.9 and 2.7 *vs* 2.1, respectively, n = 98). The first formed stools were passed after 32.2 (±8.9) hours of treatment with racecadotril compared with 30.6 (±4.7) hours with loperamide. Both treatments resolved diarrhoea within 1 to 2 days of the initiation of therapy. There was no significant difference between the 2 treatments for recurrence rates of diarrhoea (n = 97).[15]

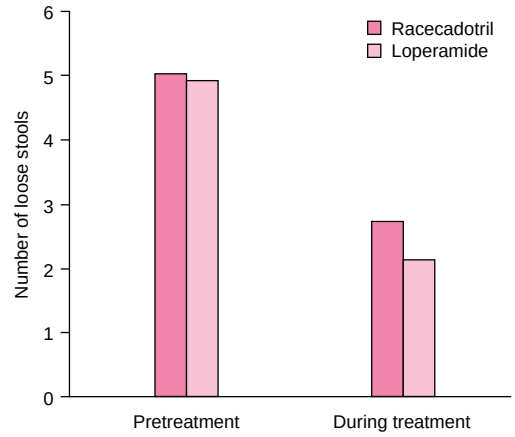


Fig. 2. Comparison of the efficacy of racecadotril and loperamide in children with acute diarrhoea.[15] In a randomised placebo-controlled double-blind study, children received racecadotril (1.5 mg/kg 3 times daily, n = 52) or loperamide (0.03 mg/kg 3 times daily, n = 50) until recovery, defined as 2 consecutive formed stools, 1 formed stool followed by 12 hours without stool production or no stool production for a period of 12 hours. Pretreatment = mean number of loose stools in the 24 hours preceding inclusion, during treatment = mean number of stools from starting treatment until recovery.

• Racecadotril (100mg 3 times daily) showed similar efficacy to loperamide (2mg 3 times daily) in a multicentre study in 147 evaluable adults with acute diarrhoea.[16] The mean number of stools until recovery (3.5 *vs* 2.9) and mean duration of diarrhoea (14.9 *vs* 13.7 hours) were similar for both treatment groups.

• Racecadotril showed similar efficacy to loperamide in 69 adults with acute diarrhoea of infectious origin.[14] Patients were randomly assigned to either racecadotril (100mg capsules) or loperamide (1.33mg capsules) and received 2 capsules on the first day of treatment followed by 2 capsules during the next 12 hours, then 1 capsule was given 3 times daily until recovery or for a maximum of 7 days. Both treatments resolved diarrhoea within 2 days of starting treatment.[14] Racecadotril was as effective as loperamide according to assessment by physicians.

• Racecadotril was as effective as loperamide-oxide (a loperamide derivative) for most efficacy assessments in 574 adults with acute diarrhoea.[13] Patients received either racecadotril (100mg 3 times daily) or loperamide [two 1mg tablets initially and 1 tablet after each unformed stool (maximum 8 tablets/day)]. Both drugs showed similar efficacy for overall resolution of diarrhoea at 24 hours (48% with racecadotril *vs* 53% with loperamide) with almost equal percentages for both antidiarrhoeals at 48 and 96 hours (approximately 87 and 98% respectively). The mean duration of diarrhoea (28.9 hours for racecadotril *vs* 26.8 hours for loperamide-oxide) and daily number of unformed stools (data not given) was similar for both treatment groups. Participants receiving loperamide-oxide had significantly fewer unformed stools ($p < 0.03$) during the total 3-day period. Physicians considered loperamide-oxide to be significantly better overall; however this was not reflected in patients' assessments.[13]

• In a nonblind randomised crossover study, 12 patients with AIDS-related chronic diarrhoea (>5 unformed stools per day for more than 1 month) received either racecadotril (100 to 300mg, orally, 3 times daily) or octreotide (50 to 150μg, subcutaneously, 3 times daily).[18] Patients received each drug for 1 week with no between-treatment washout phase, (for ethical reasons; crossover effects were considered unlikely due to the short half-life of each drug). Racecadotril significantly reduced stool frequency in comparison with the pretrial frequency for all participants (4.6 *vs* 7.0 per day, $p < 0.05$). Octreotide did not significantly reduce stool frequency, and neither treatment had a significant effect on stool weight. Of note, loperamide had previously been unsuccessfully prescribed in 11 of the 12 patients.

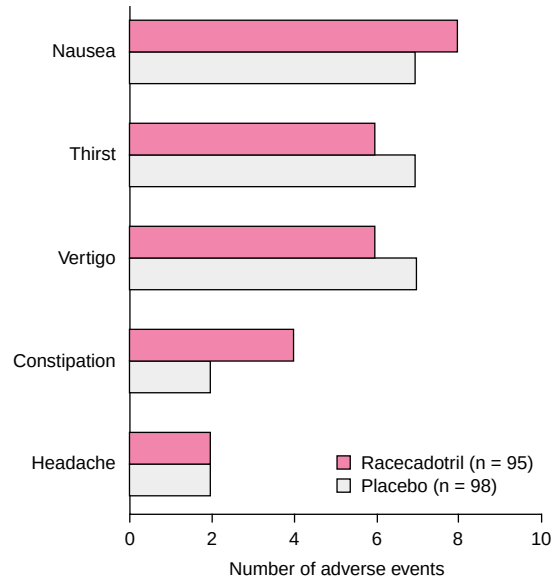


Fig. 3. Tolerability data for racecadotril.[5] In a randomised double-blind placebo-controlled trial, patients with diarrhoea of infectious origin received two 100mg capsules of racecadotril on day 1, and 1 capsule after each unformed bowel movement, until diarrhoea resolution or for a maximum of 10 days. There were no significant differences between the 2 groups.

• Several small clinical trials assessed the efficacy of racecadotril in treating delayed-onset diarrhoea in patients receiving irinotecan for colorectal cancer.[19-22] In the majority of patients, coadministration of racecadotril and loperamide resolved

diarrhoea within 48 hours.[20-22] Pretreatment with racecadotril had no effect on irinotecan-induced diarrhoea.[19,21] In a small pilot study, racecadotril significantly reduced the number of stools per day and the number of days with liquid stools ($p < 0.002$; $p < 0.02$) in patients with acute diarrhoea as a result of fluorouracil chemotherapy for metastatic colo-rectal cancer and in 1 patient receiving treatment for pancreatic carcinoma.[23]

4. Tolerability

- Racecadotril did not differ significantly from placebo in the frequency of adverse events in adults and infants with acute diarrhoea of infectious origin.[5,11] In a randomised double-blind study in 193 adults with acute diarrhoea, there was no significant difference between racecadotril and placebo in the total incidence of adverse events (16.8 *vs* 18.4%) or in the frequency of individual events (fig. 3).[5]

- Racecadotril was better tolerated than loperamide in 69 adults treated for acute diarrhoea in a randomised double-blind clinical trial.[14] In particular, constipation after resolution of diarrhoea was less frequent with racecadotril than with loperamide (8.1 *vs* 31.3%, $p < 0.02$). Racecadotril also significantly reduced the mean duration of abdominal distention ($p < 0.05$) and the number of patients experiencing abdominal distention for longer than 1 day by 46% compared with loperamide ($p < 0.05$).

- Racecadotril is well tolerated in the treatment of acute diarrhoea in children.[11,15] In a randomised double-blind placebo controlled trial in 98 children, it caused less constipation than loperamide (37 vs 58%, $p = 0.03$).[15,17] Vomiting was the most frequent adverse event associated with racecadotril in 2 studies.[11,15] The incidence of vomiting did not differ significantly from that in children receiving loperamide.[15]

5. Racecadotril: Current Status

Racecadotril has shown efficacy in patients with acute diarrhoea in well controlled clinical trials and was generally at least as effective as other antidiarrhoeal drugs. It was better tolerated than loperamide in both adults and children.

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