

## ***Drug Therapy***

### **Racecadotril**

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Enkephalins (endogenous opiate peptides) act as neurotransmitters along the entire digestive tract where they mediate intestinal absorption without affecting intestinal transit time or motility(1). They are short-lived peptides rapidly cleaved by 2 membrane peptidases: an enkephalinase and a carboxypeptidase. Enkephalinase is abundant in the gastrointestinal tract and accounts for over 85% hydrolysis of methionine and leucine enkephalins providing a potentially novel target for the treatment of acute watery diarrhea. Racecadotril or acetorphan (derived from thiorphan) through inhibition of enkephalinase reinforces the physiological activity of endogenous enkephalins and therefore shows intestinal antisecretory activity. The Drug Controller General of India approved it as an anti-diarrheal in October 2001(2). The drug has not yet been approved by the FDA (Food and Drug Administration).

#### **Structure and mechanism of action**

Racecadotril [acetorphan: N-[(R,S)-3-acetylmercapto-2benzylpropanoyl]-glycine, benzyl ester, is a lipophilic derivative of Thiorphan. It is a dipeptide with a single amide

bond developed from research into the structure-activity relationships of the enkephalinase molecule. Racecadotril is rapidly converted to thiorphan which interacts specifically with the active site of enkephalinase to produce potent blockade of the enzyme preventing inactivation of endogenous opioid peptides (enkephalins) released by submucosal and myenteric neurons. The enkephalins in turn mediate their effect through delta receptor activation that induces a selective increase in chloride absorption by inhibiting adenylate cyclase(1).

#### **Pharmacodynamics**

##### *Inhibition of enkephalinase activity*

Preclinical studies have documented selective inhibition of enkephalinase activity by racecadotril in various animal models. Intravenous administration of 1 mg/kg racecadotril in mice significantly reduced enkephalinase activity in striatal membrane fractions for approximately 8 hrs(3). Also, enkephalinase activity in hypothalamic membranes was reduced by 55, 68 and 70% one hour after intraperitoneal administration of racecadotril 10, 25 and 50 mg/kg(4). Similarly, in a double blind placebo-controlled cross-over trial on 8 human volunteers enkephalinase activity was reduced by up to 89 % using a 300 mg dose(5).

##### *Efficacy in experimental models of diarrhea*

In a randomized double-blind study on 6 adult volunteers with castor oil-induced diarrhea, racecadotril significantly reduced stool weight during the following 24 h period by 37% and stool number by 49% ( $p = 0.009$  and  $p < 0.002$ , respectively) compared with

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placebo(6). Similarly in a model employing segmental perfusion of the human proximal jejunum, cholera toxin was used to induce intestinal secretion through an intestinal perfusion technique. Acetorphan had no influence on basal water and electrolyte absorption (133 vs. 140 mL/30 cm × h). In a control group with cholera toxin alone, significant water secretion was induced (131 mL/30 cm × h). Acetorphan completely prevented this secretion by leaving an absorption rate of 27 mL/30 cm × h. Intestinal electrolyte transport was also significantly changed towards absorption by acetorphan (7). Further, in a study evaluating the oro-caecal and colonic transit times there was no significant modification in transit time linked to acetorphan treatment(8).

### Pharmacokinetics

After oral administration, racecadotril is rapidly absorbed and quickly metabolized to its active metabolite thiorphan, which in turn mediates all further actions. The activity on plasmatic enkephalinase appears 30 min after the administration. The peak plasma concentration of thiorphan is reached 60 min after administration of a single oral dose of racecadotril. The biological half-life of enkephalinase activity is 3 h. The pharmacokinetic parameters of repeated doses of racecadotril are similar on days 1 and 7 as those observed for a single oral dose.

### Therapeutic trials

The clinical efficacy of racecadotril in diarrhea in humans has been under investigation since 1992 when first such reports appeared(6). The drug has since been evaluated in children(9,11,12), adults (6,10,13), cholera(7,18), chronic diarrhea in HIV patients(19) and in chemotherapy induced diarrhea(20) in developing and developed countries (*Table I*).

### *In children*

In a well designed double blind randomized control trial in Peru on 3 to 35 months old children, racecadotril and rehydration were compared with rehydration alone in 166 boys with acute non-bloody diarrhea without severe dehydration or serious concomitant illness(9). Significant reductions were documented in 48 h stool output ( $92 \pm 12$  g/kg vs.  $170 \pm 15$  g/kg;  $p < 0.001$ ), mean total stool output ( $157 \pm 27$  g/kg vs.  $331 \pm 37$  g/kg;  $p < 0.001$ ) and median duration of diarrhea (28 vs. 52 h;  $p < 0.001$ ). The overall five-day cure rates were 84 percent in the racecadotril group and 66% in the placebo group. Seventy three (44%) children tested positive for rotavirus while bacterial pathogens were identified in 53 (32%) children. The results on stratified analysis showed the drug to be equally efficacious for rotavirus positive and negative children excepting that the mean stool output were higher in general for the rotavirus group and the diarrhea tended to last longer (72 h vs. 52 h). Cezard, *et al.*(11) documented similar results with the 24 hour stool output in the racecadotril group being 65% of that of placebo. The drug was equally efficacious in rotaviral diarrhea. Also, a  $\text{Na}^+/\text{K}^+$  ratio of less than 1 in the urine was found in 24.1% of patients receiving racecadotril and 53.3% of those receiving placebo ( $P = 0.01$ ), suggesting greater re-hydration with raceca-dotril. Cojocar, *et al.*(9) also documented similar findings using number of stools and recovery time as outcome parameters.

### *In adults*

The results of efficacy trials conducted in adults are essentially similar to those in children with a study from Brazil documenting a 24 h difference in recovery time using racecadotril(10).

**TABLE I— Clinical Efficacy of Racecadotril**

Author Year, Country	Design; Funding	Evidence grade*	Subjects	Study Groups	Outcome Variables	Results and Conclusions
Cojocar B <i>et al</i> 2002, France(9)	RCT NA	-	166 children aged three mo to three y	Alternate child rehydration + drug or racecadotril alone	Number of medical examinations in 7 days Number of stools during the first 48 h, Duration of diarrhea and weight on day 7	Racecadotril group had a significant lower number of stools (p < 0.001), faster recovery (p < 0.001), needed less additional ED visits for the same episode (p < 0.05) with no difference for the weight-gain on day 7
Cezard JP <i>et al</i> 2001, France(11)	RCT IC*	1-	172 children aged 3 mo to 4 y	Two groups- Racecadotril (n=89) vs. placebo (n=83)	Stool output in 24 h, Recovery time, ORS use and Na/K ratio in urine	During the first 48 hours of treatment, patients receiving racecadotril had a significantly lower stool output
Salazar-Lindo E <i>et al</i> 2000, Peru(12)	RCT FD†	1-	135 boys aged 3 to 35 mo with watery diarrhea	Two groups- study (n=68) Placebo (n=67)	48 h stool output, Total stool output, Duration of diarrhea, Total intake of ORS	The mean (+/-SE) 48-hour stool output was 46% less in racecadotril group (P<0.001), The total stool output, duration of diarrhea & intake of ORS was significantly less in the racecadotril group (P<0.001)
Moraes E <i>et al</i> 2001, Brazil(10)	RCT-double blind-NS‡	1+	336 adults	Two groups-racecadotril (n=175) vs. Saccharomyces boulardii (161) *3 days	Recovery time Associated symptoms like abdominal pain, distention, nausea and anorexia	In mild cases a 24-hour difference (76 hours for racecadotril vs. 52 hours) between the two groups (p=0.017) and in severe cases the difference between the groups was 17 hours (p=0.016).
Hamza H <i>et al</i> 1999, Tunisia(13)	RCT-double blind/ NA	-	70 adults	Two groups- Racecadotril vs. placebo	Stool weight and number	No difference in associated symptoms was observed in the in the two groups Significant (P = 0.025) decrease in stool weight during the first day of treatment, significantly fewer stools after 1 day of treatment (p = 0.027).
Baumer P <i>et al</i> 1992, France(6)	RCT- double blind/ IC*	1-	194 with sev. Ac. diarrhea (>5 stools /d)	Two groups- Racecadotril (n=96) vs. placebo(n=98)	Duration of diarrhea & treatment, Frequency of other symptoms, Withdrawal from study	The duration of diarrhea and treatment were diminished; (ii) withdrawal from study 0 vs. 5 (iii) the frequency of symptoms with diarrhea after two weeks was nearly halved;
Baumer P <i>et al</i> 1992, France (6)	Experimental- double blind/IC*	2+	6 human volunteers	Racecadotril and placebo one week apart in cross over format	Mean stool weight Total number of stools	Mean stool weight 672 ± 76 g/kg vs. 426 ± 83 g/kg(racecadotril)(p<0.01). Number of stools = 3.7 ± 0.3 vs 1.8 ± 0.2 (racecadotril) (p=0.002)
<b>Racecadotril vs. Loperamide</b>						
Prado D <i>et al</i> 2002 Guatemala(14)	RCT-single blind FD†	1-	945 adults	Two groups- Racecadotril (n=473) vs. loperamide (n=472)	Duration of diarrhea, occurrence and duration of abdominal pain, distension, other associated signs and symptoms	Racecadotril produced greater reduction in abdominal pain and distension than loperamide (P = 0.024 and 0.03, respectively). Duration of abdominal distension was shorter with racecadotril (P = 0.0001) constipation was less frequent (P = 0.001).
Turck D <i>et al</i> 1999 France(15)	Multicentre RCT NA	-	52 children aged 2 to 10 y	Two groups- Racecadotril vs. loperamide	Number of stools Duration of diarrhea	Both the groups passed a similar number of stools before recovery, duration of diarrhea similar in both groups. Incidence of adverse events was lower with racecadotril (11.5% vs. 22%), and more patients on loperamide had constipation (58% vs. 36.5%; P = 0.03)
Vetel JM <i>et al</i> 1999 France(16)	Multicentre RCT-double blind/ NA	-	157 adults with acute diarrhea	Two groups- Racecadotril vs. loperamide	Number of stools and duration of diarrhea	Both groups passed similar numbers of stools before recovery and the duration of diarrhea was similar in both groups. However, more patients on loperamide reported d constipation during treatment (18.7% vs. 9.8%)
Roge J <i>et al</i> 1993 France(17)	RCT-double-blind IC*	1-	69 adults with acute diarrhea of infectious origin	Two groups- Racecadotril (n=37) vs. loperamide (n=32)	Recovery Time Associated symptoms like distention, abdominal pain and copnstipation	Diarrhea resolved in both groups in nearly 2 days. With racecadotril abdominal distension vanished significantly more rapidly, and reactive constipation was less (8% versus 31% with loperamide)
<b>Racecadotril in Cholera</b>						
Alam NH <i>et al</i> 2003 Bangladesh(18)	RCT-double blind FD†	1-	110 male adult cholera patients	Two groups –placebo (n=56) Study group (n=54)	Stool output, ORS intake, Unscheduled intravenous fluid requirements, Duration of diarrhea	Racecadotril safe but no additional benefit in severe cholera in adults
Hinterleitner TA <i>et al</i> , 1987 Austria(7)	Experimental Case-control NA	2+	Ten human volunteers	Two groups-Control group- cholera toxin alone Study group-toxin +acetorphan Cholera toxin intra-jejunal	Intestinal secretion rate by jejunal perfusion technique	In a control group with cholera toxin alone, significant water secretion was induced (131 mL/30 cm × h). Racecadotril completely prevented this secretion by leaving an absorption rate of 27 mL/30 cm × h. Intestinal electrolyte transport was also significantly changed towards absorption by acetorphan.
<b>HIV associated chronic diarrhea</b>						
Beaugerie L <i>et al</i> 1996 France(19)	Open RCT- crossover NA	-	13 AIDS in-patients with refractory diarrhea fro 35 ± 8 w	13 patients were given both drugs in random order during two 1-week periods	Response was defined as a reduction by at least one-third of both daily stool number and weight.	Mean daily stool number was reduced to 4.6 +/- 1.1 with racecadotril (P less than or equal to 0.05) but was 5.6 +/- 1.2 with octreotide (NS). Daily lipid output in faeces was reduced non-significantly with racecadotril (11.5 +/- 2.3 g) but was nearly doubled with octreotide (33.7 +/- 12.0 g).

\* IC-conflict of interest (probably at least one of the authors was directly working under a pharmaceutical company manufacturing the drug)

† FD-funded by pharmaceutical company manufacturing the drug

‡ Evidence grade (26) 1++ high quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias; 1+ well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias; 1- meta-analyses, systematic reviews, or RCTs with a high risk of bias; 2++ high quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal; 2+ well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal; 2- case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal; 3 Non-analytical studies; 4 Expert opinion, NA- Not available; β-NS-not specified in article

*In cholera*

The anti-secretory efficacy of racecadotril in cholera was earlier demonstrated in experimental studies conducted in rats(3), dogs(21) and human volunteers(7) using cholera toxin induced diarrhea. However, recently in a study on 110 adult patients with severe cholera (stool output >5 mL/kg/hr in last 4-6 hours) and severe dehydration, the patients were randomized to receive racecadotril or placebo based on an expected reduction of 33% in stool output(19). Both the groups were administered doxycycline with rehydration resulting in rapid resolution within 24 h in a substantial proportion of cases. There was no significant difference in total stool output (mean  $\pm$  SD) (racecadotril  $315 \pm 228$  g/kg vs. placebo  $280 \pm 156$  g/kg), total ORS intake  $390 \pm 264$  mL/kg vs.  $369 \pm 240$  mL/kg, or duration of diarrhea  $35 \pm 15$  h vs.  $32 \pm 13$  h between the groups. It was hypothesized by the authors that the failure of racecadotril therapy was due to (a) inadequate absorption of the drug with lower than required tissue and/or serum concentrations of racecadotril due to short intestinal transit time; or (b) inadequate therapeutic effect to offset the impact of a marked secretory process in severe cholera. Thus the role of racecadotril in cases of severe watery diarrhea entails further investigation.

*In chronic diarrhea*

Racecadotril has not been evaluated in chronic diarrhea except in cases of HIV associated diarrhea(19) and irinocetam(20) induced diarrhea where it has shown some promise.

*Racecadotril versus loperamide*

Loperamide is a  $\mu$  opioid receptor agonist, which increases the transit time of intestine. Thus the fluid remains in contact with the

mucosa for a longer time aiding reabsorption. However,  $\mu$  receptor agonism can lead to decreased peristalsis, dilatation of small bowel and colon and increased tone of the anal sphincter. The intestinal stasis induced by loperamide can promote bacterial overgrowth, paralytic ileus, toxic megacolon and blind loop syndrome; hence it is not recommended for use in children below 2 years of age. In contrast, racecadotril has been shown neither to affect the intestinal transit time(8) nor does it cause bacterial overgrowth in small intestine(23).

The efficacy of racecadotril has been compared with loperamide in children(15) and adults(14,16,17). Both drugs have been found to have equivalent impact on the duration of diarrhea in three studies from France (15-17) one of which was conducted in children(15). Also, racecadotril caused earlier relief in abdominal pain and distention. Moreover, the incidence of adverse effects like constipation was higher with loperamide. This may imply that the drug is potentially as effective as loperamide with the advantage of being free from the adverse effects that preclude the use of loperamide as an anti-diarrheal agent in children.

**Investigational uses**

The drug was shown to ameliorate naloxone-precipitated opioid withdrawal symptoms by peripheral administration of the enkephalinase inhibitor in rats(24).

**Dosage, Route and Mode of Administration**

In adults, adequate plasmatic levels are maintained with the administration of 100 mg of racecadotril every 8 h, and are not affected by repeated administration or in aged patients. The recommended dose in children is 1.5 mg/kg of racecadotril every 8 hourly.

The drug is available as 10 mg, 30 mg sachet and 100 mg capsule for oral administration.

### Side effects and tolerability

The frequency and type of adverse events showed no significant differences from those occurring in placebo-treated patients in most of the efficacy trials(6,12). Headache and hypokalemia have been observed as probable side effects of racecadotril administration in one study each, warranting observation in future. Experiments have shown that racecadotril does not promote bacterial overgrowth in the small intestine(23). The drug lacks any potential for neurotoxicity, and radiolabelled studies have demonstrated that the drug does not enter the brain after oral administration(22). No potential for abuse or physical dependence has been seen.

However, in a study conducted on mouse bone marrow a decrease in macrophagic differentiation with an increase in granulocytic differentiation was documented(25). The implications of this if any in humans have not been evaluated. No studies were found on Medline search specifically directed towards the uncommon and unsolicited adverse effects.

To conclude the drug is an antisecretory agent based on the principle of enkephalinase inhibition. Clinical trials on the role of racecadotril in diarrhea published to date suggest that the drug has efficacy in reducing the recovery time and total stool output. However many of the trials quoted have been funded by companies manufacturing the drug enhancing the possibility of bias. The efficacy of the drug remains to be ascertained in South Asian countries where the etiological spectrum as well as the underlying nutritional status (including that of micronutrients like Zn) of the children may differ from elsewhere. Information related to the adverse effect

profile of the drug is limited. Thus, it may be premature to recommend the drug for general use in acute diarrheas of children.

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