SMALL INTESTINE

Efficacy and tolerability of racecadotril in the treatment of cholera in adults: a double blind, randomised, controlled clinical trial

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Background: The enkephalins, endogenous opiate substances, act as neurotransmitters along the entire digestive tract where they elicit intestinal antisecretory activity without affecting intestinal transit time or motility. Racecadotril, through inhibition of enkephalinase, reinforces the physiological activity of endogenous enkephalins and, therefore, shows intestinal antisecretory activity.

Aim: We conducted the study to determine the role of racecadotril as an adjunct to the standard treatment of cholera in adults.

Methods: The study was a double blind, randomised, placebo controlled clinical trial involving 110 adult male cholera patients who received either racecadotril or placebo in addition to standard cholera treatment. The major outcome measures (stool output, oral rehydration solution (ORS) intake, requirements for unscheduled intravenous fluid infusion, and duration of diarrhoea) were compared between the groups.

Results: Of 110 patients enrolled, 54 received racecadotril and 56 received placebo. Admission clinical characteristics were comparable between the groups. There was no significant difference in (mean (SD)) total stool output (racecadotril v placebo 315 (228) v 280 (156) g/kg), total ORS intake (390 (264) v 369 (240) ml/kg), or duration of diarrhoea (35 (15) v 32 (13) hours) between the groups. Clinical success, defined as resolution of diarrhoea within 72 hours of initiation of study intervention, was similar in both groups (racecadotril v placebo 96% v 89%). The number of patients receiving unscheduled intravenous infusions was not significantly different between the groups (racecadotril v placebo 22% v 14%). No drug related adverse effect was noted.

Conclusion: The study demonstrated that racecadotril therapy, although found to be safe, does not provide additional benefit in the treatment of severe cholera in adults.

Cholera is often a severe disease characterised by acute watery diarrhoea, vomiting, and dehydration. If not appropriately treated, the mortality rate may be as high as 50–80%.¹ The primary cause of death in cholera is hypovolaemic shock due to severe dehydration. The mechanism of fluid loss in cholera involves the production of a *Vibrio cholerae* enterotoxin which stimulates cellular adenylate cyclase in small and large intestinal mucosa and increases the intraepithelial concentration of cyclic adenosine monophosphate (cAMP), resulting in electrolyte and water secretion.^{2–5} In addition to a direct effect of the cholera toxin on the intestinal mucosa, recent observations have suggested that the enteric nervous system is also involved in intestinal water and electrolyte secretion in cholera through release of neurotransmitters.^{6–9} The treatment of cholera remains rehydration with intravenous fluids/ oral rehydration solution (ORS) together with antimicrobial agents effective against *V. cholerae*.^{10–11} Antisecretory drugs that reduce the rate of fluid loss in cholera have been sought in order to decrease fluid loss, and also to reduce the need for intravenous fluids and the severity of disease. Several drugs have been shown to have antisecretory effect in experimental animal studies^{12–15} and some of these have been tested in patients.^{13–19} Although some have been shown to reduce stool volume, these are not suitable for practical use due to adverse effects, and some drugs showed either minimal or no benefit.^{20–24} To date, none of the antisecretory drugs has been recommended for the clinical management of cholera patients.

The enkephalins, endogenous opiate substances first discovered in 1975, play an important physiological role by acting as neurotransmitters, most notably along the digestive tract where they elicit intestinal antisecretory activity without affecting intestinal transit time or motility.²² After release, they are rapidly inactivated by enkephalinase, which is present throughout the gastrointestinal tract. Racecadotril (enkephalinase inhibitor) is a dipeptide with a single amide bond, developed from research into structure-activity relationships in the enkephalinase molecule. The active metabolite of racecadotril interacts specifically with the active site of enkephalinase to produce potent blockade of the enzyme.²³ Racecadotril reinforces the physiological activity of endogenous enkephalins and shows intestinal antisecretory activity without affecting intestinal transit.²² The antisecretory mechanism involves activation of δ receptors leading to reduced secretion of water and electrolytes through reduction in intracellular cAMP.²⁴ These antisecretory and antidiarrhoeal effects have been demonstrated in dogs with cholera toxin induced secretion²⁵ and in rats and humans after cholera toxin administration.^{26–27} Some clinical studies have demonstrated greater efficacy for racecadotril in acute diarrhoea (other than cholera) compared with placebo and loperamide^{28–30} through its antisecretory mechanism. Thus

Abbreviations: ORS, oral rehydration solution; cAMP, cyclic adenosine monophosphate; ITT, intention to treat.

the aim of this study was to determine if racecadotril is useful as an adjunctive therapy to standard ORS and antibiotic treatment for cholera.

METHODS

Study design

This was a double blind, randomised, controlled clinical trial to evaluate the efficacy, safety, and tolerability of oral racecadotril in the treatment of acute *V cholerae* diarrhoea in adults. The study was conducted at the Clinical Research and Services Centre (CRSC) of the International Centre for Diarrhoeal Disease Research Bangladesh (ICDDR,B): Centre for Health and Population Research, Dhaka, Bangladesh, between May 2000 and February 2001. The study was approved by the research review and ethics committees of the centre.

Study subjects

Patients eligible for the study were males (to facilitate separate collection of stool and urine), aged 15–55 years, with a history of watery diarrhoea of less than 24 hours' duration, presenting with signs of severe dehydration (sunken eyes, reduced skin turgor, lethargy, unable to drink, and absent/uncountable radial pulse). Initial stool examinations by dark field microscopy were positive for *V cholerae* and patients passed watery stools at a rate of >5 ml/kg/h during the 4–6 hour observation (screening) period (to include the most severe cases). Patients or legal guardians (when patients were unable to provide consent themselves due to altered consciousness) gave written informed consent for participation in the study. Those who had taken antidiarrhoeal or antimicrobial drugs, and those with concomitant illnesses requiring antibiotic treatment were not eligible for the study. Prior to randomisation in the study, all patients were rehydrated with intravenous fluids containing polyelectrolytes (Na^+ 133 mmol/l, K^+ 13 mmol/l, Cl^- 98 mmol/l, and acetate equivalent to 48 mmol/l bicarbonate) at a rate of 100 ml/kg over 4–6 hours, in addition to replacement of ongoing stool losses. ORS was also allowed as soon as the patient was able to drink.

Randomisation

Patients who completed rehydration (within the 4–6 hour observation period) and fulfilled the eligibility criteria were randomised to receive treatment with either capsules of racecadotril 100 mg four hourly or look-alike capsules of placebo four hourly as a control for 72 hours or up to the time when the patients fulfilled the criteria of cessation of diarrhoea, whichever was shorter. The randomisation list was prepared by a data management company with a test to placebo ratio of 1:1 using permuted blocks of 8. Drugs (racecadotril and placebo) were supplied in sequentially numbered opaque sealed packets for individual patients (1–110), each containing four separate blister packs of six capsules each. The blisters were labelled as day 1, day 2, day 3, and redosing (redosing was required if the patient vomited up the capsule within 20 minutes).

Case management

After initial enrolment of the patient, a clinical history and physical findings were recorded by one of the investigators and treatment provided according to routine hospital practice. Immediately after randomisation (following intravenous rehydration), maintenance oral hydration therapy was started with standard WHO ORS (Na^+ 90, Cl^- 80, K^+ 20, citrate 10, and glucose 111 mmol/l). During maintenance, patients consumed ORS according to need, with a minimum volume equal to continued losses of watery or loose stools and vomit. All patients received doxycycline 300 mg as a

single dose within 20 minutes of randomisation. Food was offered according to hospital practice (breakfast at 7 am, lunch at 12 noon, and supper at 6 pm). Plain water was allowed as desired by the patients. Intravenous fluids were reinstituted in some patients where signs of severe dehydration recurred despite appropriate ORS therapy or where excessive vomiting prevented continued oral therapy.

Patients were placed in a "cholera cot" with a small central opening through which stools were collected in a bucket placed underneath the cot. All fluid intakes (intravenous, ORS, water) and outputs (stool, urine, and vomit) were measured, and vital signs and body weight were similarly recorded every four hours during the study. Stool weight was measured on an electronic scale with a precision of 1 g (Sartorius, Germany). Urine was separated in a urine collector and volume measured with a calibrated cylinder. The weight of vomit was measured by collection in a preweighed bowl by subtracting the weight of the bowl. ORS volumes and plain water consumed by patients were measured by a calibrated cylinder. Body weight was measured on admission (before intravenous rehydration), at randomisation (after intravenous rehydration), and every four hours until discharge, using the same electronic scale, which was calibrated daily using standard weights.

Laboratory investigations

Fresh stool samples were examined for the presence *V cholerae* by dark field microscopy during the 4–6 hour observation period before randomisation. Stool samples were cultured

Table 1 Admission characteristics of all patients

Variable	Racecadotril (n = 54)	Placebo (n = 56)
Age (y)		
Mean	28	29
Median (minimum, maximum)	27 (16, 50)	25 (15, 45)
Body weight (kg)		
Mean	44	43
Median (minimum, maximum)	43 (33, 59)	43 (33, 61)
Body wt at randomisation (kg)		
Mean	49	48
Median (minimum, maximum)	47 (37, 65)	48 (35, 69)
Duration of diarrhoea before adm (h)		
Mean	10	9
Median (minimum, maximum)	8 (4, 23)	8 (3, 19)
No of watery stools before admission		
Mean	11	11
Median (minimum, maximum)	10 (3, 30)	10 (4, 30)
Duration of vomiting before admission (h)		
Mean	7	6
Median (minimum, maximum)	5 (1, 21)	4 (1, 16)
No of vomits before admission		
Mean	5	4
Median (minimum, maximum)	5 (0, 12)	4 (1, 12)
Screening period		
Stool output (g/kg/h)		
Mean	15	15
Median (minimum, maximum)	13 (5, 34)	14 (5, 30)
No of watery stools		
Mean	18	19
Median (minimum, maximum)	18 (5, 41)	17 (6, 44)
ORS intake (ml/kg)		
Mean	47	50
Median (minimum, maximum)	45 (0, 116)	42 (8, 112)
IV fluids (ml/kg)		
Mean	162	148
Median (minimum, maximum)	145 (108, 234)	153 (102, 290)
Water intake (ml/kg)		
Mean	0.4	0.7
Median (minimum, maximum)	0 (0, 25)	0 (0, 20)

ORS, oral rehydration solution; IV, intravenous.

Table 2 Outcome of therapy of study patients with cholera

Variable	Racecadotril (n = 54)	Placebo (n = 56)	p Value	Difference between mean (95% CI)
Stool output day 1 (g/kg)	251 (146)	240 (114)	0.670	-11 (-60.0, 38.7)
Total stool output (g/kg)	315 (228)	280 (156)	0.343	-35 (-108.9, 38.18)
Urine output day 1 (ml/kg)	115 (64)	102 (59)	0.298	-13 (-35.51, 10.9)
Total urine output (ml/kg)	386 (136)	361 (147)	0.351	-25 (-78.79, 28.22)
ORS intake day 1 (ml/kg)	309 (162)	311 (149)	0.960	2 (-57.45, 60.37)
Total ORS intake (ml/kg)	390 (264)	369 (240)	0.662	-21 (-116.4, 74.22)
Water intake day 1 (ml/kg)	62 (39)	60 (45)	0.852	-2 (-17.42, 14.41)
Total water intake (ml/kg)	303 (90)	294 (116)	0.624	-9 (-48.93, 29.42)
Duration of diarrhoea after randomisation (h)	35 (15)	32 (13)	0.13	-3 (-7.37, 3.04)
No (%) of patients receiving unscheduled IV fluid	12 (22)	8 (14)	0.40	1.71 (0.58, 5.14)*
No (%) of patients vomited during the study period	26 (48)	34 (61)	0.25	1.66 (0.73, 3.81)*
Clinical response				
Success	52 (96)	50 (89)	1.0	0 (0, 18.64)*
Failure	1 (1.9)	0		
Relapse	1 (1.9)	4 (7.1)		
Indeterminate	0	2 (3.6)		
Isolation of <i>V cholerae</i>				
Baseline	52/54 (96)	55/56 (98)		
Day 1	30/54 (56)	29/56 (52)		
Day 2	10/54 (19)	8/56 (14)		
Day 3	6/52 (12)	5/50 (10)		
Day 4	2/10 (20)	2/9 (22)		

Values are mean (SD) or number (%).

*Odds ratio (95% confidence interval).

Difference between mean (placebo-racecadotril).

ORS, oral rehydration solution; IV, intravenous.

using standard techniques for isolation and identification of *V cholerae*, *Shigella*, *Salmonella*, and *Campylobacter* at randomisation; thereafter, stool was cultured daily only for *V cholerae*. Peripheral venous blood samples were tested for haematocrit, total and differential white blood cell counts, plasma specific gravity, blood urea nitrogen, creatinine, sodium, potassium, chloride, and bicarbonate at randomisation, at 24 hours from the time of randomisation, and at discharge. Abnormality in any test was followed until their resolution (tests were repeated daily).

All patients were observed closely until discharge (patients were discharged 24 hours after resolution of diarrhoea to observe signs of relapse). Resolution of diarrhoea was defined if patients did not have a stool for at least 12 hours or if they had two consecutive normal (formed) stools. Clinical success was defined as cessation of diarrhoea within 72 hours from the start of study medication, and those with continued watery stools for more than 72 hours were considered as clinical failures. Oral therapy failure was defined as reappearance of signs and/or symptoms of dehydration,

requiring unscheduled intravenous fluid therapy. Assessment of clinical efficacy and adverse effects could not be ascertained if the patient was withdrawn before completion of 72 hours or discharge. Duration of diarrhoea (in hours) was calculated from the time of randomisation to the last watery stool. Clinical relapse was noted if the patient's diarrhoea resolved within 72 hours but watery stools reappeared in the subsequent 24 hour period.

STATISTICAL METHODS

Sample size

A total of 110 patients were enrolled to accrue 100 evaluable "intention to treat" (ITT) patients with cholera. Sample size was determined with an expectation of a 33% reduction in total stool output with racecadotril compared with placebo, using a 5% level of significance and 80% power. The sample size calculation assumed a control mean total stool output of 273 g/kg (SD 157).³¹

Data analysis

All statistical tests were performed using SPSS PC+ (version 10). All statistical tests were two tailed, performed at the 5% level of significance. Continuous variables were compared between groups using the Student's *t* test and categorical variables were compared with the χ^2 test or Fisher's exact test, as appropriate. The Mann-Whitney U test was also employed to compare continuous variables where appropriate. Kaplan-Meier survival curves were constructed for the duration of diarrhoea and were compared by log rank test. All analyses were performed on the ITT data set.

RESULTS

In total, 194 patients were screened for the study at the CRSC of ICDDR,B of whom 110 were randomised to treatment: 54 received racecadotril and 56 received placebo. The principal reasons for non-randomisation were patients being *V cholerae* negative (81 patients) by dark field stool microscopy and refusal to participate in the study (three patients). All

Figure 1 Survival plot for duration of diarrhoea in the racecadotril and placebo groups.

randomised patients were included in the efficacy and safety evaluations. One patient from the placebo group left the hospital against medical advice before resolution of diarrhoea and was excluded from the calculation of duration of diarrhoea, while the response to therapy was reported as indeterminate. Another patient, also from the placebo group, had resolution of diarrhoea but left before completion of the study, and response to therapy was also reported as indeterminate. Baseline clinical characteristics with regard to patient age, body weight, duration of diarrhoea, duration of vomiting, purging rate, and fluid intake during the screening period were comparable between the two groups (table 1). There were no statistically significant differences between the two treatments for the major outcome variables: stool output, ORS intake, and need for unscheduled intravenous fluids (table 2). The majority of patients had resolution of their diarrhoea within 72 hours (clinical success), and success rates were similar in both groups (racecadotril *v* placebo 96% *v* 89%). Mean duration of diarrhoea and bacterial clearance were similar in both groups (table 2). Kaplan-Meier survival curves (fig 1) for duration of diarrhoea were also similar in both groups ($p = 0.7$, log rank test). Adverse experiences noted as per protocol such as vomiting, reappearance of dehydration, abdominal pain, headache, anorexia, etc., were not different between the treatment groups. No hypernatraemia (serum sodium >150 mmol/l) was observed at randomisation or discharge in either treatment group and one patient in the placebo group had mild hyponatraemia (serum sodium <130 mmol/l) at discharge.

DISCUSSION

The results of this study demonstrated that racecadotril therapy, as an adjunct to standard treatment of cholera, failed to show any additional benefit. It neither reduced the severity of illness by reducing stool output nor was there a reduction in duration of illness. The antisecretory activity of racecadotril previously demonstrated in animal models of secretory diarrhoea^{25, 26} was confirmed in a human model of secretory diarrhoea.²⁷ In all of these preclinical studies, racecadotril was given prior to introduction of cholera toxin. In our clinical trial, racecadotril treatment was started after the secretory process had been established due to cholera. Whether racecadotril is unable to reverse the secretory process of cholera could not be confirmed in this study.

Three well designed placebo controlled clinical studies^{32, 33} have shown that racecadotril is effective in enhancing recovery of acute diarrhoea in both children and adults. In the adult study,³² the severity of diarrhoea seemed to be mild and the causative agents were mostly unknown, although a few patients' stools were positive for enterotoxigenic *Escherichia coli*. This patient population is not comparable with our study patients (all of our patients were suffering from severe cholera). In both of the paediatric studies,^{33, 34} racecadotril had convincingly been able to substantially reduce stool output (approximately 50%) irrespective of the bacterial or viral aetiology of diarrhoea. Isolation of *V. cholerae* as a causative agent for diarrhoea was rare in these studies. Hence these patients also differed from ours.

The mechanism of antidiarrhoeal activity of racecadotril in diarrhoea caused by a virus is still unexplained. Further multicentre studies in non-cholera diarrhoea in adults and children might be useful to confirm the antidiarrhoeal activity of racecadotril and to establish its therapeutic application in acute watery diarrhoea other than severe cholera. Theoretically, the antisecretory effect of racecadotril should have reduced secretion and stool output in cholera. However, the results of our study failed to demonstrate such an effect. The likely explanations include: (a) inadequate

absorption with lower than required tissue and/or serum concentrations of racecadotril due to short intestinal transit time; or (b) the effect is inadequate to offset the impact of a marked secretory process in severe cholera. However, our study was not designed to examine these possibilities. Before excluding racecadotril as an effective antisecretory drug in cholera, a similar study of parenteral racecadotril might be considered in the future.

Our study clearly demonstrated that current standard therapy for acute cholera diarrhoea in adults (doxycycline removing the infecting organism, *V. cholerae*, and ORS preventing continued dehydration) was highly effective. The onset of response and reduction in stool output was rapid, with stool normalisation occurring in a substantial proportion (31%) of the study population within 24 hours. This is in contrast with the slower responses seen in patients with viral or other diarrhoeas³⁵ where a specific and highly effective antibiotic is not available. Racecadotril under these circumstances does not have a role as adjunctive therapy, and indeed it is unlikely that any drug would have sufficient effect to substantially reduce the response times of current therapy. It remains a matter of speculation whether racecadotril would be beneficial in the absence of one (antimicrobial) of the two elements of standard therapy. Such a situation is unlikely to occur while effective antibiotics form part of standard therapy.

Racecadotril was well tolerated, and the incidence of adverse experiences was no higher than that with placebo. The side effect profile was similar to placebo, and no serious events related to study treatment were observed. Also, racecadotril did not interfere with bacterial clearance.

In conclusion, the study demonstrated that the onset of response and reduction in stool output was rapid, with stool normalisation occurring in a substantial proportion of the patients within 24 hours. Under these conditions, racecadotril therapy, although found to be safe, does not provide additional benefit in the treatment of severe diarrhoea due to *Vibrio cholerae* in adults.

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