Drugs in Focus: The Use of Racecadotril in Paediatric Gastrointestinal Disease

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Abstract

Acute diarrhoea is a leading cause of morbidity and mortality in the paediatric population. Racecadotril is an antisecretory drug recommended as an adjuvant anti-diarrhoeal treatment.

In the small bowel, the enzyme neutral endopeptidase (NEP) inhibits the action of enkephalins, which prevent water and electrolyte hypersecretion. By inhibiting NEP, racecadotril allows enkephalins to exhibit their antisecretory effects. Consequently, racecadotril reduces the secretion of water and electrolytes in the small intestine, without having an effect on intestinal motility. No serious adverse events related to racecadotril have been reported.

Racecadotril has proven its efficacy as an adjuvant anti-diarrhoeal drug with a good safety profile. Its addition to oral rehydration solution (ORS) appears clinically beneficial and potentially leads to health care savings.

Learning points

- Racecadotril displays good anti-diarrheal efficacy and can be used as an adjuvant to ORS treatment.

- Racecadotril has a good safety profile.

- The use of racecadotril also leads to savings to the health care systems.

Introduction

Acute gastroenteritis (AGE) is a leading cause of morbidity and mortality in children worldwide, with an estimated 1.31 million deaths in all ages, including 449 000 children under 5 years of age (1). In developed countries, AGE leads to frequent hospital visits and admissions with higher costs of care (2–4). The main recommendations for AGE treatment are oral rehydration solution (ORS) and maintenance of usual oral feeding. Probiotics are suggested for symptom improvement (4), although 2 recent trials do not suggest they are more effective than placebo in shortening the duration of diarrhoea (5,6). In many European and Latin-American countries this has focussed attention on racecadotril, an antisecretory drug with a different mechanism of action from other antidiarrhoeal agents. It is used as an adjuvant treatment in AGE and guidelines support this recommendation (4,7). This paper reviews the mechanism of action, efficacy and safety concerns, as well as cost-efficacy issues related to racecadotril.

Methods

We performed a comprehensive search of the literature using the PubMed MEDLINE database (up to October 2019). The search strategy consisted of the following research terms: "racecadotril" OR "acetorfan" AND "children". Only papers in English were included.

Mechanism of action

Racecadotril (formerly known as acetorfan) is a pro-drug metabolised to thiorphan, its active metabolite. It inhibits selectively the enzyme neutral endopeptidase (NEP), a cell membrane peptidase, found most commonly on the epithelium of the small bowel and kidney (8). NEP has several substrates: enkephalins, atrial natriuretic peptide, brain natriuretic peptide, neurotensins and neuropeptide Y. In keeping with this, racecadotril has many potential actions and uses. It has been tested in animal models for its analgesic effects, though the results were inconclusive (8).

As for its role in hypertension, studies in animals were promising (9,10), however studies in humans failed to show an advantage over other existing drugs (11). Its active metabolite does not cross the blood-brain-barrier (8).

In the gastrointestinal tract, enkephalins act as a neurotransmitter inhibiting the formation of adenosine monophosphate cyclic (cAMP) from adenosine triphosphate, preventing water and electrolyte hypersecretion (12). Enkephalins are rapidly degraded by NEP. Enterotoxins stimulate intestinal secretory processes through increased intracellular cAMP (13). By inhibiting NEP, racecadotril allows enkephalins to exhibit their antisecretory effects (8,12,13). Consecutively, racecadotril reduces the secretion of water and electrolytes in the small intestine. Thus, it has an advantage over other antidiarrhoeal agents, such as loperamide, which reduce intestinal motility, through an opioid mechanism (8). Since it does not affect intestinal motility, adverse effects such as rebound constipation, abdominal pain and distension are not expected with racecadotril (14).

Formulation and dosages

Racecadotril is available in some European and East Asian countries and in most of South America, but not in North America. It can be found as granules for oral suspension in 10 or 30 mg sachets or as 100 mg hard capsules. The racecadotril granules are coated and mixed with a sweetener with a fruity taste such as apricot or strawberry, in an effort to improve treatment adherence.

The usual dosage is 1.5mg/kg/dose and should be given until the child passes two normal stools, although the drug is not recommended to be administered for longer than 7 days (Table 1). The maximum concentration is reached after 60 minutes from ingestion and its bioavailability is not

influenced by food ingestion (8). It is recommended to give four doses in the first day of treatment and three doses in the following days.

Efficacy

The evidence, although low quality, suggests that adding racecadotril to ORS can reduce the duration of illness, as well as the number and volume of stools passed during its course (14).

Two randomised controlled trials (n=642 children) evaluated the impact of racecadotril on the duration of diarrhoeal disease (7,15). Both studies found a significantly shorter duration of diarrhoeal disease in children receiving racecadotril *versus* children receiving placebo or no intervention. A recent meta-analysis showed a mean difference of −53.48 hours (95% CI −65.64 to −41.33) compared to placebo or no intervention (14). Both studies showed significantly less stool output in the first 48 h of treatment with racecadotril *versus* placebo or no intervention (mean difference −150 g/kg, 95% CI −291 to −8.9) (7,14,15).Another meta-analysis included five studies that compared racecadotril with smectite, a natural hydrated aluminomagnesium silicate that binds to digestive mucus and has the ability to absorb endotoxins and exotoxins, bacteria and rotavirus, (399 *versus* 395 children): two studies reported comparable efficacy, while three studies showed superiority in efficacy for racecadotril *versus* smectite (16). The same systematic review included a meta-analysis of four studies comparing racecadotril with probiotics. Two studies showed comparable efficacy and two studies reported better outcomes while on racecadotril treatment (16).

One randomised controlled trial compared racecadotril with loperamide (52 *versus* 50 children). The duration of diarrhoeal disease (mean ± standard error of mean) was similar with both treatments: 10.7±1.7 *versus* 8.8±2.3 hours (17).

In one randomised controlled trial, racecadotril was compared with kaolin/pectin. Diarrhoeal disease was shorter in children treated with racecadotril (30 *versus* 42 h) and the number of stools at 48 hours was less frequent (3.0 *versus* 6.3 stools) (14).

A more recent network meta-analysis showed that racecadotril performed modestly in reducing diarrhoeal disease, when compared with other anti-diarrhoeal interventions (18). The authors compared different anti-diarrhoeal interventions by classifying them in accordance to the quality of evidence, high and low certainty, respectively (Table 2). Then, in each group, treatments were classified based on the magnitude of the effect on reducing diarrhoea duration (best to worst interventions). The network meta-analysis placed racecadotril in the low certainty body of evidence (Table 2). In terms of reducing diarrhoea duration, racecadotril performed inferior to the best interventions, but better than the worst interventions, as shown in Table 2 (18).

In a case report of a 4 year old with microvillous inclusion disease, the authors suggest that racecadotril may have a role in limiting stool output and consecutively reducing the parental nutrition dependency in other congenital enteropathies causing secretory diarrhoea (19).

Safety

Reported adverse events of racecadotril treatment in the different studies included: vomiting, abdominal distension, abdominal pain, constipation, rashes and one case of transient raised transaminases (14,15). No serious adverse events were reported (7-11,13,14).

A meta-analysis of five studies, totalling 949 children, showed no significant differences in reported adverse events, when comparing racecadotril with placebo (OR 0.99, 95% CI 0.73 to 1.34) (14).

The number of adverse events was significantly lower in children treated with racecadotril *versus* loperamide (11.5% *versus* 22%). Significantly more children treated with loperamide had constipation (58% *versus* 36.5%) (17).

Studies comparing racecadotril and smectite reported 1.9% and 0.8% adverse events, respectively, while studies comparing racecadotril with a probiotic did not report on adverse events (16).

The post marketing pharmacovigilance reported that most adverse events were cutaneous and/or allergic: rash, erythemous/papulous reaction, urticaria, but also a few cases of erythema multiforme, erythema nodosum and angioneurotic oedema were mentioned (20).

Contraindications and interactions

Racecadotril is contraindicated in patients allergic to it and in children younger than 1 month of age. Due to the presence of sucrose as an excipient in racecadotril sachets (1g per 10 mg racecadotril), these are contraindicated in patients with fructose intolerance, glucose malabsorption syndrome and sucrase-isomaltase deficiency. Racecadotril should not be prescribed in patients with hepatic or renal impairment due to the lack of data in these populations. In diabetic patients, the amount of sucrose ingested with racecadotril should be considered in the child's total daily intake of sugar.

Cost-efficacy analysis

As stated before, the mainstay treatment of AGE is ORS. Three cost-efficacy analyses performed on available data from UK, Thailand and Malaysia showed that the addition of racecadotril to ORS is more cost-efficient that ORS treatment alone, leading to savings to the health care systems up to 900 Euros/patient (21–23).

Conclusions

Racecadotril has proven its efficacy as an adjuvant anti-diarrhoeal drug with a good safety profile. Adding racecadotril as an adjuvant to ORS treatment is not only effective and safe, but could lead to savings to health care systems.

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Table 1 Weight adapted dosage of racecadotril.

Age	First day dose	Days 2-7
< 9 kg	4x10 mg/day	3x10 mg/day
9-13 kg	4x20mg/day	3x20 mg/day
13-27 kg	4x30 mg/day	3x30 mg/day
> 27 kg	4x60mg/day	3x60 mg/day

Table 2 Effectiveness of different interventions in reducing diarrhea duration when compared with standard treatment or placebo

Certainty of evidence	Classification	Intervention	Intervention vs Standard/Placebo MD (95% CrI)
High certainty (High to moderate QoE)	*Best interventions*	**S.Boulardii + Zinc**	-39.4 (-52.4;-26.7)
		Smectite + Zinc	-35.6 (-57.6;-13.2)
	Inferior to best, better than worst interventions	**Zinc (Inpatients)**	-29.0 (-35.9;-22.1)
		Symbiotics	-26.3 (-36.1;-16.2)
		Loperamide	-17.8 (-30.3;-5.6)
	Worst Interventions	**Prebiotics**	-15.3 (-12.0;42.8)
		Zinc (Outpatients)	-12.4 (-18.4;-6.5)
Low certainty (Low to very low QoE)	*Best interventions*	**LGG + Smectite**	-51.1 (-64.3;-37.8)
		LGG	-38.0 (-45.4;-30.5)
		Probiotics + Zinc	-29.4 (-40.3;-18.6)
	Inferior to best, better than worst interventions	**Smectite**	-23.9 (-30.8;-17.0)
		Racecadotril	-17.2 (-24.6;-9.8)
		S.Boulardii	-16.5 (-23.3;-9.7)
	Worst Interventions	**Yogurt+Probiotics+LCF**	-15.6 (-56.8;26.6)
		S.boulardii + LCF	-12.3 (-30.0;6.0)
		Kaolin-Pectin	-5.3 (-33.8;22.8)

The two certainty groups, high and low, respectively, are based on the GRADE quality of evidence for the comparison of the intervention to the standard or placebo. Within each of these groups, there are 3 groups that resulted from the network meta-analysis estimates, classifying interventions as best, inferior to best and better than worst and worst, respectively. **Standard**: no other intervention in addition to rehydration. **Symbiotics:** probiotics plus prebiotics. **Prebiotics:** polysaccharides, alpha-cellulose, gum arabic, fructo-oligosaccharides and inulin. **Probiotics**: strains of probiotics apart from S. Boulardii and LGG. **MD** stands for Mean Difference (in hours); **CrI**, Credible Intervals; **QoE**, quality of evidence; **LGG**, Lactobacillus rhamnosus GG; **LCF**, lactose free formula.