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Alimentary Tract

Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis

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ABSTRACT

Background: Racecadotril is an antidiarrhoeal drug with intestinal antisecretory mechanism of action.
Aim: To assess racecadotril efficacy as an adjunct to oral rehydration solution, against oral rehydration solution alone or with placebo in childhood acute gastroenteritis.
Methods: Individual patient data meta-analysis following multilevel mixed models testing the significance of the treatment effect adjusted for baseline covariates.
Results: Nine randomised clinical trials ($n = 1384$) were identified with raw data. Baseline dehydration level and Rotavirus were found as two essential predictors influencing the outcomes. The proportion of recovered patients was higher in racecadotril groups compared with placebo, Hazard Ratio HR = 2.04, 95% CI (1.85; 2.32), $p < 0.001$. For inpatient studies, the ratio of mean stool output racecadotril/placebo was 0.59 (0.51; 0.74), $p < 0.001$. For outpatient studies, the ratio of the mean number of diarrhoeic stools racecadotril/placebo was 0.63 (0.51; 0.74), $p < 0.001$.
Conclusion: Dehydration level and Rotavirus at baseline are essential adjustments to compare treatments. As an adjunct to oral rehydration solution, racecadotril has a clinically relevant effect in reducing diarrhoea (duration, stool output and stool number), irrespective of baseline conditions (dehydration, Rotavirus or age), treatment conditions (inpatient or outpatient studies) or cultural environment.

1. Introduction

1.1. Rationale

Acute gastroenteritis (AGE) is a very common disorder, particularly in emerging countries, where it constitutes one of the major health complications for infants and young children. Amongst the causes of death in children under five in the world, diarrhoeal diseases are still the second cause with 16%, just after the acute respiratory infections [1].

Oral rehydration solution is the cornerstone of AGE therapy to prevent and cure dehydration that dominates the prognosis, following miscellaneous guidelines [2–8]. In addition to this standard reference therapy, an adjuvant medication might prove useful insofar as it is safe and reduces dehydration duration and accelerates return to normal state. The efficacy of these adjuncts in combination with oral rehydration solution has been recently studied: probiotics [9,10] such as lactobacilli or some yeasts (*Saccharomyces boulardii*), smectite [11] and racecadotril [12].

Racecadotril prolongs endogenous enkephalin action by inhibiting enkephalinase at the intestinal level, and thus, increases their intestinal antihypersecretory effect [13–15]. Its efficacy in infants and children suffering from AGE has been assessed in various clinical randomised trials (RCTs) [16–25].

These trials differed in duration, selection of efficacy endpoints, and were conducted in different countries with various cultural contexts. Systematic reviews were reported in recent years

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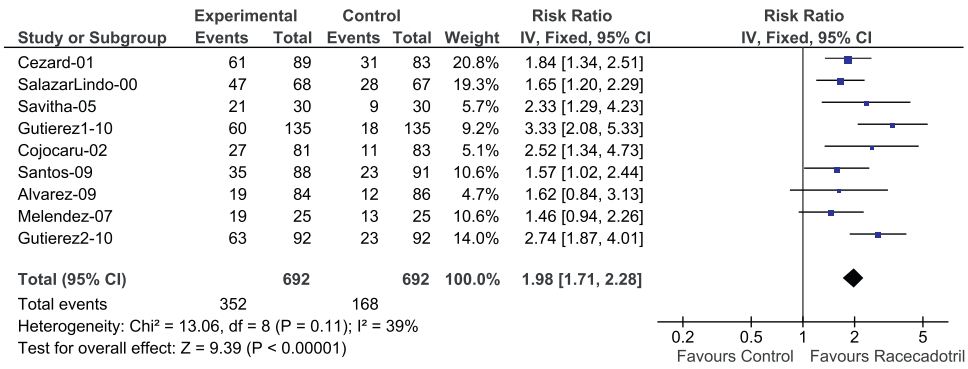

Fig. 1. Results of individual studies and meta-analysis on responder proportion. Responders defined as patients with a short diarrhoea duration (less than 2 days). Summary means adjusted for baseline conditions (Rotavirus, dehydration).

[12,26–31]. However, (a) these reviews only included a small part of existing trials, (b) the treatment effect was estimated by meta-analyses from literature (MAL) in pooling different endpoints, such as duration of diarrhoea, symptoms sum scores, and stool output into unitless effect size obscuring the clinical interpretation, (c) the suspected strong influence of baseline conditions (dehydration level, Rotavirus, etc.) was never investigated. The treatment overall efficacy was never adjusted for these variables and whether efficacy remains constant depending on baseline conditions was never questioned [32,33].

1.2. Objectives

We evaluated the effectiveness of racecadotril compared with placebo in collecting the largest number of trials and taking advantage of Individual Patient raw Data (IPD) in four main purposes: (a) to homogenise the calculation of the studied endpoints with the same definition across trials, (b) to identify the baseline predictors of oral rehydration solution therapy response out of consideration of treatment, (c) to assess the overall racecadotril + oral rehydration solution efficacy compared with oral rehydration solution alone, in adjusting for relevant baseline conditions, and (d) testing the invariance of this efficacy to baseline severity conditions and possible responder sub-groups. Racecadotril safety was investigated elsewhere [34] and not of concern in this work.

2. Methods

2.1. Eligibility criteria

We included all the RCTs where at least racecadotril and placebo were randomised, without restriction on language or publication, and characterised by an acceptable methodological quality (defined as a Chalmers Score [37] >50).

Participants: Infants and children, from 1 month to 15 years old, male or female, of any ethnic group, suffering from AGE, whatever the presumed origin.

Interventions: Oral rehydration solution in combination with racecadotril sachets, whatever dosage or duration treatment and behavioural intervention.

Comparisons: Oral rehydration solution alone or with placebo or equivalent (in particular, kaolin-pectin).

Outcomes: the duration of diarrhoea and number of diarrhoeic stools were calculated on the period between the first drug intake and the last unformed stool before recovery. Recovery was defined by the occurrence of two consecutive formed stools or no stool for 12 h. Diarrhoea duration expected to be documented for all the studies, constituted our first main endpoint. As inpatient and outpatients generally involve different measurements, stool output during the first 48 h and the total number of diarrhoeic stools until recovery were the two other endpoints specific to inpatient and outpatient trials, respectively.

2.2. Information sources, search, and study selection

Studies up to December 31st, 2010 were identified from electronic search and manufacturer information (see Appendix A).

2.3. Data collection process and data items

The different steps of data extraction were acquisition, checking, updating and file constitution. A pre-project consisted in a careful review of each study case report form (CRF).

All the randomised patients excluded from the original analysis and not contained in the existing data base (for instance when trials was analysed on a per protocol basis), were added from original CRFs.

When necessary, contact was established with the authors to discuss on reliability on some data and missing values, any change from original data decided with agreement of local authors.

We identified the available variables:

a) *Baseline*: Study centre, country, treatment, age, gender, height, weight, body mass index (BMI, kg/m^2), diarrhoea duration before inclusion (hours), body temperature (°C), dehydration level in three categories according to WHO classification [2], pathogens detected in stools (Rotavirus, bacteria), number of diarrhoeic stools in the last 24 h before onset of treatment, stool output during the 4 first hours before treatment onset.
b) *Follow-up*: Duration of follow up, duration of medication, and end of trial status. Some patients were expected to interrupt the trial prematurely. The exact reason for this interruption was needed to associate a patient with therapy failure or success.
c) *Endpoints*: Diarrhoea duration (six out of the nine studies) was previously defined. For inpatient studies, stool output was recorded every 4 h for 48 h at least. For outpatient studies, the number of diarrhoeic stools was recorded from patient self-forms.

2.4. Risk of bias in individual studies

The methodological quality of each study was assessed using Chalmers scale [37]. Sequence generation and allocation concealment were carefully studied, as well as the adequacy of blinding and handling of incomplete outcome data (cf. Appendix A).

Table 1
Characteristics of included studies.

Number	Study[a]	Year	Country	Sponsor	Allocation concealment	Blinding	ITT	Completeness to follow-up	Age (months)	Category patients	Duration	End point	Chalmers
1	Cezard	2001	France	Y	Adequate[b]	Y	Y	168/172	3–48	In	≤5 days	SO_{48}	73
2	Salazar Lindo	2000	Peru	Y	Adequate	Y	Y	135/135	3–35	In	≤5 days	SO_{48}	75
3	Savitha	2006	India	N	Unknown	Y	Y	60/60	3–60	In	≤5 days	DD & ORS	71
4	Cojocaru (Cheron)	2002	France	N	No (alternative)	N	Y	164/164	3–36	Out	≤7 days	NME	75
5	Santos (Sánchez)	2006	Spain	(n)	Adequate	N	Y	137 on D2 103 on D7	3–36	Out	≤7 days	NDS	54
6	Alvarez Calatayud	2009	Spain	(n)	No	N	Y	148	3–36	Out	≤7 days	NDS	52
7	Gutiérrez-Castrellón	2008	Mexico	(n)	Unknown	Y	Y	247/270	1–24	In	≤5 days	SO + need rehydration	77
8						Y	Y	184/184	1–60	Out	≤5 days	NDS	72
9	Melendez Garcia	2007	Guatemala	N	Randomised	N	Y	50/50	3–71	Out	≤5 days	NDS	71

Inclusion criteria were common: at least 3 watery (or diarrhoeic) stools during the last 24 h before inclusion.
Termination of diarrhoea had the same definition: occurrence of two consecutive formed stools or 12 h without any bowel movement.
Dosage of racecadotril was common, in agreement with SPC: 1.5 mg/kg *tid*, except for study 9 with unprecised dosage.
Size, efficacy/safety analysed populations.
DD, diarrhoea duration.
NME, number of medical exams during the week after starting treatment.
ITT, intention-to-treat analysis.
SO_{48}, stool output during the first 48 h.
ORS, oral rehydration solution.
NDS, total number of diarrhoeic stools.

[a] Paediatric studies designed by the first author of publication (main investigator, if different). Sponsored (Y) or not (N). (n) when the sponsor provided study drugs with unrestricted grant without any involvement in the collection, analysis or interpretation of data.

[b] According to the protocol (including more details than Cezard's publication) with randomisation table, sex stratification.

Table 2
Excluded studies.

Study	Year	Country	Sponsor	Study design & reason for exclusion	Size
Turck	1999	France	Y	RCT *vs* loperamide	52/50
Debbabi[a]	1995	Tunisie	Y	Open, pharmacokinetic, no control group	10
Ben Becher[a]	2000	Tunisie	Y	RCT, pharmacokinetic, *vs* dexecadotril	12/13
Amil Dias[b]	2008	Portugal	N	Open, non-randomised, observational, *vs* ORS alone	79/67
Chacón [24]	2008	Venezuela	N	Open, one group, observational	3679

ORS: oral rehydration solution. Paediatric studies, sponsored (Y) or not (N).
[a] Unpublished studies (data from Bioprojet Pharma) – adult studies were not included.
[b] Amil Dias J. Racecadotril in acute diarrhoea – Multicentre Observational Study. WCPGHAN 3, Iguazu, August 2008:P0297 [Abstract].

2.5. Statistical techniques

For stool output and the number of diarrhoeic stools, we used a specific IPD two-level multilevel model (patient/trial), by considering random treatment effect, fixed study effect, and adjusting for baseline predictors selected following a backward strategy [38]. Diarrhoea duration was compared in estimating Hazard Ratios by Cox Proportional Hazards model stratifying on study [39].

3. Results

3.1. Study selection

We found a total of 69 documents relating nine distinct RCTs (Table 1). RCTs were based placebo controlled [16–18,22], excepted Cojocaru et al. [19] and Melendez Garcia and Rodriguez [23] (using kaolin-pectin as control treatment), and Santos et al. [20] and Alvarez-Calatayud et al. [21] (oral rehydration solution alone). The excluded (essentially observational) studies are listed in Table 2. The raw data were found available for all selected trials, and all the authors agreed to collaborate to data management update.

3.2. Study characteristics

The nine RCTs were compared by sample size, study duration, selection criteria, visit intervals, and study outcome measures (Table 1). Although, the internal validity summarised by Chalmers score was acceptable for all the trials, Alvarez-Calatayud study [21] raised concerns on randomisation/selection, and Santos study [20] was characterised by an important number of missing patients (27%). In conformity with our eligibility criteria, we included the nine trials in the main selection, and the subset of studies in excluding the two latter studies was used for sensitivity purposes.

In total, 1384 patients were available. The sample size found for each study was identical with the published results, except for Santos and Alvarez-Calatayud studies for which we added patients randomised but lost to follow up and we associated them as therapy failure. The analyses were carried out both on this intention to treat population but also in using the same sample size as analysed in the original papers ($n = 1358$). Each study was found comparable between treatment groups (Table 3). Outcome: 1238 (89.5%) of the patients terminated on time, 22 patients (1.6%) interrupted for adverse event, 21 patients (1.6%) for concomitant illness not related with diarrhoea, 37 (2.7%) for aggravation or hospitalisation, 40 patients (2.9%) for parental refusal to continue, and 26 (1.9%) were lost to follow up. No difference between treatment groups was found except for aggravation/hospitalisation (3.6% and 1.7% for placebo and racecadotril groups, respectively, $p = 0.029$).

The median age of 12 months was similar for all the studies except higher value for Melendez study. Salazar-Lindo and Gutierrez-Castrellon only considered male children. Weight was comparable between treatment groups and between studies, except slightly higher value in the Melendez study. Rotavirus and pathogens were documented in all the studies, except for Cojocaru, where pathogens were only tested for children with stool containing blood. Inpatients studies (Cezard, Salazar-Lindo, Savitha, Gutierrez-1) were characterised by a higher baseline dehydration level than outpatient studies (Cojocaru, Santos, Alvarez-Calatayud, Melendez-Garcia, Gutierrez-2). The number of stools at pre-trial times (Table 3) did not show differences.

3.3. Synthesis of individual patient data results

The median values for the three endpoints are descriptively reported for each treatment group, separated between Rotavirus and dehydration categories (Table 4).

Table 3
Baseline values of each study.

First author (main investigator)	Placebo[a]	RC[a]	Total[b]	Age[c]	IQ[c]	Gender[d]	Weight[e]	Duration[f]	Dehydration[g]	Rotavirus[h]	NDS[i]	Stool output[j]
Cezard	83	89	172	11	[6, 16]	0.41	8.99	43.25	1.16	0.39	6.35	361
Salazar-Lindo	67	68	135	11	[8, 17]	0	8.81	50.40	0.68	0.54	9.05	761
Savitha	30	30	60	12	[9, 18]	0.38	7.42	71.60	0.78	0.68	9.33	1145
Cojocaru (Cheron)	83	81	164	10	[7, 15]	0.57	9.04	40.74	0.46	0.10	8.30	
Santos (Sanchez)	91	88	179	12	[7, 18]	0.42	9.70	74.68	0.23	0.49	7.49	
Alvarez-Calatayud	86	84	170	15	[8, 24]	0.46	10.57		0.57	0.45	8.40	
Gutierrez-1	135	135	270	12	[11, 13]	0	10.92	22.63	1.61	0.54	9.73	949
Melendez Garcia	25	25	50	32	[16, 39]	0.46	12.13	50.08	0.80	0.64	10.08	1920
Gutierrez-2	92	92	184	18	[14, 21]	0.49	12.18	14.96	0.86	0.49	5.18	
Overall	692	692	1384	12	[9, 19]	0.33	10.11	41.13	0.86	0.46	8.01	853

[a] Number of patients for the placebo and racecadotril (RC) groups.
[b] Total sample of the study.
[c] Median age (months) and Interquartile IQ Range.
[d] Proportion of female children.
[e] Mean weight (kg).
[f] Mean duration of diarrhoea (h) before inclusion.
[g] Mean of dehydration in three categories according to WHO classification [2].
[h] Proportion of patients with Rotavirus (except for Cojocaru' study: percentage of pathogens – only tested for children with bloody stool).
[i] Number of Diarrhoeic stools during the day before baseline.
[j] Stool output at baseline (gr).

Table 4
Three endpoints for dehydration categories, Rotavirus presence/absence, and placebo *vs* racecadotril (RC).

		No Rotavirus			Rotavirus		
Dehydration categories:		Mild	Moderate	Severe	Mild	Moderate	Severe
Diarrhoea duration (days)[a]	Placebo	1.2 ±0.7	2.1 ±1.0	2.2 ±0.7	2.1 ±1.0	2.8 ±1.3	3.7 ±0.8
	RC	0.9 ±0.5	1.7 ±1.3	1.4 ±0.4	0.9 ±0.9	1.9 ±1.1	2.4 ±0.8
Number of diarrhoeic stools[a]	Placebo	8.8 ±4.4	9.2 ±4.0	10.1 ±3.0	10.7 ±5.4	11.8 ±5.3	11.0 ±4.9
	RC	6.5 ±4.0	5.5 ±4.5	13.0 ±6.1	8.9 ±5.9	5.7 ±4.3	8.4 ±7.3
Stool Output (kg)[a]	Placebo	0.35 ±0.31	0.81 ±0.63	1.02 ±0.54	0.95 ±0.59	1.34 ±0.88	1.64 ±1.36
	RC	0.35 ±0.21	0.48 ±0.44	0.62 ±0.45	0.48 ±0.49	0.81 ±0.61	0.75 ±0.53

[a] Median (± Interquartile). From the beginning of the treatment.

Table 5
Summary of individual patient data statistical models.

	DD[a] $n = 1384$, HR (95% CI)	SO[b] $n = 637$, GMR (95% CI)	NDS[c] $n = 695$, RR (95% CI)
Baseline NDS	–	–	1.04 (1.01; 1.09)
Rotavirus	0.73 (0.64; 0.83)	1.42 (1.23; 1.65)	1.22 (1.15; 1.30)
Dehydration level	0.87 (0.78; 0.97)	1.57 (1.36; 1.80)	–
Treatment	2.04 (1.85; 2.32)	0.59 (0.51; 0.74)	0.63 (0.51; 0.74)

All mentioned effects with $p < 0.001$ level.
[a] Duration of diarrhoea (DD) was studied by Cox Proportional Hazards regression (determination $R^2 = 0.554$, Hazard Ratios (HR) reported).
[b] Stool output (SO): Logtransformed SO was analysed by two level mixed Linear Model (determination $R^2 = 0.234$). The geometric mean ratio (GMR) of racecadotril (RC) over placebo (PL) is 0.59 (or 41% less SO on RC group compared with PL) and SO mean of patients with Rotavirus is 42% higher compared with patients without Rotavirus.
[c] Total number of diarrhoeic stools (NDS) was analysed by a generalised mixed model assuming Poisson distribution ($R^2 = 0.312$), with a mean ratio NDS_{RC}/NDS_{PL} of 0.63.

3.3.1. Duration of diarrhoea

Diarrhoea duration before inclusion (Table 3) was not different within placebo group (41.76 ± 38.61 h) and racecadotril group (40.50 ± 56.72). The overall median diarrhoea duration after inclusion was 2.17 days, with 2.81 and 1.75 days for placebo and racecadotril, respectively. The highly significant predictors were dehydration level (HR = 0.87/dehydration level, or 13% less healed patients per level), and Rotavirus (HR = 0.73) (Table 5, $p < 0.001$). More than two times more patients recovered at any time in racecadotril compared with placebo (HR = 2.04, [1.85 to 2.32], $p < 0.001$). No significant interaction (all p values >0.25) were found between treatment and dehydration, Rotavirus or type of study (inpatient/outpatient) or country (European countries opposed to other). Results were very similar for infants (<1 year) (HR = 2.01, [1.71 to 2.36], $n = 714$, $p < 0.001$) and toddlers (>1 year) (HR = 2.16, $n = 670$, [1.83 to 2.57], $p < 0.001$). The heterogeneity amongst studies was small ($I^2 = 0.28$).

3.3.2. Stool output

Stool output was only available on inpatient studies ($n = 637$). The significant predictors were similar to diarrhoea duration model (Table 5). The mean ratio racecadotril/placebo was 0.59 [0.51 to 0.74], $p < 0.001$. Interactions between treatment and Rotavirus, dehydration level were not significant, and few between-study heterogeneity was found ($I^2 = 31$).

3.3.3. Number of diarrhoeic stools

Number of diarrhoeic stools was documented for all the outpatient studies ($n = 695$). The significant predictors were number of diarrhoeic stools during the day before treatment and Rotavirus infection. The mean ratio racecadotril/placebo was 0.63 [0.47 to 0.85], $p < 0.001$ (Table 5), without significant between study heterogeneity ($I^2 = 0.26$).

3.4. Risk of bias across studies

A test on the linear regression coefficient between effect sizes and their standard error did not provide suspicion on publication bias ($p = 0.456$). No significant decrease of odds ratio was observed with year of publication, between trials sponsored by the industry and investigator initiated, or between published and unpublished trials.

3.5. Additional analyses

Sensitivity analysis: In repeating all the analyses by excluding Alvarez-Calatayud and Santos studies, results were almost similar with a relative difference of less than 5% for all the measures of treatment effect. We repeated all the analyses in using the sample size originally used by all the individual studies ($n = 1358$). No results varied of more than ±2%.

Responder analysis: A patient can be considered as responding to the therapy when diarrhoea duration is short. In observing an overall median of diarrhoea duration = 2.3 days, we arbitrarily defined a short duration when diarrhoea duration was less than 2 days. Following this definition, the responder proportions were 25.8% and 50.3% in placebo and racecadotril groups, respectively. By adjusting for dehydration and Rotavirus, the absolute risk difference was 24.7% [19.8 to 29.7] and the associated number needed to treat was NNT = 4.04 [3.36 to 5.05]. We also determined the Relative Risk RR = 1.98 [1.71 to 2.28], and there was few differences amongst studies (Fig. 1, $p = 0.11$, $I^2 = 0.39$).

Secondary need of care: Three of the five studies performed with outpatients, reported the secondary need of care. The comparison between racecadotril and placebo groups was non significant once [20] and was significantly in favour racecadotril twice, with a lower number of physician or hospital visits for unresolved diarrhoea [19,21]. The need for i.v. rehydration was also significantly less frequent in racecadotril group as compared to placebo group (4/35 *vs* 12/37, $p < 0.05$) [19].

Safety analysis: The number of patients with adverse event was not statistically different: 11.6% (81/698) in the racecadotril group and 10.1% (70/695) in the control group. The number of patients needed to harm (NNH) was 65 [29 to 125].

4. Discussion

This sample of 1384 patients based on nine RCTs constitutes the first individual patient data meta-analysis related on oral rehydration solution adjuncts in childhood acute gastroenteritis,

and gathers the largest number of trials and patients on existing racecadotril meta-analyses. These data are coming from several countries with different cultures: India, Peru, Guatemala, Spain, France and Mexico. Obvious heterogeneities were found between data in terms of inclusion criteria, type of patients, and used endpoints (Table 1).

We also had the advantage of a wide spectrum of baseline identification: 54% of these patients were older than 1 year of age, thus enabling to compare the treatment effect amongst infants and toddlers/children. Also, whereas the first studies restrained to male patients, both genders are now compared. Finally, we collected data coming from both outpatients and hospitalised patients, to compare patients with high or moderate baseline severity.

To account for these multiple differences, traditional MAL analyses are very limited. We conducted a full IPD approach, essentially based on individual data from the original CRFs. This has disadvantage: data collection is a very hard and long work, IPD is much less usual technique thus more difficult to read, and also more complex to report. However, an IPD has the unique advantage to control for all the existing variables. In a MAL, results are collected from tables in publications: we have no insurance on the uniqueness of the studied endpoint, it is very difficult to evaluate a treatment under various baseline conditions, as subgroups analyses are very seldom reported in publications, and baseline severity cannot be accounted for. Only individual data provide the unique possibility to homogenise the endpoints across studies, to adjust for baseline heterogeneities, and also to question whether the studied drug benefit is confirmed on the whole population of patients, or is only active in patients subgroups defined by particular profile at baseline.

In this analysis, we first suggest a simple and determinant model to predict oral rehydration solution outcome, out of any treatment consideration. Baseline dehydration level and Rotavirus constitute two essential additive and negative prognostic predictors on all the endpoints. This simple model based on two baseline covariates seems to remain invariant across countries and cultures.

In parallel, we demonstrated that no other variable was able to predict the outcomes in particular age, weight, gender, body temperature, abdominal circumference, other pathogens detected in stools. The absence of effect of age or weight, may seem surprising for stool output. However, this endpoint was specific to inpatients studies were infants were predominant with homogeneous age and weight.

Out of its epidemiological scope, this predictive model has methodological implications when testing oral rehydration solution strategies. In adjusting for this model, the sample size of the trial can be reduced. Based on our results of determination, the sample size could be reduced by approximately 30% compared with an adjusted test (as it was done in the previous papers). Finally, we show that adjustment is easy: baseline measurement can be limited to dehydration and Rotavirus.

Based on these principles we studied racecadotril efficacy. To provide clinically relevant results, we concentrated on statistically compelling significance ($p < 0.001$). Racecadotril was observed to reduce stool output in inpatient studies (43% reduction compared with placebo), and number of diarrhoeic stools in outpatient studies (38% relative reduction compared with placebo).

In this pathology, a short diarrhoea duration reduces dehydration risk. If one day remains an optimistic value, 2 days can be considered as the shortest realistic duration (the median value was 2.3 days), which justifies our suggestion of a maximum of 2 days to define a short diarrhoea duration, thus a therapy success. By adjusting for Rotavirus and dehydration level, the proportion of responders was twice larger in racecadotril group, and the associated number needed to treat NNT, i.e. around 4, can be considered as clinically relevant.

We also successfully tested whether overall drug efficacy remained similar in sub-populations with different baseline conditions. The benefits over placebo on stool output, number of diarrhoeic stools, diarrhoea duration remained unchanged irrespective of baseline dehydration level, with or without Rotavirus, for both inpatients and outpatients, and apparently independent of countries or cultural context. At the opposite, the efficacy of other antidiarrhoeal drugs, as known from previous researches, seems to be limited to subgroups, such as the small subgroup of Rotavirus positive patients [35] for diosmectite or the subgroup of malnourished patients for zinc [36].

We compared our results with previous similar reviews on racecadotril: a first meta-analysis identified three studies [12], in which the authors conclude into an overall efficacy, but, as most of their data originate from inpatient studies, formulated doubts for minor gastroenteritis. Another question was that the available trials were industry sponsored. In our analysis including four inpatients and five outpatients studies, mixing various baseline severity, we provide evidence of overall racecadotril efficacy. We failed to find any significant difference between sponsored trials (2), investigator-initiated trials where only drugs were provided by the manufacturer (4), and strictly independent trials (4) (Table 1). A second meta-analysis [26] selected only two RCTs [16,17] and used the proportion of unresolved diarrhoea at the fifth day of treatment as the main endpoint. As confirmed here, almost all the patients recovered much before, thus this endpoint does not seem appropriate, in particular in a context of an acute gastroenteritis associated with severe dehydration. We suggest a more realistic threshold of 2 days for evaluating therapy success in this pathology.

5. Limitations

Although clinical evidence of the efficacy of racecadotril added to oral rehydration solution is provided in this analysis, the economic utility of this compound remains to be demonstrated. Such an objective requires a much more important data collection task, including accounting of medical resources, need of care, especially the need of i.v. rehydration and hospitalisation.

The efficacy of racecadotril was shown independent of age; however this data collection only concerns infants, toddlers or very young children. Few studies with older children were found and they were not included as they were performed *vs* a comparator such as loperamide, and not placebo [25].

Racecadotril safety was briefly reported in this analysis, and investigated elsewhere [34] on much wider post-marketing data bases: Amongst 14.54 million paediatric patients, the individual case safety report occurrence was 1/338,000. In data base, the occurrence of adverse events (AEs) and withdrawals due to AE were not greater in the racecadotril group than in the control group [34].

In this analysis, only racecadotril was compared with placebo. Other alternative symptomatic treatments exist, such as zinc, diosmectite, probiotics, but only placebo controlled trials were conducted without direct comparison. This absence of evidence between the alternatives is shown through the lack of consistency of current guidelines and official recommendations [2–8]. Appropriate meta-analyses enabling Mixed Treatment Comparisons are needed for this purpose.

6. Conclusions

Our data have gathered a variety of baseline conditions and cultural contexts and constitutes a large data base collected at individual patient level to assess the effects of adjunct treatment to oral rehydration solution in child acute gastroenteritis.

A predictive model of recovery was invariably identified based on only two variables: dehydration level and Rotavirus. This model remained constant over all the other baseline variables and all the cultural groups.

Racecadotril was found with a clinically relevant effect in reducing diarrhoea (duration and stool output and number), and this effect was independent of baseline states (dehydration, Rotavirus), treatment conditions (inpatient or outpatient studies), or between-country cultural disparities.

Oral rehydration solution is obviously the cornerstone of childhood acute diarrhoea therapy, and one valuable way to reinforce and extend its use, seems to add an agent able to reduce stool output, number of diarrhoeic stools and duration of diarrhoea without safety concern. The present results suggest that the response may come from the addition of an intestinal purely antisecretory agent.

Conflict of interest statement

None declared.

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Appendix A, B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.dld.2011.03.001.

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