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ORIGINAL RESEARCH ARTICLE

Comparative efficacy of antidiarrheal activity of DIAREX, an ayurvedic formulation vs. racecadotril in children with acute diarrhea

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ABSTRACT

Nonspecific antidiarrheals (allopathic and ayurvedic) are routinely used in clinical practice along with routine treatment in the management of acute diarrhea.Studies comparing their efficacy are very few, although they are used extensively by clinicians. This prospective observational study was carried out at two private clinics run by pediatricians to compare the efficacy, safety, and tolerability of DIAREX, an ayurvedic formulation versus racecadotril in the treatment of acute diarrhea.

Children aged 2 years to 10 years who presented to the clinic with acute diarrhea and fulfilling selection criteria were enrolled and divided into two treatment groups viz, DIAREX and racecadotril. Data collection was done using predesigned forms and questionnaires. The groups were comparable clinically and demographically at enrolment.

Outcome measures used were 1) Time required for improvement in stool consistency2)Frequency of stools until recovery 3) Duration of diarrhea, after initiation of treatment.

Racecadotril improved stool consistency in less time compared to DIAREX (23.07h vs 29.00h). Patients on racecadotril passed 3.85±0.11 stools before recovery, while patients on DIAREX passed 5.26± 0.27stools.Rapid improvement in stool consistency and frequency was found with racecadotril compared to DIAREX. However, there was no significant difference between racecadotril and Diarex as far as duration of diarrhea was concerned. (39.43±1.47h Vs. 42.77±1.48h;*P*> 0.05).Although DIAREX was found to be clinically useful to relieve the symptoms of acute diarrhea in children, racecadotril was more effective.

Key words: Acute diarrhea, Racecadotril, DIAREX, Nonspecific anti diarrheals, Children

INTRODUCTION

Diarrhea is a major health problem in developing countries like India. Acute diarrhea is major cause of morbidity and mortality in children. It is defined as history of at least three loose or watery or unformed stools in a minimum period of 24 hours and usually for the duration of less than 7 days.[1]

It is very often self-limiting within few days. [2]

Antibiotics play very limited role and do not alter the course of illness.[3,4]However, children are prone to develop dehydration and complications.ORS forms mainstay in treatment of acute diarrhea; [5]but its use does not reduce frequency & volume of stools or the duration of diarrhea. This in turn has led to its limited acceptance at the community level.[6]However, An effective antidiarrheal drug which reduces the frequency and duration of diarrhea is needed. Therefore, the World Health Organization has recommended that drug treatment be added to rehydration therapy, as long as the drug used has proven safety and efficacy in the pediatric population.[7]Hence, in clinical practice, nonspecific antidiarrheals like racecadotril and DIAREX(allopathic and ayurvedic) are commonly used by clinicians along with the routine treatment so as to hasten the recovery and to give psychological reassurance to patients/parents.[8,9,10]

Racecadotril is the first intestinal antisecretory drug introduced in the market. It is a specific enkephalinase enzyme inhibitor that exhibits intestinal antisecretory activity without affecting intestinal transit, that is gut motility. It is widely used in adults as well as in children for acute diarrhea.

Several studies comparing efficacy of racecadotril with loperamide have been reported in the literaturebut no study has been reported comparing its efficacy with DIAREX. Hence, this study was designed to compare the efficacy, safety and tolerability of DIAREX and racecadotrilin the treatment of acute diarrhea in children.DIAREXis a herbomineral ayurvedic preparation, in which herbs are mixed with shankhabhasma and is available in tablet form(Table 1).

Table 1: Composition of Diarex Tablet

No.	Ingredients	Quantity (mg)
i	Kuda (Holarrhenaantidysenterica)	245
ii	Guduchi (Tinospora cordifolia)	16
iii	Bael (Aegle marmelos)	245
iv	Dadim(Punica granatum)	82
v	Shankhbhasma	61
vi	Musta (Cyperus rotundus)	51

This DIAREX formulation was tested for efficacy in adults in treatment of diarrhea.[11] Efficacy studies in children are few and are small and not scientifically planned.[12]

AIM AND OBJECTIVES

Aim: To compare the efficacy of DIAREX with that of racecadotril in children with acute diarrhea.

Objectives: To compare the efficacy, safety, and tolerability of DIAREX versus racecadotril in the treatment of acute diarrhea in children.

PATIENTS AND METHODS

Setting: This was a prospective, observational study done in clinical settings for a period of 18 months. Two private clinics, run by registered medical practitioners (pediatricians), were selected after obtaining their informed written consent.

Ethics Committee Approval: The study protocol was approved by Institutional Ethics Committee of MIMER Medical College, Talegaon, Pune

Study Population: Children suffering from acute diarrhea presenting with 3 or more unformed stools in 24 hours and fulfilling the selection criteria (Table2) were enrolled in the study. Informed written consent was obtained from one of the parents. They were divided into two treatment groups- racecadotril and DIAREX at the discretion of pediatrician. In addition,both groups were treated with routine antidiarrheal drugs.

Baseline demographic and clinical characteristics were recorded.

Following baseline data were collected : age,sex, weight, immunization status, history of fever, vomiting, or other symptoms,degree of dehydration, prior use of any medication.

Duration of diarrhea, character of stool (watery, mucoid, bloody etc), consistency of stool, were also noted. A child could be enrolled only once.

SELECTION CRITERIA

Table 2: Inclusion Criteria

1. Age: 2 - 10 years
2. Acute Diarrhea of varied etiology
3. Duration of diarrhea of less than 2 days
4. Diarrhea with mild co - morbidity

Table 3: Exclusion Criteria

1. Age : <2yrs,> 10 yrs
2. Chronic, iatrogenic or bloody diarrhea
3. Severe diarrhea and/or severe dehydration
4. Severe malnutrition
5. Drug History: antibiotics, pre/probiotics and/or zinc supplements or any other nonspecific anti-diarrheal drug
6. Significant systemic illnesses

DATA COLLECTION AND DATA ANALYSIS

After recording case history and clinical examination by pediatrician, prescription audit was conducted. Prescriptions were analyzed in detail. Administration of concomitant medications such as antipyretics, antiemetics were recorded. Parents of children were informed in detail the study protocol in simple and lucid language, before obtaining their consent.

A questionnaire was provided to them and they were instructed to fill and record the details of the diarrheal episodes of the child till recovery. They were sensitized to report the adverse effects like abdominal distension, drowsiness, lethargy, vomiting or constipation. All the information was recorded in a predesigned form, including the details of treatment drugs, which was filled on the enrollment day and on follow up days. Follow up was done on 3^{rd},$5^{th}$and 7^{th} day of treatment. A telephonic check was carried out daily. Any episode of complication, adverse effect or need for unscheduled use of intravenous fluids was recorded.

OUTCOME VARIABLES

EFFICACY CRITERIA

1. Primary efficacy criterion: was duration of diarrhea : time between initiation of treatment and production of the final diarrheal stool.[13]
2. Secondary efficacy criteria consisted of frequency of stools until recovery and time needed for improvement in stool consistency.[14,15]

Tolerability and safety were evaluated by recording the adverse effects experienced during treatment.

Recovery was defined as
1. Production of two consecutive normal stools
2. Production of one normal stool followed by 12 hours with no stool production.
3. No stool production for a period of 12 hours[8]

STATISTICAL ANALYSIS

Statistical analysis was done using the SPSS (Statistical Package for the Social Science) version 17 for windows. Tests used were- Student's unpaired "t" test, ANOVA, Chi-square, Post hoc Tukeys test as required. All the values are expressed as Mean ± SEM. P value of <0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Total 253 children were enrolled, 175 in racecadotril group and 78 in DIAREX group.
Both the groups tolerated the treatment well and continued the medications as advised till the end of treatment. The base-line parameters are shown in table 4.There was no significant difference between two groups at enrolment.

Table 4: Base-line parameters of patients on enrolment

Sr.No	Particulars	DIAREX	Racecadotril
1	Number of children	78	175
2	Age (y)	7.05 ± 0.19	4.16±0.14
3	Sex (M:F)	40:38	84:91
4	Body weight (kg)	20.54 ± 0.38	15.03 ± 0.27
5	Immunization status Fully Immunized (%) Partially Immunized (%)	 55 (71) 23 (29)	 143 (82) 32 (18)
6	Dehydration No Dehydration Some Dehydration	 47 31	 97 78
7	Duration of diarrhea before enrolment (h)	40.62 ± 1.70	41.55 ± 1.27
8	Frequency of stools/day	5.49 ± 0.21	5.18 ± 0.14
9	Vomiting(No.of children	09	18
10	Fever (No.of children)	14	21

Values are mean ± SEM

ASSESSMENT OF EFFICACY

There was significant difference in time needed for improvement in stool consistency between racecadotril and DIAREX (23.07 h vs.29.00h; $P< 0.05$). Thus,racecadotril improved stool consistency in less time compared to DIAREX. Patients on racecadotril passed 3.85 ± 0.11 stools before recovery, while patients on DIAREX passed 5.26± 0.27stools. This indicates racecadotril was more effective in reducing frequency of stools compared to DIAREX. There was no significant difference between racecadotril and Diarex as far as duration of diarrhea was concerned. (Table 5)

Table 5: Efficacy of DIAREX and racecadotril

Group	DIAREX (n=78)	Racecadotril (n=175)
Time needed for improvement in stool consistency (h)	29.00 ± 1.32	23.07 ± 1.11*****
Stool frequency	5.26 ± 0.27	3.85 ± 0.11*****

Duration of diarrhea (h)	42.77 ± 1.48	39.43 ± 1.47

Values are mean ± SEM
* means P < 0.05

SAFETY EVALUATION

Of the 253 patients studied, no severe adverse events were observed in any child.Overall occurrence of adverse events was significantly higher in racecadotril group (34.86%) compared to DIAREX (17.95),P < 0.05.

Vomiting and headache were most commonly reported symptoms in racecadotril group (8.57% and 12%).11 patients from racecadotril group complained of abdominal pain which was relieved by appropriate drugs and this adverse event was not observed with DIAREX.

The cause of headache with racecadotril is not known but was relieved without medications.

Table 6: Distribution of adverse events in study groups

Group	DIAREX	Racecadotril	P value
	n=78	n=175	
Vomiting	5(6.41)	15 (8.57)	< 0.05
Fever	9(11.54)	5 (2.86)	< 0.05
Abd. Pain	0	11 (6.3)	< 0.05
Drowsiness	0	5 (2.86)	< 0.05
Headache	0	21 (12)	< 0.05
Rash	0	1 (0.57)	> 0.05
Others *	0	3 (1.71)	<0.05

*Others means nausea, weakness, bodyache, irritability, excessive crying etc.

Present study examined several aspects ofracecadotril andDIAREX supplementation. Stool consistency and frequency,which are main concerns of the parents are taken care of by both these drugs.Both these drugs resolved the symptoms of acute diarrhea rapidly and effectively.In the present study DIAREX was found to be as effective as racecadotril in reducing duration of treatment (39.43±1.47h vs. 42.77±1.48h).

In this study,racecadotril was more effective in reducing the frequency of loose motions and also improved the stool-consistency earlier than DIAREX. This difference might be due to presence of multiple ingredients in DIAREX,having multiple actions in contrast to allopathic drug racecadotril which has specific action. However,the duration of diarrhea was comparable in the two groups. The symptomatic relief seen with these non-specific antidiarrheals may reduce suffering of child, parents and caretakers to a large extent. This might also facilitate the use of ORS, which forms the mainstay of treatment of diarrhea.

The results obtained in the present open label study are preliminary in nature and require further scientific studies with larger sample size.This study did not take into consideration other associated symptoms.

CONCLUSION

In this comparative study, DIAREX was found to be clinically useful to decrease the symptoms in acute diarrhea in children and was comparable to racecadotril. However, racecadotril,although associated with more adverse events, was more effective. Diarex may be used as complementary to routine treatment of acute diarrhea,if there is concern about the adverse events with racecadotril.

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CONFLICT OF INTEREST

Nil

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