Safety and Tolerability of Nonspecific Antidiarrheals in Children with Acute Diarrhea

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ABSTRACT

Introduction: In clinical practice, nonspecific antidiarrheals are most commonly used by clinicians along with routine treatment to hasten the recovery. This study was conducted to to study the safety and tolerability of these nonspecific antidiarrheals in children with acute diarrhea.

Material and Methods: This was a prospective, observational study done in clinical settings for a period of 3 years at two pediatric clinics and at a tertiary care hospital. Children were divided into 5 treatment groups (viz, control, racecadotril, Mebarid, Diarex and loperamide) at the discretion of the pediatrician. One questionnaire was provided to parents to record the details about the course of diarrhea and parents were sensitized to report any adverse event.

Results: Overall occurrence of adverse events was significantly higher in racecadotril group (34.86%) compared to other groups (C:23.16%, M:21.14%, D:17.95%, L:17.65%).

Conclusion: These agents may be safe, effective and inexpensive addition to the routine treatment of acute diarrhea.

Keywords: Acute Diarrhea, Diarex, Loperamide, Mebarid, Racecadotril, Nonspecific Antidiarrheals, Safety

INTRODUCTION

Acute diarrhea accounts for significant morbidity and mortality in children.[1] It is also a cause of anxiety and economic burden to parents of affected children as well as the nation. In developing countries it is mostly infectious in origin and is very often self limiting.

Acute diarrhea is defined as diarrhea occurring within a minimum period of 24 hours and lasting usually for less than 7 days.[1] Antimicrobial agents have limited role as most episodes of diarrhea are caused by viruses and enterotoxigenic E.coli.

Antibiotics do not alter the course of illness.[2,3] ORS forms the mainstay in treatment of diarrhea.[2-4] Its use prevents and corrects dehydration, reduces the morbidity and mortality; but it does not reduce frequency and volume of stools or the duration of diarrhea.[3] Therefore, an effective anti-diarrheal treatment to prevent / reduce dehydration by reducing the frequency and duration of diarrhea would be beneficial. Hence, in clinical practice, nonspecific antidiarrheals (allopathic and ayurvedic) are commonly used by clinicians along with routine treatment, to hasten the recovery and to provide psychological relief.[5-7]

This study was conducted to to study the safety and tolerability of these nonspecific antidiarrheals in children with acute diarrhea. In our pilot study, it was observed that racecadotril, loperamide, Mebarid, and Diarex were the most commonly advised nonspecific antidiarrheals. Therefore,these agents were included in the study.

Mebarid, a polyherbal preparation contains Bael, Ajmoda, Lodhara, Dadim, Badishep, Daruhalad, Jaiphal, Sunth, Ativis and Kuda. Diarex is a herbomineral ayurvedic preparation containing Kuda, Guduchi, Bael, Dadim, Shankh bhasma and Musta.

Study aimed to evaluate the Safety and tolerability of nonspecific antidiarrheals in children with acute diarrhea in routine clinical practice

MATERIAL AND METHODS

This was a prospective, observational study done in clinical settings from April 2011 to March 2014. The study protocol was approved by Institutional Ethics Committee. It was conducted at following centres after obtaining their permission.

1. Pediatric clinic (secondary care hospital), Talegaon, Pune, Maharashtra.
2. Pediatric clinic (secondary care hospital), Chakan, Pune, Maharashtra.
3. Tertiary care hospital, Talegaon, Pune, Maharashtra.

Study population and study design: Children suffering from acute diarrhea and fulfilling the selection criteria (Table 1) were enrolled into the study. Their parents were informed about the study in simple and lucid language. Informed written consent was obtained from the parents and ascent was obtained from

children between 7 to 10 years. Baseline demographic and clinical charecteristics were recorded (Table 3)

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Children were treated at the discretion of the pediatricians, who were explained about the study. All children received oral rehydration therapy (ORT).The antidiarrheals were prescribed till recovery. Control group consisted of patients who did not receive any nonspecific antidiarrheal. Exclusion criteria are shown in table 2.

Data collection and data analysis: Prescription audit was conducted and prescriptions were analyzed in detail.

1. Age: 2 - 10 years.
2. Acute diarrhea of varied etiology.
3. Duration of diarrhea of < 2 days.
4. Diarrhea with mild co – morbidity.
5. No h/o of treatment with antimicrobials/antidiarrheals/antimotility drugs within the preceding 7 days.

Table-1: Inclusion criteria

1. Age < 2 and > 10 years.
2. Iatrogenic / bloody diarrhea / or severe diarrhea e.g. cholera.
3. Diarrhea with severe dehydration / significant systemic illnesses.
4. Children with severe malnutrition (BW<50% of expected for that age)
5. Children receiving pre / probiotics and / or zinc supplements nonspecific antdiarrheal drug not included in this study

Table-2: Exclusion criteria

Administrations of concomitant medications such as antipyretics, antiemetics were recorded. A questionnaire was provided to parents and they were instructed to fill and record the details of the diarrheal episodes till recovery. All the information was recorded in a predesigned CRF (Case Report Form) Follow up was done on 3rd, 5th and 7th day of treatment. A telephonic check was carried out daily. Parents were sensitized to monitor and report the adverse events like vomiting, abdominal pain, abdominal distension, headache, constipation, drowsiness, lethargy etc., as early as possible. Any episode of complication, adverse effect reported by parents were recorded in CRF.

STATISTICAL ANALYSIS

Statistical analysis was done by appropriate methods using SPSS version 17 and primer of biostatistics. Data obtained are expressed as mean ± SEM. P<0.05 was considered as significant.

RESULTS

600 patients were enrolled and out of which 584 successfully completed the study as per the protocol. Sixteen patients did not turn for the follow up; however, telephonic feedback was obtained successfully. Hence the data have been expressed of all 600 patients. Overall compliance in our study was good (90%). The base-line parameters are shown in Table 3. There was no significant difference between groups.

Parameters	Control (n=190)	Racecadotril (n=175)	Mebarid (n=123)	Diarex (n=78)	Loperamide (n=34)
Age(y)	4.79±0.16	4.16±0.14	4.43±0.20	7.05±0.19 *	7.65±0.26 *
Sex (M:F)	103:87	84:91	54:69	40:38	19:15
Weight (Kg)	16.07±4.24	15.03±3.62	15.45±4.47	20.54±3.32*	21.59±3.06*
No dehydration Some dehydration	102 (54) 88 (46)	78 (45) 97 (55)	69 (56) 54 (44)	31 (40) 47 (60)	20 (59) 14 (41)
Duration of diarrhea before enrolment (h)	45.16±1.13	41.55±1.27	42.24±1.34	40.61±1.70	39.84±2.35
Frequency of stools/day	4.98 ±0.12	5.18 ±0.14	5.27 ±0.17	5.49±0.21	5.68±0.30
Vomiting (No.of children)	24 (13)	18 (10)	26 (21)	9 (12)	5 (9)
Fever (No.of children)	35 (18)	21 (12)	11 (9)	14 (18)	3 (9)
Comedication: Antiemetics Antpyretics (No.of children)	 12 (50) 21 (60)	 8 (44) 15 (71)	 19 (73) 10 (91)	 6 (67) 10 (71)	 5 (100) 2 (67)
Antibiotics for co-morbidity (No.of children)	40 (21)	37 (21)	30 (24)	25 (32)	4 (12)
Values are mean ± SEM. Figures in bracket indicate percentage. * P < 0.05					

Table-3: The base-line clinical and demographic features of patients in various groups in the study

Group	Adverse event		Total (%)
	Yes (%)	No (%)	
Control	44 (23.16)	146 (76.84)	190 (100)
Racecadotril	61 (34.86)*	114 (65.14) *	175 (100)
Mebarid	26 (21.14)	97 (78.86)	123 (100)
Diarex	14 (17.95)	64 (82.05)	78 (100)
Loperamide	6 (17.65)	28 (82.35)	34 (100)
Total	151 (25.17)	449 (74.83)	600 (100)
* P < 0.05, The overall adverse events in the various groups of antidiarrheal agents were comparable to that of control. However children in the racecadotril group suffered significantly more adverse events.			

Table-4: Distribution of adverse events in various study groups

Group	Control	Racecadotril	Mebarid	Diarex	Loperamide
	n=190	n=175	n=123	n=78	n=34
Vomiting	5 (2.6)	15 (8.57)	7 (5.69)	5(6.41)	0
Fever	7 (3.68)	5 (2.86)	9 (7.32)	9(11.54)	0
Abd. Pain	18 (9.5)	11 (6.3)	9 (7.32)	0	5 (14.71)
Drowsiness	0	5 (2.86)	0	0	1 (2.94)
Headache	0	21 (12)	0	0	0
Rash	0	1 (0.57)	0	0	0
Others *	14(7.37)	3 (1.71)	3 (2.4)	0	0
*Others include nausea, weakness, bodyache, irritability and excessive crying.There was significant difference in incidence of adverse events like fever, abdominal pain, vomiting, others between study groups. Drowsiness was not observed with non-allopathic antidiarrheals.					

Table-5: Details of adverse event wise distribution of children in various study groups

Assessment of safety

Safety was assessed by recording the adverse events observed during treatment.

DISCUSSION

All patients tolerated the treatments well and the adverse events observed were mostly mild and transient. No serious adverse events were reported in the study.

Overall occurrence of adverse events was significantly higher in racecadotril group (34.86%) compared to other groups (C:23.16%, M:21.14%, D:17.95%, L:17.65%). Lehart et al (2012)[8] in their recent systematic review reported that 11.6% of children experienced adverse events with racecadotril. However,This study mainly included infants and very young children (median age 12 months) in data analysis and also the aetiology and severity of diarrhea is likely to differ from the present study place.

Vomiting and headache were most commonly reported symptoms in racecadotril group (8.57% and 12%).

Vomiting: There was statistically significant difference of adverse event vomiting between study groups ($P < 0.05$)

The occurrence of vomiting was found to be more in racecadotril group (8.57%) compared to control group (2.6%) and loperamide group (0%).

But children did not have more than one or two bouts of vomiting and hence very few required treatment for it.

Vomiting was one of the common adverse event reported in study by Sjaweska et al,[9] however it was seen equally in control groups as well. 51% and 52% children in racecadotril and placebo group reported vomiting respectively in a double blind comparative study by Salazar-Lindo.[10] These findings are different from the present study.

Vomiting is a frequently seen symptom in children with acute diarrhea. Hence, it is unlikely to be due to treatment with racecadotril.

Headache: Incidence of headache was significantly higher in racecadotril group (12%). This adverse event was reported in 2.1% of adult patients receiving racecadotril in Prado et al (2002)[11] study. This was a single blind, multicentre, comparative study conducted in 945 outpatients with acute diarrhea from developing countries. Present study recorded high incidence of headache.The cause of headache with racecadotril is not known. This adverse event was not reported in other groups.

Fever: Incidence of fever was found to be more with the non-allopathic antidiarrheal agents viz.Diarex (11.54%),Mebarid (7.32%) as compared to control, racecadotril and loperamide groups ($P < 0.05$).

Abdominal pain: Incidence of abdominal pain was more in loperamide group (14.71%) compared to racecadotril (6.3%), Mebarid (7.32%) and Diarex (0%) groups. However this incidence was not statistically significant compared to the control group (9.5%).

Rebound constipation was a common adverse effect reported with loperamide in previous studies,[12,13,6] but we did not observe this adverse event in present study. Serious adverse events were not observed in present study with loperamide.

Drowsiness: Only 2.94% children complained of drowsiness in loperamide group. But there was no statistically significant difference between it and racecadotril (2.86%). This CNS related adverse event was not observed with non-allopathic antidiarrheals.

Li S-TT et al (2007)[14] in their systematic review and meta-analysis studied 13 RCTs to evaluate the efficacy and safety of loperamide in children (n=1788) younger than 12 y. This study reported high incidence of mainly CNS related and gastrointestinal adverse events in children receiving loperamide (10.1%) compared to those on placebo (2.1%). Similarly Turck et al (1999)[6] reported high incidence of adverse events with loperamide (22%) compared to racecadotril (11.5%) in children.

In present study significant CNS related or gastrointestinal adverse events were not seen with loperamide as reported in above studies.[6,7]

Skin itching was reported as a frequently occuring adverse event (28.6%) with racecadotril by Wang et al (2005)[13] in their study comparing racecadotril and loperamide in adults. However, in the current study this adverse event was not observed in children. Other adverse events like nausea, weakness, irritability etc. were reported by less than 10% of children belonging to control group as well as other treatment groups but none were severe.

Ayurvedic drugs (non-allopathic drugs) are claimed to be free of adverse effects and are considered risk free and this notion is popular in Indian community. However, present study differs from previous studies which have reported no adverse events with non-allopathic antidiarrheals like

Diarex. We observed adverse events in 21.14% and 17.95% with Mebarid and Diarex respectively.

Antiemetics and analgesics were pescribed for 7 (4 from racecadotril and 3 from Mebarid group) and 3 (Diarex group) children respectively and they recovered within 1 day.

However these adverse events might also be due the disease condition, that is acute diarrhea.

Tolerability

In the present study, both allopathic and non-allopathic antidiarrheals were well tolerated by the study population. The adverse events reported were mild to moderate;resolved without any treatment and did not require stoppage of medications in any of the patients at any stage of treatment.

CONCLUSIONS

The nonspecific antidiarrheal agents used in the study may be safe, effective and inexpensive addition to the routine treatment of acute diarrhea.

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