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Smectite in Acute Diarrhea in Children: A Double-Blind Placebo-Controlled Clinical Trial

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Summary: Dioctahedral smectite (DS) a natural adsorbent clay capable of adsorbing viruses, bacteria, and other intestinal irritants in vitro, is claimed to possess beneficial "antidiarrheal" properties. This study tested the effect of DS on the duration of diarrhea and the frequency and amount of liquid stools. Ninety well-nourished boys, aged 3–24 months, with acute watery diarrhea and mild, moderate, or severe dehydration were included in a randomized double-blind, placebo-controlled trial. After initial rehydration, they received DS or placebo (1.5 g freshly dissolved in 50 ml of water, four times daily for 3 days) along with oral rehydration solution (ORS) and adequate feeding. The clinical characteristics of both groups were comparable on admission. Patients in the smectite group had a significantly shorter duration of diarrhea (mean ± SD, 54 ± 16 vs. 73 ± 13 h) and significantly fewer stools (2.6 ± 0.8 vs. 3 ± 0.7 on second day; 1.9 ± 0.7 vs. 2.4 ± 0.7 on third day; and 11.3 ± 3.2 vs. 13.8 ± 3 overall). The amount of liquid stools was not significantly reduced. Weight gain at 24, 48, and 72 h and on recovery was significantly higher in the smectite group despite the comparable fluid and food intake in both groups. These results suggest a beneficial effect of DS in shortening the duration of diarrhea and reducing the frequency of liquid stools in children rehydrated with ORS. **Key Words:** Smectite—Adsorbents—Antidiarrheal—Acute diarrhea—Diarrhea management.

Oral rehydration therapy (ORT) has been universally accepted as the most effective weapon in the struggle against acute diarrhea, and widespread use of the oral rehydration solution (ORS), recommended by the World Health Organization (WHO) for the prevention and management of dehydration (1), has achieved a dramatic decline in the mortality and morbidity from diarrheal diseases (2–4). Unfortunately, ORT does not significantly reduce the volume, frequency, or duration of diarrhea. This limitation raises a practical problem since a major concern of parents and, consequently, health care providers during diarrhea is the frequency and volume of the child's stools. Hence, there is a need to find out an adequate agent that could reduce the volume, frequency, and duration of diarrhea. The choice of a particular drug, however, is not easy. To be recommended for human use, an antidiarrheal should have a high therapeutic index, it should be safe even when used without extensive medical supervision, and it should be compatible with ORT, effective in diarrhea of different etiologies, and inexpensive (5).

The use of antibiotics and antimotility and antisecretory drugs has been ineffective and sometimes accompanied by serious side effects (6–10). On the other hand, some adsorbents have been found to be free from serious consequences. One of these, dioctahedral smectite (DS), was classified in 1981 by the Food and Drug Administration (FDA) as "safe as an over-the-counter drug" (11).

DS is a natural adsorbent clay formed of fine sheets of aluminomagnesium silicate (12,13). Because of its nonfibrous crystalline structure, DS possesses substantially more adsorbent properties than other clays used as antidiarrheal agents (12). In in vitro and animal experiments, DS has been found

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to adsorb viruses, bacteria, bacterial toxins, and other intestinal irritants, thus protecting the intestinal mucosa (14–20). Moreover, some open clinical studies found smectite to be a safe, well-tolerated, and effective antidiarrheal. Ours is the first randomized, double-blind, placebo-controlled clinical study to determine if the use of DS as an adjuvant to ORT has any beneficial effect on the frequency, amount, and duration of diarrhea in infants and young children. Initial results were previously published (21).

MATERIALS AND METHODS

This randomized, double-blind, placebo-controlled, 1-year clinical trial was conducted at Elshatby Children's Hospital, Alexandria, Egypt. It included 90 well-nourished boys (weight-for-height $\geq$80% of NCHS standards), aged 3–24 months, who had acute watery diarrhea for $\leq$5 days, with mild, moderate, or severe dehydration (1). Children with prolonged diarrhea, overt malnutrition, or any major systemic illness were excluded.

The number of patients included in the study was based on a worthwhile shortening of 30% in the mean duration of diarrhea using standard statistical methods with a type I error of 5% and a power of 90% (22). Approval of the Scientific Ethical Committee of the Alexandria Faculty of Medicine and informed consent of the boys' parents were obtained.

Patients fulfilling the inclusion criteria were selected from a large number of children with diarrhea presenting to the rehydration unit of the hospital during peak morning hours, a maximum of two patients being admitted at a time. On admission, length and nude weight were measured using a Seca-Correcta weighing scale with 10-g accuracy, and children were examined to assess their clinical status and degree of dehydration. They were then rehydrated either orally with ORS (mild and moderate cases) or i.v. with Ringer's lactate solution (severe cases), according to WHO guidelines (1).

Following initial rehydration, children were allocated to receive either DS or placebo according to a block randomization done and kept by the Diarrheal Disease Control Programme, WHO, (Geneva, Switzerland). The study being double-blind, each patient was given a numerically coded envelope containing 12 sachets, each containing 1.5 g of DS or placebo to be taken (freshly dissolved in 50 ml of water) four times daily for 3 days under the supervision of an investigator. Both drug and placebo were supplied by Beaufour-Ipsen, France, via the WHO. The placebo, which was made with cellulose, glucose, and vanilline, could not be distinguished from the drug. Feeding was standardized according to WHO guidelines (1).

Patients were kept in the hospital until termination of diarrhea (passage of two consecutive well-formed stools) or a minimum of 3 days. Data were collected and recorded on admission (0 h), at 2, 4, 6, and 12 h, and then every 12 h until recovery. Data included feeding pattern before and during diarrhea, frequency of diarrhea and vomiting, duration of diarrhea (from 0 h to last liquid stool), and duration of vomiting (from 0 h to last vomiting). The amount of liquid stools was measured to the nearest gram (expressed as g/g of body weight), using the difference between the weights of the dry and wet disposable diapers. Urine was collected separately using urine-collecting bags. An accurate record, to the nearest milliliter, of the amount of ORS, plain fluids, milk formula, and semisolid foods actually consumed by each patient was obtained.

Laboratory studies on admission included routine stool analysis for parasites and enzyme-linked immunosorbent assay (ELISA) screening for rotavirus antigens (23); this analysis was performed to characterize the population studied. No stratification was made; therefore, no attempt was made to analyze the data in subgroups.

Patients from both groups were considered to be "treatment failures" but were still included in the statistical analysis if they manifested, at any time, an aggravation of diarrhea, vomiting, or dehydration necessitating unscheduled i.v. fluid therapy.

SPSS-PC software and IBM-PC hardware were used for the statistical description and analysis of data. An unpaired t test was performed on interval data with normal distribution and equal variance; otherwise, nonparametric tests (Mann–Whitney U and Wilcoxon rank-sum W) were used. χ^2 analysis was done for comparison of discrete variables, and a Z test was used for comparison of percentages. The level of significance was 5%.

RESULTS

Smectite and placebo groups had comparable clinical characteristics on admission (Tables 1 and 2). We did not have any treatment failures or withdrawals from the study. In Table 3, statistical comparison shows that patients in the smectite group

TABLE 1. *Preintervention findings: mean ± SD*

Presenting features	Smectite (n = 45) No.	Mean	SD	Placebo (n = 45) No.	Mean	SD	p[a]
Age (mo)	45	7.9	5.2	45	10.1	6.0	0.055
Diarrhea							
Duration before admission (days)	45	1.6	0.8	45	1.4	0.6	0.150
Frequency in last 24 h	45	7.3	1.5	45	7.3	1.5	0.983
Vomiting							
Duration before admission (days)	37	1.3	0.5	38	1.2	0.4	0.255
Frequency in last 24 h	37	2.1	0.8	38	1.8	0.9	0.056
Weight on admission (kg)	45	7.1	1.9	45	7.8	2.0	0.071

[a] Nonparametric Mann–Whitney U and Wilcoxon rank-sum W tests.

had a significantly shorter duration of diarrhea, a significantly decreased frequency of liquid stools on the second and third days of treatment, and a significantly decreased total number of liquid stools. Moreover, from the second day onward, the probability of resolving the acute diarrheal condition was significantly greater in patients taking smectite than in those on placebo (Fig. 1). After 48h, 19 patients (42%) of the group receiving smectite were free of diarrhea, while this was true of only 6 patients (13%) receiving placebo. While diarrhea remained unresolved after 3.5 days in 20% of patients taking placebo, it was resolved in all taking smectite. However, the mean amount of liquid stool was not significantly reduced. Similarly, Table 4 shows that there were no significant differences in the duration and frequency of vomiting, the time needed for rehydration, and the time to first voiding of urine. Table 4 also shows that the amounts of ORS and i.v. and oral fluids needed for rehydration and maintenance were comparable in both groups, except on the third day, when a significantly smaller amount of ORS was consumed by the smectite group. The amounts of milk formula and semisolid foods consumed were comparable in both groups.

TABLE 2. *Preintervention findings: percentages*

	Smectite (n = 45) No.	%	Placebo (n = 45) No.	%	χ^2
Degree of dehydration					
Mild	24	53.3	31	68.9	
Moderate	19	42.2	14	31.1	3.65
Severe	2	4.4	0	0.0	
Feeding pattern since start of diarrhea					
Breast-feeding only	13	28.9	15	33.3	
Breast-feeding and cow milk	1	2.2	4	8.9	
Breast-feeding and cow milk and semisolids	0	0.0	0	0.0	4.45
Breast-feeding and semisolids	6	13.3	5	11.1	
Milk or formula	13	28.9	7	15.6	
Milk and semisolids	8	17.8	11	24.4	
Semisolids only	4	8.9	3	6.7	
Presence of vomiting	37	82.2	38	84.4	0.001
Rotavirus present (ELISA)	7	15.6	8	17.8	0.08

The weight gains (expressed as percentage of the weight of patient after rehydration) at 24, 48, and 72 h after starting rehydration and at recovery were significantly higher in the smectite than in the placebo group (Table 5).

DISCUSSION

According to our results, freshly dissolved dioctahedral smectite, in a dose of 1.5 g four times daily for 3 days, significantly shortened the duration of acute watery diarrhea in infants and young children. DS also achieved a significant reduction in the frequency of liquid stools from the second day of treatment. On the other hand, it had no significant effect on the amount of liquid stools, rehydration requirements, food consumption, and duration and frequency of vomiting. However, children treated with smectite had a significantly higher weight gain than those in the placebo group despite the comparable fluid and food consumption.

The taste of smectite was acceptable to the children, and its administration was not accompanied by any side effects.

Our findings are in harmony with those of previous studies on smectite (12,24–25). While most such studies were not double-blind, they all reported safety, good tolerance, and a beneficial effect of dioctahedral smectite on the duration of diarrhea. Reduction in the amount of stools was reported only by Louchet and Chapoy (26).

Similar results were reported with cholestyramine, which significantly shortened the duration of

TABLE 3. *Clinical outcome of diarrhea and vomiting*

Clinical outcome	Smectite (n = 45)			Placebo (n = 45)			
	No.	Mean	SEM	No.	Mean	SEM	p[a]
Duration of diarrhea (h)	45	54.1	2.35	45	72.9	1.98	0.001[b]
Number of diarrheal stools							
0–6 h	45	2.8	0.2	45	2.9	0.2	0.481
6–24 h	45	4.7	0.2	45	4.9	0.2	0.407
24–48 h	42	2.6	0.2	45	3.0	0.1	0.016[b]
48–72 h	26	1.9	0.1	39	2.4	0.1	0.013[b]
Total	45	11.3	0.48	45	13.8	0.45	0.001[b]
Amount of liquid stools (g/kg of body weight)							
0–6 h	45	25.5	1.15	45	24.0	1.2	0.451
6–12 h	45	22.6	1.4	45	22.8	1.3	0.901
12–24 h	45	19.4	1.0	45	19.7	1.2	0.913
24–48 h	42	20.5	1.4	45	21.4	1.2	0.283
48–72 h	26	15.8	1.7	39	17.5	1.0	0.290
72 h	8	12.1	2.7	23	15.4	1.3	0.095
Total	45	97.9	5.2	45	110.9	6.3	0.065
Duration of vomiting (h)	45	14.5	1.46	42	18.6	1.43	0.077
Frequency of vomiting							
0–6 h	45	0.9	0.13	42	0.8	0.12	0.768
6–12 h	45	1.0	0.13	42	0.9	0.12	0.215
12–24 h	29	0.5	0.23	27	0.7	0.15	0.215
24–48 h	8	0.2	0.17	9	0.4	0.23	0.133
48–72 h	3	0.4	0.11	0	0.0		—
72 h	0	0.0		0	0.0		—
Total	45	2.6	0.25	42	2.8	0.24	0.224

[a] Nonparametric Mann–Whitney U and Wilcoxon rank-sum W tests.
[b] Significantly different from placebo group.

watery diarrhea although it did not significantly reduce the total stool volume (9,27). However, cholestyramine, which is a nonabsorbable anion exchange resin, is known to possess a strong affinity to bind many substances including the bicarbonate from ORS (28); it also has a peculiar taste.

Being unabsorbed from the GI tract, DS exerts its antidiarrheal effect through protection of the intestinal mucosa from the damage caused by diarrheogenic agents (14–17) and by diminishing mucolysis and destruction of the mucous membrane (18). DS was proved in experimental studies to protect against *Escherichia coli* in calves and rabbits (15,18), *Campylobacter jejuni* in mice (19), cholera toxin in dogs (17), rotavirus in calves (14), and a myriad of other substances including bile salts and T-2 mycotoxin (16,25). The effect of DS on mucosa may be partially responsible for the faster recovery of the lactulose/mannitol urinary ratio in children receiving DS (29). However, this mucoprotective effect was not found to interfere with normal absorption. On the contrary, DS favored the absorption and counteracted the excretion of water induced by pathogenic *E. coli*. This effect was accompanied by a considerable augmentation in the absorption of sodium, chloride, bicarbonate, and magnesium (18) and may explain the higher weight gain of the smectite group we found despite comparable intake of fluids and food in the two groups.

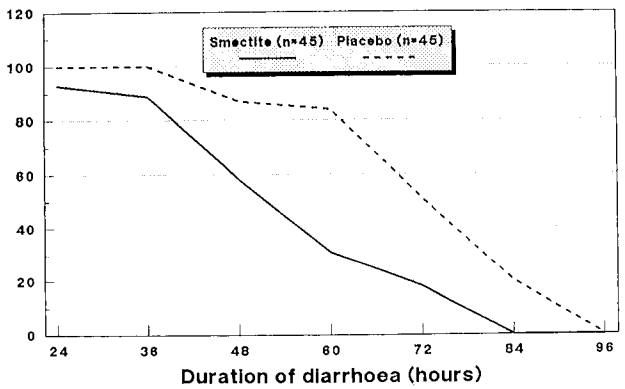

FIG. 1. Percentage of patients whose diarrhea remained unresolved during 96 h of treatment with smectite or placebo; a statistical difference between the two groups was observed after 24 h.

It can be concluded that dioctahedral smectite exerts a beneficial effect in shortening the duration of diarrhea, reducing the frequency of liquid stools, and enhancing weight gain in children with acute

TABLE 4. *Rehydration requirements and food intake*

Variables	Smectite (n = 45) No.	Mean	SEM	Placebo (n = 45) No.	Mean	SEM	p[a]
Time of first voiding of urine (h)	45	5.9	0.2	45	5.7	0.14	0.347
Time needed for initial rehydration (h)	45	4.2	0.16	45	4.2	0.11	0.545
Amounts of ORS (ml/kg)							
0–6 h	45	60.5	2.8	45	59.8	3.1	0.837
6–24 h	45	49.9	2.5	45	45.6	2.4	1.014
24–48 h	42	19.6	1.5	45	17.4	1.6	0.178
48–72 h	26	8.0	1.2	39	12.5	1.2	0.041[b]
72 h	8	3.8	2.0	23	5.7	1.2	0.451
Total	45	137.3	5.56	45	136.4	6.8	0.756
Amounts of i.v. fluids (ml/kg)	2	525.0		1	750.0		
Amounts of water and plain fluids: (ml/kg)							
0–6 h	45	9.4	0.8	45	8.9	0.6	0.580
6–24 h	45	34.6	2.1	45	34.7	1.7	0.646
24–48 h	42	34.7	2.1	45	29.7	1.5	0.055
48–72 h	26	36.8	3.1	39	31.6	2.0	0.176
72 h	8	25.4	3.1	23	23.4	2.3	0.527
Total	45	115.4	5.8	45	115.7	5.8	0.965
Milk or formula (ml/kg)							
6–24 h	45	18.0	2.9	45	18.9	3.3	0.969
24–48 h	42	24.9	3.8	45	22.1	3.8	0.561
48–72 h	26	29.4	5.8	39	21.2	4.0	0.294
72 h	8	23.6	1.0	23	14.4	4.0	0.325
Total	45	76.7	11.9	45	70.7	2.3	0.711
Semisolids (ml/kg)							
6–24 h	45	20.1	1.9	45	17.4	3.5	0.252
24–48 h	42	28.3	2.3	45	24.9	2.4	0.254
48–72 h	26	35.9	3.1	39	29.7	2.8	0.159
72 h	8	14.6	5.3	23	17.1	2.7	0.667
Total	45	88.0	6.7	45	79.4	7.5	0.417

[a] Nonparametric Mann–Whitney U Wilcoxon rank = sum W tests.
[b] Significant.

diarrhea rehydrated with ORS. The drug is acceptable, safe, and well-tolerated and did not interfere with ORT and normal feeding. The same conclusions were reached by the WHO committee on diarrheal disease (30), although the committee was not in favor of recommending DS use in view of the additional cost when oral rehydration therapy is by itself life-saving. However, we believe that cost is more than offset by the reduction in the duration of diarrhea, in the time spent by the parents to take care of their children, and in the length of hospital stay (31).

TABLE 5. *Weight gain as percentage of rehydrated weight*

	Smectite (n = 45) No.	Mean	SD	Placebo (n = 45) No.	Mean	SD	p[a]
After 6 h	45	1.0	0.07	45	0.8	0.06	0.059
After 24 h	45	0.8	0.1	45	0.6	0.07	0.023[b]
After 48 h	45	1.1	0.1	45	0.6	0.07	0.004[b]
After 72 h	45	1.2	0.1	45	0.8	0.07	0.002[b]
On recovery	45	1.3	0.1	45	0.8	0.07	0.002[b]

[a] Nonparametric Mann–Whitney U and Wilcoxon rank = sum W tests.
[b] Significant.

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