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# Smectite in the Treatment of Acute Diarrhea: A Nationwide Randomized Controlled Study of the Italian Society of Pediatric Gastroenterology and Hepatology (SIGEP) in Collaboration With Primary Care Pediatricians

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**ABSTRACT**

**Background:** Childhood gastroenteritis is associated with considerable health costs. The natural clay dioctahedral smectite increases intestinal barrier function and is effective against infectious diarrhea in children in developing countries. The purpose of this work was to investigate the efficacy of smectite in Italian children with acute diarrhea of mild to moderate severity.

**Methods:** A national, prospective, randomized, case-controlled study was performed in collaboration with primary care pediatricians. Children seen by pediatricians for acute gastroenteritis were treated with oral rehydration solution (ORS) alone or ORS with smectite. Parents returned a form in which total duration of diarrhea, incidence of vomiting and fever, persistence of diarrhea for more than 7 days and hospital admissions were recorded.

**Results:** Eight hundred four children with acute diarrhea were randomly assigned to treated or control groups. Administration of smectite was associated with significant reduction of the duration of diarrhea, as judged by stool frequency and consistency. The incidence and duration of vomiting and fever were not different. Diarrhea lasted more than 7 days in 10% of treated and in 18% of control children ($P < 0.01$). Hospital admission was necessary in seven treated and six control children. No side effects were observed.

**Conclusions:** Smectite reduces the duration of diarrhea and prevents a prolonged course. It may therefore consistently reduce the costs of gastroenteritis. ***JPGN 32:71–75, 2001.*** **Key Words:** Diarrhea—Gastroenteritis—Intestinal infection—Smectite—Treatment. © 2001 Lippincott Williams & Wilkins, Inc.

Gastroenteritis remains a common problem in industrialized countries and is associated with substantial costs for both the family and society. It is estimated that the cost of an episode of diarrhea requiring a physician visit is as high as $290 (U.S.) in the United States, half of which is related to missed workdays (1). As a consequence, the economic impact of gastroenteritis is directly related to the duration of the disease. The expected annual incidence of childhood gastroenteritis in Italy is as high as 1,600,000 episodes per year (2). If the U.S. costs were applied to Italian children, a total of 325 million dollars would be needed per year, not including hospital expenses.

The key treatment for acute diarrhea is fluid–electrolyte replacement, which is achieved with oral rehydration solution (ORS). However ORS has no effect on either the duration of diarrhea or the volume of fluid loss (3). Agents that could be safe and effective in reducing the duration of diarrhea, would therefore be a valuable therapeutic resource.

An active search for drugs to treat gastroenteritis has been conducted in recent years, to reduce the duration of diarrhea and its costs and to prevent severe complications. Dioctahedral smectite (DS), a nonsystemic aluminosilicate of pyhillitic structure, has been shown in studies in vitro to protect the intestinal mucosal barrier and to adsorb toxins, bacteria, and rotavirus (4,5). Smectite

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modifies the physical properties of gastric mucus, counteracting mucolysis induced by bacteria (6). It also repairs intestinal mucosal integrity, as suggested by the normalization of the urinary lactulose-mannitol ratio in children with acute diarrhea (7). In addition, DS fully restores the barrier properties of human intestinal cell monolayers after exposure to tumor necrosis factor (TNF)-α in an Ussing chamber experimental model (8).

Preliminary clinical evidence suggested that DS is effective in shortening the duration of diarrhea and enhancing weight gain. However, most of this evidence was obtained in children from developing countries admitted to hospitals for diarrhea (9,10).

The purpose of this work was to prospectively investigate the efficacy of DS in Italian children with acute diarrhea of mild to moderate severity who were brought to the offices of primary care pediatricians. This population represents the bulk of children with gastroenteritis in the preschool age and therefore is the obvious target for such treatment.

## METHODS

Acute diarrhea was defined as three or more loose or liquid stools per day. Children aged 3 months to 5 years, with acute-onset diarrhea of mild to moderate severity, according to standard criteria, were enrolled by primary care pediatricians (family pediatricians in the public health system in Italy), in the period March 1998 through February 1999. The first two children seen each month by each pediatrician were enrolled. It was recommended that children be enrolled based on the capacity of their parents to report reliable information.

Exclusion criteria were the administration of antibiotics, probiotics, or other drugs considered to be active in the intestine in the prior 3 weeks; the onset of diarrhea more than 48 hours before being seen by the pediatrician; a weight-height ratio below the 5th percentile; and any chronic disease or immunosuppressive condition or treatment.

Patients were randomly allocated to either the control or the treated group, on a systematic one control subject-to-one treated subject basis. The former received 60 mM Na ORS alone; the latter received ORS with DS. Dioctahedral smectite (Diosmectal; Malesci S.p.A., Florence, Italy) was prescribed for 5 days at a dose of 3 or 6 g/day in 2 divided doses in subjects younger or older than 1 year, respectively. All patients were rehydrated during the first 4 to 6 hours, according to the recommendations of the ad hoc Committee of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (11), and administration of DS began. All children were refed early with full-strength, lactose-containing milk and with their usual diets, as currently recommended (3,12).

Parameters of efficacy were the total duration of diarrhea, as judged by the number of stools per day and their features—scored as 3, liquid; 2, semiliquid; 1 loose; 0, normal—as described previously (13); the incidence of vomiting and fever (body temperature >38°C); the number of children with an unusually protracted (>7 days) course of diarrhea; and the number of children admitted to the hospital. The duration of diarrhea was expressed in hours, and it was considered to last from the first to the last liquid–loose stool output preceding the return of normal stools.

The parameters of efficacy were carefully recorded by the mothers of children, who were required to complete and return a form with detailed day-by-day information to the pediatrician. They were specifically requested to report how long the drug was taken by the child and why it was eventually discontinued before 5 days. However, all children who refused to take DS were included in the treated group in the analysis of results, because this was considered to be a field study. The forms were returned to the pediatrician within 1 week of recovery from diarrhea and delivered to a blind assessor for statistical analysis. Less than 10% of the forms were not returned or were incomplete and were eventually excluded from analysis.

The study design was discussed with 60 family pediatricians taking part in the study from northern, central, and southern Italy. It was agreed that the information would be limited to the stated parameters, which were considered to be the usual endpoints for such a treatment. Performance of a placebo-controlled study was judged to be impractical, because of the nature of the drug under investigation and its taste. Of 60 pediatricians, 42 provided patients to be enrolled in this study (see the Appendix).

The study protocol was approved by the Research Committee of the Italian Society of Pediatric Gastroenterology and Nutrition (SIGEP). Informed consent was obtained from the parents of enrolled children.

### Statistical Analysis

Analysis of variance (ANOVA) was used to evaluate intergroup differences. Duration of diarrhea was expressed as mean ± SD. The *t*-test and the $\chi^2$ test were applied as appropriate. To overcome potential effects of biases related to the large number of colleagues taking part in the study and therefore of subjects enrolled, data were corrected for potentially confounding variables: the age of children enrolled and the severity of diarrhea, judged by the number of stool outputs at the enrollment. Duration of diarrhea was therefore expressed as raw data and as data corrected for covariance. Data were analyzed by SPSS version 6 (SPSS Inc., Chicago, IL, U.S.A.).

## RESULTS

Both groups were comparable for sex, prevalence of fever, and vomiting at the enrollment. The duration of

**TABLE 1.** *Features of patients at the enrollment*

| | ORS (n = 406) | ORS + DS (n = 398) | *P* |
|---|---|---|---|
| Enrolled/Eligible (%) | 89 | 92 | NS |
| Age (months) | 29.8 ± 16.9 | 26.9 ± 19.2 | $P < 0.01$ |
| Males (%) | 39 | 42 | NS |
| Fever (%) | 57 | 59 | NS |
| Vomitus (%) | 64 | 62 | NS |
| Stool outputs on day 1 | 5.0 ± 2.2 | 5.5 ± 2.6 | $P < 0.05$ |
| Duration of diarrhea pretreatment (hr) | 34 ± 6 | 31 ± 5 | NS |

ORS, oral rehydration solution; DS, dioctahedral smectite; NS, not significant.

Data are expressed as mean ± SD or %.

diarrhea pretreatment was also similar (Table 1). A slight, although significant difference in the mean age and in the severity of diarrhea was detected, indicating that children receiving DS were younger and that diarrhea pretreatment was more severe than in control subjects (Table 1). Both these variables were corrected for in the analysis of the results.

A total of 898 children were eligible, and 804 were enrolled in the study. Ninety-four children were eventually excluded, because either their parents did not report the information required or they did not comply with the inclusion criteria. Of the 804 children enrolled, 398 received ORS, and 406 received ORS and DS.

Approximately 80% of children had mild dehydration, and 20% had moderate dehydration. Microbiologic investigation was performed in 80 children and showed positivity for rotavirus in 34 and the presence of a bacterial agent in 8. No established enteric pathogen was identified in the other 38 stool specimens.

The mean duration of diarrhea was reduced in children receiving DS. Specifically, administration of DS was associated with a significant progressive decrease in the number of stool outputs (Fig. 1), and it also was associated with a significantly more rapid improvement in consistency of stools (Fig. 2). Both these effects were evident beginning the day after treatment.

To see whether the effects of DS were related to age or to the severity of diarrhea, data were analyzed after correction for covariances, as detailed in the Methods section. Results are reported in Table 2. The significant difference in the duration of diarrhea between children receiving DS and the control subjects was maintained when results were corrected for age and number of stools pretreatment.

Overall, diarrhea lasting more than 7 days was recorded in 116 of 804 children (14%). These included 44 of 406 (10%) treated children and 72 of 398 (18%) control children. Therefore, administration of DS was associated with significant reduction of a prolonged course of diarrhea ($P < 0.01$).

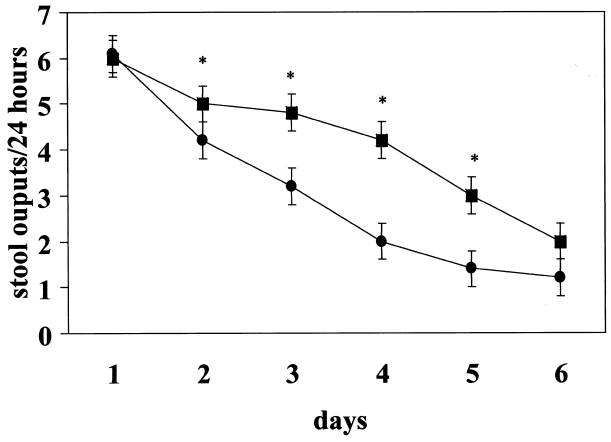


**FIG. 1.** Frequency of stools in children receiving oral rehydration solution (ORS; ■) or ORS and dioctahedral smectite (DS; ●). Administration of DS was associated with significant reduction of the number of stools (*$P < 0.05$).

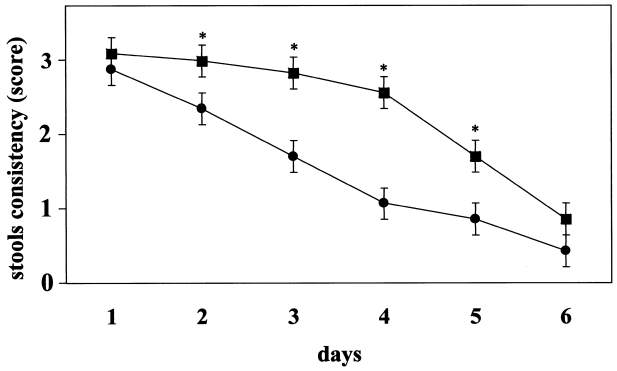


**FIG. 2.** Consistency of stools in children receiving oral rehydration solution (ORS; ■) or ORS and dioctahedral smectite (DS; ●). Stools were scored as 0 (normal), 1 (loose), 2 (semiliquid), or 3 (liquid). Administration of dioctahedral smectite (DS) was associated with a significant increase in the consistency of stools (*$P < 0.05$).

There were 13 admissions to the hospital, including 7 children in the treated group, and 6 in the control group. In all children needing hospital care, diarrhea resolved within a few days without any further problem.

The incidence and duration of vomiting and fever were not different in the two groups at enrollment. However, both these symptoms were equally reduced in treated and control children in subsequent days (Fig. 3). No side effects potentially related to the administration of DS were observed.

The number of children who totally refused DS was 30 (2.8%). The rate of refusal of DS grew progressively in parallel with improving clinical condition, and as many as 20% of children did not complete the expected 5 days of treatment. Parents were required to report the reason for refusal, and the most common was "bad taste" (Fig. 4).

As reported in the Methods section, all children who refused DS were included in the treated group in the analysis of the results. When children who refused to take DS were excluded from the analysis, the statistical significance of the differences between treated and control children was further increased.

## DISCUSSION

Although acute gastroenteritis is a self-limited disease, an increasing number of therapeutic strategies are being tested with the purpose of actively treating it. In the past, several substances have been used such as cholestyramine, loperamide, kaolin, pectin, and diphenoxylate (14–17). However, none of these drugs is presently regarded as effective, and in some patients, potentially serious side effects have been described (18).

More recently, good results have been obtained with selected probiotics, although it is still unclear whether

**TABLE 2.** *Duration of diarrhea in children treated with smectite (DS) and in controls (ORS)*

| | ORS | ORS + DS | *P* |
|---|---|---|---|
| Duration (hr) | 119 ± 23 | 96 ± 21 | <0.001 |
| Corrected for age and for no. of stools on day 1 | 119 | 99 | <0.001 |

DS, dioctahedral smectite; ORS, oral rehydration solution.
* Raw data + SD and data corrected for covariates.

their efficacy is limited to viral agents or extended to enteropathogenic bacteria (19,20).

There is evidence that DS matches the criteria of an antidiarrheal agent. In vitro it appears to have a wide spectrum of efficacy against enteropathogenic microorganisms and their products (4–7). It also possesses a protective effect against intestinal damage (8).

In vivo evidence includes studies from developing countries. A study performed in an Egyptian hospital, a center designed by the World Health Organization (WHO) for clinical trials in acute diarrhea, showed that children had a reduced duration of gastroenteritis and faster gain of body weight when they received DS, in comparison with control subjects treated with ORS only (9). Similar results were obtained in Thai children (10).

We sought to investigate the efficacy of DS in the typical population of children with diarrhea of mild to moderate severity that necessitated a visit by primary care pediatricians. In this setting, acute gastroenteritis represents a major problem because of its frequency and is associated with substantial economic losses in Western countries.

With the collaboration of family pediatricians we were able to enroll a very large population. All children were treated with oral rehydration and were refed early, according to recent authoritative guidelines for European children (11,12).

The results of this study clearly showed that DS reduces the duration of diarrhea and that this effect is real rather than cosmetic. Indeed, the consistency of stools improved (which was theoretically due to a cosmetic effect), but the number of bowel movements also decreased. Correction of covariances added to the significance of the results, because children who received DS were in worse condition than control children, because they were younger and had an increased number of stools at enrollment.

An additional important effect of DS was the reduced risk of persistent diarrhea. It should be noted that the choice of 7 days as a cutoff for persistent diarrhea was somewhat arbitrary, although others have used the same cutoff (20). Of note, several pediatricians taking part in the study pointed out that parents' anxiety builds in the presence of a long course of diarrhea, leading to a specific request for effective drugs.

We have few data on the cause of diarrhea, because microbiologic investigation was not required for inclusion, as agreed with participating pediatricians. However, the available data suggest that the cause in the population enrolled reflects that previously reported in large epidemiological studies in Italy, performed in children with similar features and showing a major role for rotavirus, *Campylobacter* and *Salmonella* in childhood acute gastroenteritis (21).

DS had no effect on vomiting and fever, in keeping with previously reported findings (9). This may be explained either by an effect limited to the intestine or by the small number of children with vomiting or fever in both the control and the treated groups.

Hospital admission was necessary in only 13 children, corresponding to 0.8% of the group, with no difference between treated and control subjects. A much larger sample size would be needed to determine whether DS effectively prevents hospital admission in children with these features.

Finally, there was a rather high rate of noncompliance, although refusal of DS was initially limited. A progressively increased number of children refused to take DS in parallel with recovery from diarrhea. This is probably to be expected in light of the unpleasant taste of the drug, as judged by the responses to the questionnaire. However, there was probably no further need for the drug in those who tended to refuse it when they were recovering from diarrhea. The children who refused DS were similar in sex, age, and severity of diarrhea to those who complied with the regimen, and all were included in the treated group.

The results of this study beg the question of actively treating diarrhea. It has been suggested that the use of ORS is not as widespread as it should be, because it does not meet the expectations of the families of children with diarrhea, who require a drug that, in association with ORS, could promptly stop the manifestations of diarrhea without significant effects (22). An effective and safe treatment is available, which may be considered not strictly necessary, because gastroenteritis is usually a

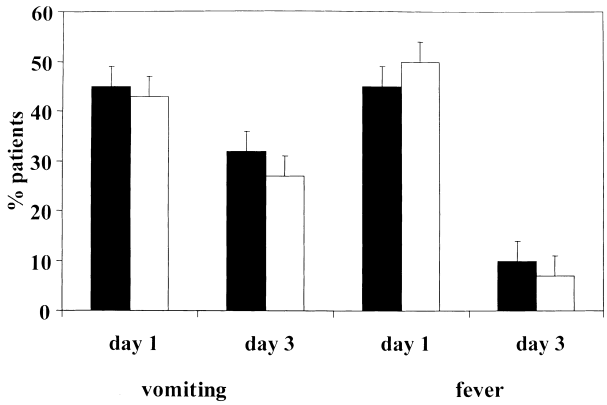


**FIG. 3.** Incidence of vomiting and fever (>38°C) at the onset of diarrhea and after 3 days in children receiving oral rehydration solution (ORS; *filled bars*) or ORS + dioctahedral smectite (DS; *open bars*). The DS had no effect on the incidence of vomiting and fever.

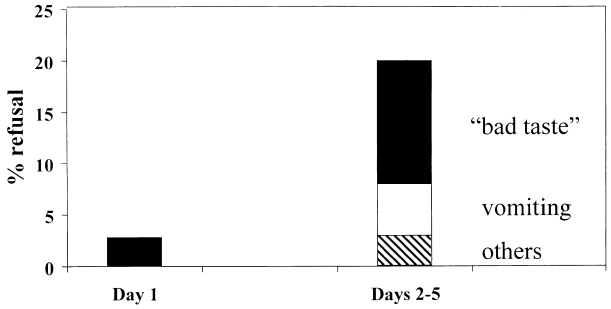


**FIG. 4.** Percentage of children who refused to take DS on day 1 (total refusal) and on subsequent days. The rate of noncompliance increased in parallel with recovery from diarrhea. Most of the children who refused to take DS did so because of "bad taste."

self-limited disease. However, duration of diarrhea was reduced by approximately 20% (i.e., by 1 day), and it seems reasonable to speculate that a parallel reduction of costs may be expected. This corresponds to approximately $60 (U.S.) per episode (1). It should be noted that the cost of full treatment with DS is approximately $5 (U.S.) per child, with a potential substantial impact on health costs.

In addition, DS is effective in preventing a prolonged course of diarrhea that adds to its efficacy. Thus, there are several reasons to support an active treatment of diarrhea and include cost-effective and clinical considerations, as well as the concept that the use of an adjunctive drug might be effective in increasing the use of ORS itself (22).

However, we stress the importance of ORS as the essential treatment for diarrhea, warning that there is no treatment that can in any way replace the simple and inexpensive water and salt replacement treatment for acute gastroenteritis.

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## APPENDIX

The following pediatricians took part to the study and were responsible for enrolling children: C. Addamo, F. Andreoli, R Arigliani, A. L. Artesi, C. Bo, G. Bottaro, L. Cafarotti, G. Carrassi, A. Carlucci, G. Cerimoniale, M. Ciarrocchi, R. Cionini, A. D'Angelo, G. Esposito, L. Ferraro, A. Fontanella, F. Freschi, S. Fulgido, A. Gennaro, C. Gilistro, C. Infesta, A. Lamborghini, F. Locche, M. R. Maestro, B. Malamisura, G. Marullo, B. Ortone, P. Pancheri, V. Parisi, A. Pascalizzi, M. Pierattelli, D. Porretta, L. Rossi, E. Sarra, R. Sassi, A. V. Sotgia, M. Stancati, S. Tagliavini, S. Tamassia, M. G. Toma, G. Tuteri, and M. Valente.