Oral Diosmectite Reduces Stool Output and Diarrhea Duration in Children With Acute Watery Diarrhea

CHRISTOPHE DUPONT,* JIMMY LEE KOK FOO,‡ PHILIPPE GARNIER,§ NICHOLAS MOORE,‖ HÈLÈNE MATHIEX–FORTUNET,§ and EDUARDO SALAZAR–LINDO,¶ for the PERU AND MALAYSIA DIOSMECTITE STUDY GROUPS

*Paris Descartes University, Cochin Saint-Vincent de Paul Hospital, Paris, France; ‡Kuala Terengganu Hospital, Kuala Terengganu, Malaysia; §Ipsen, Medical Department, Boulogne-Billancourt, Paris, France; ‖INSERM U657, Bordeaux University & Hospital, Bordeaux, France; and ¶DS Consult, Surco, Lima, Peru

Background & Aims: **Diosmectite is a clay used to treat children with acute watery diarrhea. However, its effects on stool output reduction, the key outcome for pediatric antidiarrheal drugs, have not been shown.** ***Methods:*** **Two parallel, double-blind studies of diosmectite efficacy on stool reduction were conducted in children 1 to 36 months old in Peru (n = 300) and Malaysia (n = 302). Inclusion criteria included 3 or more watery stools per day for less than 72 hours and weight/height ratios of 0.8 or greater. Exclusion criteria were the need for intravenous rehydration, gross blood in stools, fever higher than 39°C, or current treatment with antidiarrheal or antibiotic medications. Rotavirus status was determined. Diosmectite dosage was 6 g/day (children 1–12 months old) or 12 g/day (children 13–36 months old), given for at least 3 days, followed by half doses until complete recovery. Patients were assigned randomly to groups given diosmectite or placebo, in addition to oral rehydration solution (World Health Organization).** ***Results:*** **Children in each study had comparable average ages and weights. The frequencies of rotavirus infection were 22% in Peru and 12% in Malaysia. Similar amounts of oral rehydration solution were given to children in the diosmectite and placebo groups. Stool output was decreased significantly by diosmectite in both studies, especially among rotavirus-positive children. In pooled data, children had a mean stool output of 94.5 ± 74.4 g/kg of body weight in the diosmectite group versus 104.1 ± 94.2 g/kg in the placebo group ($P = .002$). Diarrhea duration was reduced by diosmectite, which was well tolerated.** ***Conclusions:*** **These results show that diosmectite significantly decreased stool output in children with acute watery diarrhea, especially those who were rotavirus-positive.**

Acute diarrheal diseases are the second most common life-threatening conditions worldwide among all infectious diseases in children younger than 5 years old. Globally, 1.3 billion episodes occur annually, with an average of 2 to 3 episodes per child.[1–3]

According to the World Health Organization,[4] the management of acute watery diarrhea always includes immediate rehydration by oral rehydration solution (ORS) or intravenous fluids for more severe dehydration,[2,5,6] maintenance of breastfeeding and/or early refeeding, and use of antibiotics in selected cases such as bloody diarrhea.

Diosmectite is a natural clay widely used for the treatment of acute watery diarrhea in children, for which it has shown relevant pharmacological properties.[7–9] Diosmectite shortens diarrhea duration[10–14] and normalizes transit.[10] To date, however, the effect of diosmectite on stool output, the key outcome for pediatric antidiarrheal drugs,[15] has not been shown.[16] Among the treatments proposed for acute watery diarrhea, only bismuth and racecadotril, an enkephalinase inhibitor, have shown decreased stool output.[17,18]

We conducted 2 parallel, double-blind, placebo-controlled studies in Peru and Malaysia to determine the actual effect of oral diosmectite on stool output reduction in acute watery diarrhea in infants and children as an adjunct to the currently recommended ORS formula.[4]

Methods

Subjects

The Peru and Malaysia studies included children with acute watery diarrhea, in primary care hospitals.

According to previous studies it was expected that the decrease of total 72-hour stool output would be 30 g/kg of bodyweight with active drug compared with placebo, with a common standard deviation (SD) of 80 g/kg. For rejection of a 2-sided null hypothesis with a type I error of 5% and a type II error of 20%, at least 112 patients had to be included per group. We decided to include 300 patients in total in each study, 150 on diosmectite and 150 on placebo.

Inclusion Criteria

Patients had to be aged 1 to 36 months, with a weight (in kg) to height (decimeters) ratio of at least 0.8 to rule out malnutrition, with at least 3 watery stools per day (moderate acute watery diarrhea) for less than 72 hours with at least 1 watery stool during the 12 hours before inclusion, and dehydration signs requiring the use of ORS according to World Health Organization guidelines. Only male children were included to separate stools from urine by using modified diapers with urine bags attached.

Exclusion criteria were severe dehydration requiring intravenous rehydration, gross blood in stools, fever of 39°C or higher, recent history of diarrhea, previous history of persistent diar-

Abbreviations used in this paper: AE, adverse event; CI, confidence interval; ORS, oral rehydration solution; SD, standard deviation.

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rhea, previously diagnosed malabsorption disease, current treatment with an antidiarrheal medication, drug-induced diarrhea, or any other treatment possibly interfering with the study drug. Exclusively breastfed children or children unable to drink also were excluded.

Study Design

The 2 studies were randomized, placebo-controlled, double-blind, multicenter trials conducted in compliance with Good Clinical Practices (US Food and Drug Administration 21CFR-1A part 50 subpart D concerning children in clinical investigations; European Clinical Trials Directives 2001/20/EC and 2005/28/EC, corresponding to ICH E6), the Declaration of Helsinki (Release of Edinburgh, Scotland, October 2000), and Peruvian and Malaysian regulatory texts related to protection of persons participating in biomedical research. At least one parent or the legal representative of the patient gave written informed consent. Studies were registered at www.ClinicalTrials.gov under the identifiers following: NCT00352989 for the Malaysia study, and NCT00352716 for the Peru study.

Interventions

Children were randomized at visit 1 in sequential ascending order within each center to be treated with either diosmectite (Smecta; Ipsen, Paris, France) or placebo, in addition to ORS. The study drug was dispensed by the investigator only. For each study, the sponsor-assigned biostatistician prepared a list of treatment allocation codes to be kept confidential until approval was received for the study to be unblinded for analysis.

Diosmectite is a powder for oral suspension in sachet, composed of 3.000 g diosmectite, 0.004 g vanillin, 0.007 g sodium saccharin, and 0.749 g glucose monohydrate (147 mOsm/L). Placebo, specifically developed for these studies, was an identical powder, composed of 1.000 g titanium dioxide, 1.181 g maltodextrin (Roquette Glucidex IT 38, Lestrem, France), 0.004 g vanillin, 0.007 g saccharin sodium, 2.150 g glucose monohydrate, and 0.018 g caramel coloring E150B (46 mOsm/L). Placebo was identical to diosmectite in size, weight, color, smell, taste, and appearance, and was inert, as shown on an animal model of watery diarrhea (data not shown). The dosing regimen was that used commonly by pediatricians: for children younger than 12 months, 2 sachets per day for 3 days and then 1 sachet per day; dosage was doubled for older children. After 3 days, children were discharged from the hospital and half the dosage of drug was continued until complete recovery. Complete recovery was defined as the first formed stool onset followed by either a nonwatery stool or a 24-hour period without stool. This was assessed using the data reported by the parents in a diary.

The 245 mOsm/L ORS formulation was used according to standard practice and current World Health Organization guidelines: the volume of ORS used was equivalent to the volume of stool until the end of the risk of dehydration.[4] The same ORS, a powder in sachets to be diluted in 1 L of water (Hidrax; Medifarma S.A., Lima, Peru), was used in both studies. Early refeeding was promoted. For children partially breastfed, the mother stayed in the hospital.

Objectives

The primary objective was to compare the efficacy of diosmectite with that of placebo on stool output reduction in children with acute watery diarrhea. The secondary objectives were to compare diosmectite and placebo for diarrhea duration and safety.

Efficacy

Primary outcome measure. The 72-hour cumulative stool output, in g/kg baseline body weight, was measured over the 72 hours after the first sachet intake, regardless of whether the watery diarrhea had stopped or not. Study nurses measured stool output by deducting the weight of a dry diaper from that of the soiled diaper, using daily calibrated electronic scales with a precision of 1 g. Special diapers were prepared by cutting a circle in the area corresponding to the child's penis. An anti-allergic tape then was placed at the edge of the circle and stuck on a urine collection bag, thereby adapting the open end to the circle. The procedure for stool collection was standardized in each center by means of specific training meetings.

Secondary criterion. Blind review of data found that the stool consistency reported differed between Peru and Malaysia. Although all of the children had a formed stool by the end of the study in Peru, only 60% of the children had a formed stool by the end of the study in Malaysia. Therefore, it was decided under blind conditions, in accordance with the 3 study coordinators, that diarrhea duration would be defined according to country specificities: time from the first sachet intake to the first formed stool for Peru, to the first soft or formed stool for Malaysia, followed by a nonwatery stool or 24 hours without stools.

Rotavirus Status

The rotavirus status of a stool sample collected at inclusion was assessed after confirmed inclusion, using an enzyme-linked immunosorbent assay (Ridascreeen; R-Biopharm, Darmstadt, Germany) in Peru and a rotavirus latex agglutination test (Rotalex; Orion Diagnostica, Espoo, Finland) in Malaysia. This did not influence inclusion status.

Tolerability

Treatment-emergent adverse events (AEs) were defined as any AE occurring or increasing after the first treatment administration and before the last treatment was given. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 9.1. Patients were counted only once within the same body system.

Statistical Analyses

All analyses were prespecified and performed on intent-to-treat populations. Variables were described by mean and SD, median and range, and number and percentage. Tests were 2-sided and the level of significance (α) was set at .05. The Wilcoxon test was used for quantitative variables without normal distribution. The chi-squared and the Fisher exact tests were used for qualitative variables.

The main analysis was the comparison of diosmectite and placebo with regard to the primary outcome (72-hour cumulative stool output) adjusted to rotavirus status. It was analyzed using analysis of variance with 2 factors (treatment group and rotavirus status) for data of individual studies.[19] Interaction between 2 factors was kept in the model if the P value was .15

or less.[20] Diarrhea duration was described using the Kaplan–Meier survival curve and compared using the log-rank test.

We also analyzed the pooled individual data of these 2 studies, conducted simultaneously in Peru and Malaysia according to the same design, inclusion/exclusion criteria, methodology, and training of investigators and nurses, using analysis of variance with 3 factors (treatment, rotavirus status, and study).[19]

Statistical analyses were performed by CRC (Kuala Lumpur, Malaysia) for the Malaysia study, and by Fovea (Rueil-Malmaison, France) for the Peru study, under the supervision of Professor Nicholas Moore (INSERM U657 Bordeaux, France) and Elisabeth Leger-Picherit (Head of Biometry, Ipsen, Boulogne-Billancourt, France).

Results

Peru Study

Study populations. Three hundred patients were included in the intent-to-treat population (153 in the placebo group and 147 in the diosmectite group) between June 23, 2006, and February 1, 2007, in 11 primary care hospitals located in Lima (n = 9), Huacho (n = 1), and Ica (n = 1). Seventy-eight major deviations to the protocol were observed in 40 patients: 5 inclusion criteria were not respected, 39 patients were hospitalized for fewer than 70 hours, and 34 had treatment exposure for less than 48 hours. The per-protocol population was therefore 260 patients, 128 in the diosmectite group and 132 in the placebo group.

Children had a mean (±SD) age of 12.5 ± 6.1 months, a mean weight of 9.35 ± 1.67 kg, and a mean height of 75.3 ± 7.3 cm, with no difference between study groups. Mean (±SD) total amount of ORS intake during the hospitalization period was 1426 ± 983 mL. There was no significant difference between the diosmectite and placebo groups for rotavirus status or ORS use.

Efficacy. Mean (±SD) 72-hour cumulative stool output was lower in the diosmectite group (102.0 ± 65.5 g/kg) than in the placebo group (118.8 ± 92.5 g/kg) ($P = .032$) (Table 1). Diarrhea lasted significantly shorter with diosmectite (median, 68.17 h; 95% confidence interval [CI], 60.25–85.02 h) than with placebo (median, 118.92 h; 95% CI, 94.92–140.50 h) ($P < .001$). This result was found in both the rotavirus-negative and the rotavirus-positive children. In rotavirus-negative children, median diarrhea duration was 71.1 hours (95% CI, 60.3–108.8 h) with diosmectite versus 119.8 hours (95% CI, 102.4–148.8 h) with placebo ($P < .001$) (Figure 1). In rotavirus-positive children the median diarrhea duration was 66.8 hours (95% CI, 53.8–69.8 h) with diosmectite and 107.3 hours (95% CI, 69.5–146.3 h) with placebo ($P < .001$).

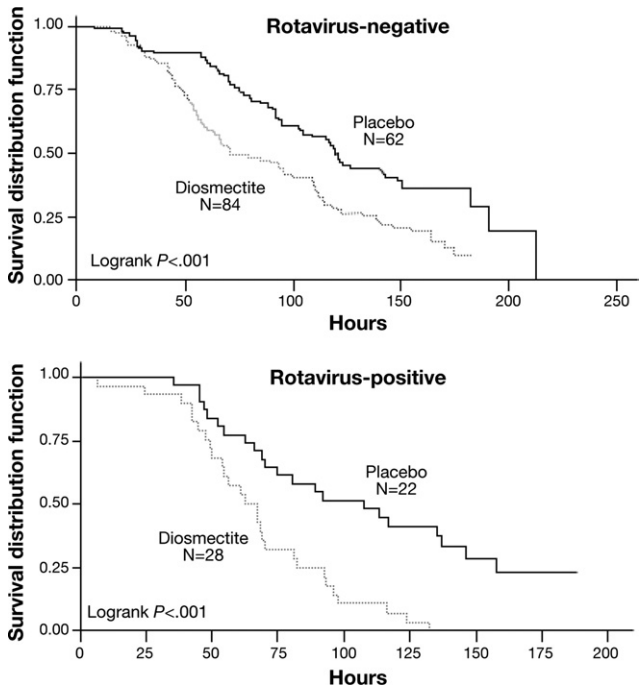

Figure 1. Diarrhea duration in the diosmectite and placebo patients in the Peru study according to rotavirus status, Kaplan–Meier survival curves are shown.

Secondary analyses of primary outcome showed that rotavirus-positive patients had a significantly higher cumulative stool output (169.2 ± 109.7 g/kg) than rotavirus-negative patients (93.9 ± 61.2 g/kg) ($P < .001$). Interaction between treatment efficacy and rotavirus status was at a P level of .132. In rotavirus-positive patients, the mean 72-hour stool output was lower with diosmectite (146.9 ± 90.1 g/kg) than with placebo (187.9 ± 122.1 g/kg) ($P = .039$). No significant difference was found in rotavirus-negative patients ($P = .488$).

Table 1. Seventy-Two–Hour Stool Output in the Diosmectite and Placebo Groups (g/kg)

	Diosmectite		Placebo		
	N	72-h stool output, g/kg	N	72-h stool output, g/kg	*P*
Peru study	126	102.0 ± 65.5	132	118.8 ± 92.5	.032
Rotavirus +	26	146.9 ± 90.1	31	187.9 ± 122.1	.039
Rotavirus −	100	90.3 ± 52.0	101	97.6 ± 69.3	.488
Malaysia study	142	87.9 ± 81.2	144	90.7 ± 94.0	.007
Rotavirus +	18	91.8 ± 103.0	16	184.5 ± 192.4	.002
Rotavirus −	124	87.4 ± 78.0	128	79.0 ± 65.9	.434
Pooled data	268	94.5 ± 74.4	276	104.1 ± 94.2	.002
Rotavirus +	44	124.3 ± 98.3	47	186.8 ± 147.2	<.001
Rotavirus −	224	88.7 ± 67.5	229	87.2 ± 67.9	.878

NOTE. Pooled data are presented as mean ± SD and according to rotavirus status from the results of the Peru and Malaysia studies.

Malaysia Study

Study populations. A total of 302 patients were included in the intent-to-treat population (150 in the placebo group and 152 in the diosmectite group) between July 11, 2006, and March 24, 2007, in 17 primary care hospitals located throughout Malaysia. Twenty-nine major deviations to the protocol were observed in 17 patients: 3 inclusion/exclusion criteria not respected, 13 patients hospitalized fewer than 70 hours, 11 had treatment exposure for less than 72 hours, 1 prohibited concomitant medication was used and 1 patient had gross blood in stools during the first 72 hours. The per-protocol population was therefore 285 patients, 140 in the diosmectite group and 145 in the placebo group.

Children had a mean (±SD) age of 15.9 ± 8.5 months, a mean weight of 9.02 ± 2.05 kg, and a mean height of 77.3 ± 8.7 cm, with no difference between study groups. Mean (±SD) total amount of ORS intake during the hospitalization period was 1022 ± 674 mL. There was no significant difference between the diosmectite and placebo groups for rotavirus status or ORS use.

Efficacy. The mean (±SD) 72-hour stool output was lower with diosmectite (87.9 ± 81.2 g/kg) than with placebo (90.7 ± 94.0 g/kg) ($P = .007$) (Table 1). Diarrhea lasted significantly shorter with diosmectite (median, 25.1 h; 95% CI, 20.50–29.00 h) than with placebo (median, 32.6; 95% CI, 27.5–39.3 h) ($P < .001$). In rotavirus-negative children, diarrhea lasted significantly shorter with diosmectite (median, 24.2 h; minimum–maximum, 0–129 h) than with placebo (median, 32.4 h; minimum–maximum, 0–152 h) ($P = .002$) (Figure 2). In rotavirus-positive children, the difference in diarrhea duration was not statistically significant between placebo (median, 31.6 h; minimum–maximum, 0–114 h) and diosmectite (median, 16.4 h; minimum–maximum, 0–76 h) ($P = .244$).

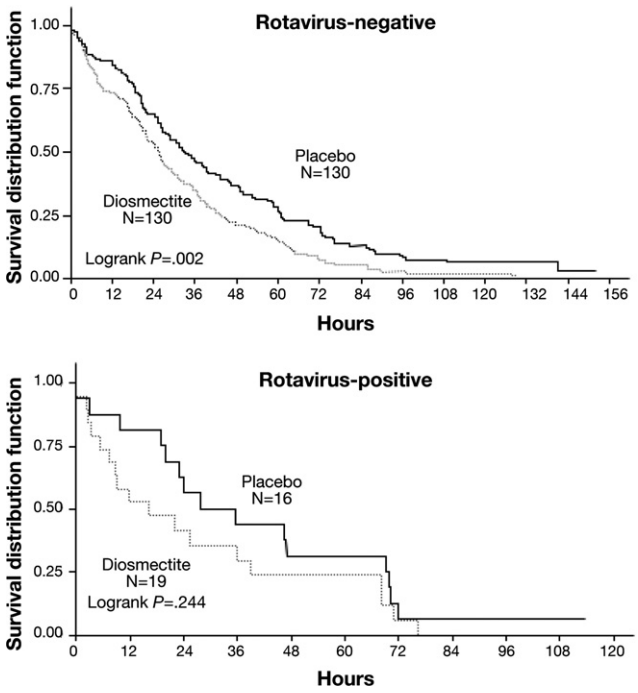

Figure 2. Diarrhea duration in the diosmectite and placebo patients in the Malaysia study according to rotavirus status, Kaplan–Meier survival curves are shown.

As for the Peru study, secondary analyses of primary outcome showed that cumulative stool output was significantly higher in rotavirus-positive patients (135.4 ± 156.5 g/kg) than in rotavirus-negative patients (83.1 ± 72.1 g/kg) ($P < .001$). A significant interaction between treatment efficacy and rotavirus status was found ($P = .001$). In rotavirus-positive patients, the mean 72-hour cumulative stool output was twice as low in the diosmectite group (91.8 ± 103.0 g/kg) than in the placebo group (184.5 ± 192.4 g/kg) ($P = .002$). No significant difference was found in rotavirus-negative patients ($P = .434$).

Pooled Efficacy Data

The mean (±SD) 72-hour stool output was lower with diosmectite (94.5 ± 74.4 g/kg) than with placebo (104.1 ± 94.2 g/kg) ($P = .002$). Adjusted means on unbalanced rotavirus factor (least-squares means ± standard error of the mean) were 105.5 ± 6.7 g/kg with diosmectite versus 134.8 ± 6.6 g/kg with placebo, a 30% reduction in 72-hour stool weight.

In secondary analyses, a significant rotavirus effect ($P < .001$) and a significant interaction between treatment and rotavirus status ($P = .001$) were found. A study effect was found ($P = .035$) but there was no interaction between treatment and study ($P = .724$). A significant treatment effect was found in rotavirus-positive patients ($P < .001$) but not in rotavirus-negative patients ($P = .878$). Rotavirus-positive diosmectite-treated patients had a lower mean (±SD) stool output (124.3 ± 98.3 g/kg) than rotavirus-positive placebo-treated patients (186.8 ± 147.2 g/kg).

Tolerability

In Peru, 185 AEs were reported, of which 145 were treatment-emergent AEs, 18 were serious (Table 2). In Malaysia, 135 AEs were reported, of which 110 were treatment-emergent AEs, and 20 were serious. Most frequent treatment-emergent AEs were fever and vomiting. No difference in frequency of AEs was observed between diosmectite and placebo.

Discussion

The present studies show that diosmectite, used as an adjunct therapy to the ORS currently recommended by the World Health Organization,[4] decreased 72-hour stool output in children, particularly if rotavirus-positive, and shortened the duration of acute watery diarrhea.

This study shows a significant effect of diosmectite on stool output, studied as a primary outcome, and diarrhea duration.[7,10–14,21] In a previous study, Madkour et al[13] showed that diosmectite shortens diarrhea duration in children and decreases the number of stools. Similar reductions in stool output in acute watery diarrhea were shown only for bismuth[17] and racecadotril.[18] Furthermore, the efficacy of diosmectite we showed on stool weight is supported by the fact that the placebo we have used has a lower osmolarity than diosmectite (46 vs 147 mOsm/L, respectively). The significant result found with diosmectite is therefore probably an underestimation of its real efficacy. It also is noteworthy that this effect of diosmectite was found despite decreased total stool output over the past decade, as illustrated by the lower stool output found in the present study compared with previous studies conducted under similar conditions, which strengthens our findings.[13,17,18] As shown by a Cochrane review by Hahn et al,[22] this may be the

Table 2. AEs Reported in the Peru and Malaysia Studies

	Diosmectite, n (no. of patients)	Placebo, n (no. of patients)	Either, n (no. of patients)
Peru study			
AEs	91 (70)	94 (67)	185 (137)
Treatment-emergent AEs	68 (55)	77 (56)	145 (111)
Fever	10 (10)	13 (13)	23 (23)
Vomiting	7 (7)	13 (13)	20 (20)
Pharyngitis/ nasopharyngitis	14 (14)	5 (5)	19 (19)
Diarrhea	2 (2)	7 (7)	9 (9)
Rhinitis	6 (6)	2 (2)	8 (8)
Others[a]	29	37	66
Serious treatment-emergent AEs[b]	6 (6)	12 (11)	18 (17)
Malaysia study			
AEs	61 (48)	74 (55)	135 (103)
Treatment-emergent AEs	51 (41)	59 (43)	110 (84)
Fever	11 (11)	12 (12)	23 (23)
Vomiting	4 (4)	6 (6)	10 (10)
Dermatitis contact	4 (4)	4 (4)	8 (8)
Rhinorrhea	1 (1)	4 (4)	5 (5)
Others[a]	31	33	64
Serious treatment-emergent AEs[b]	8 (8)	12 (11)	20 (19)

NOTE. Results are expressed as the number of events and the number of patients concerned. In case of multiple treatment-emergent AEs being reported for the same patient with the same wording, the strongest relationship to the compound, and the maximum severity were retained in statistical analyses.

[a]Each represented less than 2% of the patients. Anal discomfort, constipation, dehydration, rash, respiratory tract infections, and skin irritation were included.

[b]Serious treatment-emergent AEs were not considered treatment-related by investigators.

result of the use, since 2004, of an ORS of decreased osmolarity (245 vs 311 mOsm/L previously).

Diosmectite has been used for years in the treatment of acute watery diarrhea with an excellent safety record, further documented here. This positive safety profile could be owing to a therapeutic effect restricted to the luminal side of the intestine, thus avoiding any side effect related to interaction with gut motility, such as constipation, bacterial proliferation, and toxic megacolon.[23–25] Moreover, we found that diosmectite reduces diarrhea duration. This, in addition to the reduction of stool output volume, supports its use as an adjunct treatment to ORS.[21] Our data therefore suggest that diosmectite could be cost effective in the management of acute watery diarrhea. In children whose disease necessitates hospitalization, shortened diarrhea duration is beneficial for the social, professional, and financial situation of the parents,[23,24] especially in low-income countries where the high prevalence of acute diarrhea is not matched by adequate health insurance.

Many studies have focused only on the water-binding effect of clays and subsequent modification of stool form. However, if diosmectite were only binding water, it would have delayed recovery without altering stool volume. Therefore, the decreased stool weight and time to recovery we have found with diosmectite strongly supports the already demonstrated effect of diosmectite on other factors than water-binding and stool form. Diosmectite adsorbs bacteria, viruses, and bacterial toxins,[8,26–31] has a covering effect and interacts with intestine,[7] has a protective effect against intestinal inflammation induced by tumor necrosis factor-α,[9] and, as we have shown previously, diosmectite increases the absorptive capacity of the intestinal mucosa.[7]

In 1985, Edelman[32] stated the characteristics of the ideal antisecretory compound for the treatment of infectious diarrhea: inhibits fluid secretion or stimulates fluid absorption by intestinal mucosa, onset of action within minutes, limited constipating effects, high therapeutic index, noninterference with recovery of local bowel function, minimal central nervous system effects, low abuse potential, and low cost. These appear globally met by diosmectite, in terms of both efficacy and safety.

In the present study, diarrhea duration was shorter and stool output was lower in Malaysia than in Peru. Shorter diarrhea duration in Malaysia mostly is owing to different definitions between countries: time from the first sachet intake to the first formed stool for Peru, and time from the first sachet intake to the first soft or formed stool for Malaysia. Indeed, it was found during blind review that a very high proportion (40%) of the Malaysian children had no formed stool by the end of the study, which was not found in Peruvian children (0% without formed stool). To be in accordance with the specificities of this country, and before treatment allocation code was unblinded, the definition of diarrhea duration was modified in the Malaysia study, which gave a shorter mean diarrhea duration. Nevertheless, the fact that Malaysian children had fewer formed stools and lower stool output is interesting and several hypotheses may be raised to explain these findings. Because rotavirus infection increases stool output,[18,33,34] increased stool output may be related to the twice-higher incidence of rotavirus infection in Peruvian children (22%), as compared with Malaysian children (12%). A second explanation may be that stool consistency and stool weight may have been altered by a higher incidence of malnutrition in Malaysian children.[35] This is supported by their lower mean body weight as compared with Peruvian children (9.0 vs 9.4 kg), despite a higher mean age (15.9 vs 12.5 mo). Finally, this also may be related to social differences between these 2 countries (eg, alimentary habits, period of weaning), which may lead to differences in usual stool consistency in these children younger than 36 months of age, or to different estimations of what is a formed stool. However, additional epidemiologic data are required to explain this unexpectedly high proportion of children without formed stool in the Malaysia study.

Although they were not designed with this aim, the present studies showed that diosmectite was particularly efficient in rotavirus-positive children. This may be related to both the higher stool output in rotavirus-positive patients and pharmacological properties of diosmectite. Rotavirus increases the severity of diarrhea, especially with regard to stool output.[18,33,34] The increased efficacy of diosmectite in rotavirus patients could be related to the fact that a pharmacological effect is more likely shown when symptoms are more pronounced. On the other hand, rotavirus induces a secretory process at the enterocyte level that could be counteracted by diosmectite. A previous double-blind study of intestinal permeability in children with acute diarrhea showed that, in addition to the effects cited previously, diosmectite increases mannitol absorption, thus suggesting an increased absorptive capacity of the intestinal mucosa with diosmectite.[7] Nonetheless, the design of the

present studies does not allow us to do more than raise hypotheses about this particular efficacy of diosmectite in rotavirus-positive children. Specific pharmacological studies therefore should be conducted to deepen this very interesting and unexpected finding.

Nevertheless, although diosmectite appears more efficacious in rotavirus-positive children, many countries cannot afford systematic rotavirus testing. Because rotavirus-negative patients are no worse off when using diosmectite, and generally have less severe diarrhea than rotavirus-positive patients, there is in fact no disadvantage in using diosmectite in rotavirus-negative patients. On the contrary, our results show a clear disadvantage in not using diosmectite in rotavirus-positive children, which have more severe diarrhea and are at higher risk of complications. The public health point of view is therefore in favor of the use of diosmectite in the treatment of acute watery diarrhea in children.

In conclusion, because it decreases stool output and the duration of diarrhea, especially in cases associated with rotavirus, the virus that causes severe diarrhea, diosmectite could be recommended as an adjunct therapy to the currently recommended ORS[4] for the management of acute watery diarrhea in children.

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Reprint requests

Address requests for reprints to: Eduardo Salazar-Lindo, MD, DS Consult, Avenue El Polo 740, Office C-410, Surco, Lima 033, Peru. e-mail: esalazar@dsconsultsac.com; fax: (51) 1-435-6533.

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The Peru Diosmectite Study Group: Dante Figueroa Quintanilla, Pablo Huamaní Echeccaya: Instituto Especializado de Salud del Niño, Lima, Peru; Carlos Hurtado Rubio, Luis Chucas Asencio: Hospital San Juan de Lurigancho, Lima, Peru; Luis Alvarado Martinez: Hospital de Vitarte, Lima, Peru; Victoria Reto Valiente, Carlos Hironaka Ichiyanagui: Hospital Nacional Hipólito Unanue, Lima, Peru; Isabel Reyes Acosta, María Isabel Caciano Jares: Hospital Emergencias Pediátricas, Lima, Peru; Jessika Leon Arias, Christian Carnero Sanchez: Hospital Municipal Los Olivos, Lima, Peru; Hilda Vega Ponte, Soledad Garay Tegashira: Hospital de Huacho, Huacho, Peru; Carlos Huamani Ruiz: Hospital Nacional San Bartolomé, Lima, Peru; Juan Carlos Tirado: Clínica San Juan Bautista, Lima, Peru; Elsa Chea Woo, Aldo Maruy Saito: Hospital Nacional Cayetano Heredia, Lima, Peru; and Patricia Castillo Raez: Hospital de Ica, Ica, Peru.

The Malaysia Diosmectite Study Group: Jimmy Lee Kok Foo, Radhiah Binti Abu Bakar: Hospital Kuala Terengganu, Terengganu, Malaysia; Teh Keng Hwang, Leong Ming Chern: Alor Setar Hospital, Kedah, Malaysia; Yogeswary Sithamparanathan, N. Nachal: Tengku Ampuan Rahimah Hospital, Klang Selangor, Malaysia; Etherajan Theranirajan: Kluang Hospital, Johor, Malaysia; Soo Min Hong, Nor Mahani: Kajang Hospital, Selangor, Malaysia; Chan Lee Gaik, Hii King Ching: Sarawak General Hospital, Kuching, Malaysia; Aisyah Mohd Rivai: Kulim Hospital, Kedah, Malaysia; Nazrul Neezam: Hospital Sultan Haji Ahmad Shah, Temerloh, Pahang, Malaysia; Revathy Nallusamy, Jasvinder Kaur: Pulau Pinang Hospital, Pulau Pinang, Malaysia; Tan Kah Kee, Wilson Pau Shu Cheng: Seremban Hospital, Negeri Sembilan, Malaysia; Neoh Siew Hong, Saiful Rijal bin Muhamad: Taiping Hospital, Perak, Malaysia; Chin Choy Nyok, Selva Kumar: Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia; Norrashidah Hj Abdul Wahab, Faizah Mohamed Jamli: Hospital Serdang, Selangor, Malaysia; Kuan Geok Lan, Chin Fook Hin: Malacca Hospital, Malacca, Malaysia; Ng Su Yuen: Teluk Intan Hospital, Perak, Malaysia; Choo Choong Ming: Sungai Petani Hospital, Sungai Petani, Kedah, Malaysia; and Nga Shih Hang: Seri Manjung Hospital, Perak, Malaysia.

Conflicts of interest

Hélène Mathiex-Fortunet and Philippe Garnier are Ipsen employees.

Christophe Dupont, Jimmy Lee Kok Foo, Nicholas Moore, and Eduardo Salazar-Lindo have received honoraria and/or compensation in regards to the study, as an investigator, coordinator, or expert, in relation with the time spent on the study. The authors declare no conflict of interest in regards to the present article derived from the study, for which no compensation or stipend was received. There is no organic or regular relationship between the authors and Ipsen. The authors own no shares in Ipsen and no member of their immediate family is employed by Ipsen. Guillaume Hébert, from SC Partners, assisted in preparing the manuscript, according to a contract between Ipsen and SC Partners. The sponsor participated in study design, choice and set-up of centers, training for standardized stool collection, providing of materials (scales, diapers, World Health Organization oral rehydration solution), data monitoring, data collection, and preparation of the clinical study report.

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