

CONTROL STUDY OF ORAL REHYDRATION SOLUTION (ORS)/ ORS + DIOCTAHEDRAL SMECTITE IN HOSPITALIZED THAI INFANTS WITH ACUTE SECRETORY DIARRHEA

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Abstract. Dioctahedral smectite, a non systemic anti-diarrheal agent, is mucoprotective and absorbs enterotoxins and rotavirus as demonstrated in animal models. Smectite has been successfully used in various countries in children and adults with acute diarrhea. This study was to assess the efficiency of smectite associated with rehydration in infants with acute secretory diarrhea. Sixty-two hospitalized Thai infants, aged 1-24 months, with acute secretory diarrhea were randomly divided into 2 groups receiving (1) oral rehydration solution (ORS) (30 cases), (2) ORS and Smectite (3.6 g/day) (32 cases). Both groups were comparable for age, weight, nutritional status and duration of symptoms before treatment. All 62 infants received lactose free formula and chicken rice soup as the standard diet. Stool frequency, weight change and duration of diarrhea were recorded. The mean duration of diarrhea was 84.7 ± 48.5 hours in group 1, and 43.3 ± 25.1 hours in group 2 ($p = 0.005$). The number of infants with diarrhea was significantly lower in group 2 on Day 1 ($p < 0.01$) and Day 3 ($p = 0.001$); furthermore 27% of infants in group 1 and 3% in group 2 had still diarrhea on Day 5. The stool frequency and weight changes were not statistically different in the two groups. No major side effects were observed except two cases of vomiting and hardened stools. It is concluded that (1) Smectite shortens the course of acute secretory diarrhea in Thai infants; (2) smectite may reduce the occurrence of prolonged diarrhea; furthermore (3) in our study dioctahedral smectite was found to be safe in children aged 1 to 24 months.

INTRODUCTION

Acute diarrhea is still an important cause of morbidity and mortality in Southeast Asia. In Thailand, during 1988, National health statistics reported 715,467 diarrheal cases and 606 deaths. In Bangkok, the two main pathogens among children are rotavirus and enterotoxigenic *Escherichia coli* (Lexomboon *et al*, 1981). During the acute phase of diarrhea, several changes in the intestinal barrier are noted, such as the loss of mucus, decrease or disappearance of the glycocalyx and microvilli and complete destruction of the enterocytes and exposure of the chorion (Charritat, 1986). The

disappearance of defence barriers and the immaturity of enterocytes increase the duration of diarrhea and malnutrition (Rossi and Labenthal, 1984). The first step in the management of acute diarrhea is to prevent dehydration by oral rehydration therapy (Kasemsarn and Varavithya, 1980), in association with antibacterial treatment in specific cases (Lexomboon, 1990). Anti-diarrheal drugs are usually regarded as less important. Dioctahedral smectite (DS) is a non systemic aluminosilicate of phyllic structure which has been shown to interact with mucus glycoproteins (Allen and Leonard, 1985), and to increase the mucus gel, both quantitatively (Rateau and Parier, 1979) and qualitatively (Droix-Lefaix *et al*, 1985). Furthermore, it has been shown that DS binds pathogens responsible for diarrhea such as rotavirus (Droix-Lefaix *et al*, 1986), *E. coli* (Rateau *et al*, 1982), *Vibrio cholerae* (Fioramonti and Bueno, 1985), *Campylobacter jejuni* (Droy *et al*, 1985) and substances potentially aggressive during diarrhea such as bile salts (Nguyen-Phuoc and Vatier, 1984) and non digested sugars (Bueno and Fiora-

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monti, 1984). Double blind clinical trials in Europe (Lachaux *et al*, 1986) and Egypt (Madkour *et al*, 1991) showed that DS reduced the duration of symptoms by 30% compared to oral rehydration salts (ORS) alone.

This study was performed to assess the efficiency, acceptability, and the safety of DS associated with rehydration in hospitalized Thai infants with acute secretory diarrhea.

MATERIALS AND METHODS

Sixty-two Thai infants of both sexes, aged 1-24 months presenting with acute secretory diarrhea associated with mild or moderate dehydration, have been hospitalized in the Department of Pediatrics, Chulalongkorn Hospital (n = 36), or in the Pediatric Diarrheal Unit, Children's Hospital (n = 26), Bangkok, Thailand. Acute diarrhea was defined as 3 or more liquid stools per day, less than 3 days prior to admission.

Patients were randomly divided into two groups receiving : 1. Oral rehydration solution (ORS) alone (n = 30); 2. ORS and DS (n = 32).

The composition of the ORS (Pedialyte*, Abbott Laboratories was Na⁺, 45mmol/l; K⁺, 20mmol/l; Cl⁻, 35mmol/l; citrate, 30mmol/l; dextrose, 25g/l. calories 100/l).

Diocahedral smectite was supplied by Beaufour Ipsen International (c/o Pacific Healthcare, Bangkok, Thailand). DS was mixed in 30 ml of water and given orally; 1.5 g at the beginning of the rehydration and then after; 1.5 g/12 hours for children below 3 kg; 1.5 g/8 hours for children between 4 and 10 kg; 1.5 g/6 hours for children from 11 to 15 kg. The minimal treatment time with DS was 48 hours, and the maximal treatment time was 120 hours.

All 62 cases received lactose free formula or breast feeding and chicken rice soup as the standard diet.

Stool culture for enteropathogens and the latex agglutination test for rotavirus were performed in all patients.

The exclusion criteria were: infants who received medical treatment during the past two days, children below one month or above 24 months, severe

dehydration, a serious illness or a recognized chronic disease, third degree PEM malnutrition (classified by the Division of Nutrition, Department of Health, Ministry of Public Health, Bangkok, Thailand), diarrhea due to *V. cholerae*, or dysentery.

Patients were examined 24, 48, 72, 96 and 120 hours after admission. On this occasion, the following data were recorded and written: number of bowel motions during the last 24 hours, consistency of the stools, body weight (by weighing children on a scale sensitive to 10g), weight gain or loss compared with the previous examination; in case of normalization of the transit, duration of the diarrhea (from the first drug administration to the passage of the last liquid stool prior to a formed stool), ORS and plain water intake (in ml/kg of admission body weight) during the past 24 hours.

Statistical analytic methods

Patients maintained in the analysis : All patients were maintained in the analysis.

Estimation of missing data : Weight data missing after Day 0 were estimated from the value obtained at the preceding visit.

Statistical tests : Qualitative variables were compared by the X² test or using the exact Fisher test with 2 × 2 contingency tables when one of the theoretical populations was less than 5. Quantitative variables were compared by Student's *t* test (no significant difference in variance between the 2 groups pre-checked by Fisher's test). A difference was considered statistically significant for a p level less than 0.05.

Informed consents were obtained prior to the inclusion. This study was approved by the Ethical Committee for Human Research of the Chulalongkorn University Medical School.

Study population

Between the study and the control groups there were no statistical differences for age, weight, height, type of feeding, nutritional status, body temperature, degree of dehydration, vomiting and also the duration of diarrhea, stool frequency and

stool consistency (Tables 1 and 2). In the study group, the sex ratio (M/F) was significantly higher ($p = 0.02$).

Stool cultures grew only 6.67% and 9.37% in control and study group respectively while organisms were *Salmonella C* and *Aeromonas* spp. Rotavirus was identified in stools of 3.3% and 18.75% of control group and study group respectively. Also *Clostridium difficile* toxin could be assayed in 5.5% of each group.

RESULTS

The mean duration of diarrhea in the control group was 84.7 ± 48.5 hours (range 20 - 240 hours) compared with the study group $x = 43.3 \pm 25.1$ hours (22 - 120 hours) ($p = 0.001$). The normalization of stools was indicated in the Table 3.

The side-effects for DS were recorded as a refusal of drug in 2 cases by vomiting and resolving when changing the time of administration to before meals. Two cases of hardened stools were also observed but becoming soft 24 hours after the discontinuation of the drug.

DISCUSSION

In Southeast Asia, children below 5 have several episodes of acute diarrhea per year. In Thailand an attack rate from 1.5 to 5 bouts per child per year has been reported in children under 5 (Kasemsarn and Varavithya, 1980). In this study performed in hospitalized Thai infants, dioctahedral smectite in association with ORS significantly reduced the duration of acute diarrhea compared to ORS alone. That confirmed previous results reported by several investigators in diarrheal children (Lachaux *et al*, 1986; Madkour *et al*, 1991; Thzi-Lakhasi and Ben Allom, 1985). DS has been previously shown not to interfere with the intestinal absorption of ORS (Kheroua *et al*, 1987) which means that both therapies can be prescribed at the same time. More interestingly, DS can also decrease the percentage of children with persistent diarrhea, which may be particularly beneficial for prevention of chronic diarrhea. A similar outcome has been recently reported in another study in ambulatory management of Thai diarrheal children (Lexomboon *et al*, personal communication).

Table 1
Baseline data (1).

Parameter	Control (n = 30)	Study (n = 32)	p
Sex M : F	0.6 : 1	1.9 : 1	0.02
Age (months)	6.4 \pm 5.1	7.3 \pm 5.2	0.50
(80% age < 1 year)			
Weight (Kg)	6.0 \pm 2.7	6.5 \pm 2.1	0.37
Height (cm)	66.7 \pm 10.6	66.0 \pm 10.3	0.90
Feeding :			
Breast milk	5 (17%)	2 (6%)	
Breast + bottle	7 (24%)	9 (28%)	
Cow's milk	19 (66%)	23 (72%)	
Others	10 (34%)	43 (41%)	
Nutrition status :			
normal	25 (83%)	29 (91%)	
1° malnutrition	3 (10%)	2 (6%)	
2° malnutrition	2 (7%)	1 (3%)	

Table 2
Baseline data (2).

Parameter	Control (n = 30)	Study (n = 32)	p
Body temp (°C)	37.4 ± 0.4	37.5 ± 0.9	0.48
Dehydration			
No	2 (7%)	0	0.23
< 5%	16 (53%)	21 (66%)	
5-9%	12 (40%)	11 (34%)	
Vomiting			
No	13 (43%)	16 (50%)	0.60
Yes	17 (57%)	16 (50%)	
Duration of diarrhea (hours)	44.8 ± 20.5	44.0 ± 20.6	0.89
Frequency of stool/day	8.2 ± 3.3	9.0 ± 5.7	0.49
< 3	2 (7%)	2 (6%)	
3 - < 5	4 (14%)	7 (22%)	
> 5	23 (79%)	23 (72%)	
Stool consistency			
liquid	29 (97%)	28 (88%)	
mucus	4	5	

The improvement can be explained by the physical and pharmacological properties of smectite which acts both at the pre-enterocyte barrier and at the enterocyte barrier (Rateau and Paier, 1979; Droix-Lefaix *et al* 1985; Droix-Lefaix *et al*, 1986; Rateau *et al*, 1982; Fioramonti and Bueno, 1985; Droy *et al*, 1985; Nguyen-Phouc and Vatiar, 1984; Bueno and Fioramonti, 1984).

In our study cases due to invasive pathogens were excluded, but DS can also be used in association with antibiotic therapy in cases of invasive diarrhea, if the administration of both drugs is separated by 1 hour.

No problem of tolerance was noticed with DS, even in very young infants aged 1 month. Only a few cases of vomiting and constipation were reported. DS was associated with 4% side effects including refusal of treatment in 2%, in a large scale study involving 3,614 infants in France (Auger *et al*, 1981). This particular safety has to be emphasized while other antidiarrheal agents are potentially responsible for major side effects (Dupont and Hornick, 1973) such as paralytic

ileus (Murtaza, 1989) or deaths (Butta and Tahir, 1990).

In conclusion, dioctahedral smectite has been shown to shorten significantly acute secretory diarrhea in hospitalized Thai infants. It can also reduce the occurrence of persistent diarrhea; furthermore DS was safely used in children aged 1 to 24 months.

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Table 3

Results.

		Control n = 30	Study n = 32	p
Mean duration of diarrhea (hours)		84.7 ± 48.5	43.3 ± 25.1	p = 0.005
Stool's consistency				
Liquid	D1	66%	23%	p < 0.001
	D3	23%	18%	p = 1.00
Mucus	D1	3%	30%	p < 0.001
	D3	23%	18%	p = 1.00
Body weight (kg)	D1	6.2 ± 2.7	6.7 ± 2.1	
	D3	6.1 ± 2.7	6.7 ± 2.0	
Weight gain (g)	DO-D3	112 ± 212	176 ± 331	p = 0.36
Liquid intake (ml)	D1	390 ± 257	507 ± 330	p = 0.15
	D3	200 ± 223	120 ± 201	p = 0.17
Normalization of stools	D1	1 (3%)	10 (31%)	p < 0.01
	D3	17 (57%)	30 (94%)	p = 0.001
	D5	22 (73%)	31 (97%)	p = 0.01
Frequency of stool/day	DO-D1	7.5 ± 3.3	6.2 ± 3.4	p = NS
	D1-D2	5.9 ± 3.2	4.0 ± 3.2	p = NS
	D2-D3	4.5 ± 3.0	3.4 ± 3.7	p = NS

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