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GASTROENTEROLOGY

Efficacy of dioctahedral smectite in treating patients of diarrhea-predominant irritable bowel syndrome

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abdominal bloating, diosmectite, functional gastrointestinal disorder, irritable bowel syndrome, Rome criteria.

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Abstract

Background and Aim: Dioctahedral smectite (DS) is natural adsorbent clay useful in treating acute diarrhea. The aim of this study was to determine DS efficacy on patients with diarrhea-predominant irritable bowel syndrome (D-IBS in a phase III-, 8-week-randomized, double-blind, placebo-controlled trial.

Methods: The 104 patients who met the D-IBS Rome II criteria were randomized to receive either DS ($n = 52$) or placebo ($n = 52$) treatment for 8 weeks (three sachets daily). The primary efficacy endpoint was the changes of the visual analog scale (VAS) score of IBS overall disorder and pain/discomfort-related symptoms after treatment on days 28 and 56, respectively. Other outcome measures included improvement of bowel movement disorders. The therapeutic global response was assessed by the patients and investigators at each visit, as was drug safety.

Results: Both treatments diminished overall disorder at each visit ($P < 0.01$), with respect to primary efficacy. This effect was further observed in DS-treated patients on day 56 ($P = 0.0167$). Placebo had no effect on the VAS score of pain/discomfort at any visit, whereas DS improved this score on days 28 and 56, respectively ($P < 0.05$). DS and placebo similarly diminished bowel disorders at each visit; however, only DS improved abdominal bloating ($P < 0.01$). The global therapeutic responses evaluated by the patients and investigators were similarly distributed. The study drug was well tolerated during the 8-week period.

Conclusion: DS seems acceptable to treat D-IBS patients, particularly for pain-related symptoms.

Introduction

Irritable bowel syndrome (IBS) is part of the larger group of 'functional gastrointestinal disorders' that share common features in terms of motor, sensory and psychosocial dysfunctions, central nervous system relationships, and approaches to patient care.[1,2] Reported IBS prevalences usually occur in approximately 10–20% of the adult population worldwide. IBS impairs the quality of life of sufferers, leading to excessive physician visits and abseentism (from work or school).[3–8] Until now, IBS diagnosis has been based on the recommended criteria. At least four well-known diagnostic criteria in terms of Manning,[9] Rome I,[2] Rome II,[2] and Rome III[2,3] have been recommended. IBS pathophysiology is still being debated. Current hypotheses include gastrointestinal (GI) tract dysmotility,[10] altered visceral or central sensitivity,[3,4,11] disordered autonomic functions,[12,13] release of inflammatory mediators,[3,14,15] and psychosocial disturbances.[2,3,5,16,17] Therefore, no unique treatment is always useful based on these diverse mechanisms. For example, the various modalities that have been the options for treating IBS ranged from reassurance, education, to newly-developed receptor agonists or antagonists.[1,3,4,18–21] Basically, treatment is usually tailored to the main IBS symptoms, such as diarrhea, constipation, and pain.[1,3,7] Apart from regular medication, there is now a trend to use either herbal drugs or probiotics to treat IBS.[22–24]

Dioctahedral smectite (DS), the natural adsorbent clay formed of fine sheets of aluminomagnesium silicate, is efficient in attenuating the severity of acute diarrhea in children.[25] Interestingly, an early report indicated its efficacy on patients with chronic colonopathies.[26] As an efficient and safe drug for the treatment of acute diarrhea,[27,28] we were interested in whether DS could offer efficacy for diarrhea-predominant IBS (D-IBS) patients diagnosed based on the Rome criteria. This phase III, randomized, double-blind, placebo-controlled clinical study attempted to determine whether the use of DS had any beneficial effects on D-IBS patients.

Methods

Patients

This study was conducted between August 2000 and July 2001 as a single-center trial. Inclusion criteria were as follows: patients of

both sexes, aged between 20 and 80 years, presenting typical D-IBS symptoms, and having met the Rome II criteria for a minimum of 1 year. Exclusion criteria were pregnancy or lactation, surgery on GI tract except appendectomy, malabsorption diseases, hyperthyroidism, inflammatory bowel diseases, connective tissue diseases, severely progressive diseases, diabetes, psychiatric disorders, substance abuse, milk intolerance, use of drugs known to influence GI motility and alert symptoms for IBS diagnosis, such body weight loss, fever, and bloody stools. In addition, patients aged ≥40 should not have had a colon organic disease (except diverticulosis) via colonoscopic or radiological examination since the onset of their IBS symptoms.

Drug trial

The D-IBS patients who met the entry criteria were randomly assigned to 8 weeks (56 days) of three daily treatments with either DS or placebo taken orally 30 min before each meal. The randomization schedule was constructed by a computer-generated random code system. The medication was packed in sachets which contained either 3 g of DS (3 g diosmectite, 0.75 g monohydrated glucose, 0.007 g saccharin sodium, and 0.004 g vanilla) or 3 g of placebo (0.8 g hydrated glucose, 1.1 g corn starch, 0.008 g saccharin sodium, 0.192 g talcum power, 1.11 g maltose dextrins, 0.006 g caramel coloring [E150], and 0.004 g vanilla). Both the DS and placebo sachets were identical in appearance and supplied by Beaufour Ipsen (Paris, France). All of the patients were instructed to immediately drink a well-stirred suspension containing a sufficient amount of water. Initially, they were given the study drug for a total of 4 weeks, a diary card, and rescue agent. At the end of the 4-week period, the patients returned to the study office and any unused drugs and rescue agents were returned. They were given a similar study drug for another 4 weeks, and rescue agents were dispensed again. The study was conducted as monotherapy. If the presenting diarrhea was too severe, loperamide could be used as the rescue agent.

Efficacy evaluation

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (Taiwan), and informed consent was obtained in all cases prior to the study. One hundred and four D-IBS patients were enrolled based on the above criteria. They were assessed at baseline (day 0), the 4th week (day 28), and the 8th week (day 56) of treatment, respectively. Data on IBS symptoms, treatment response, and side-effects were recorded. The patients themselves evaluated their overall IBS disorder using the visual analog scale (VAS) on a scale of 0–10 (absence to intolerance). In addition, the abdominal pain/discomfort intensity was recorded at each visit using a horizontal 100-mm VAS ranging from 0 = no pain to 100 = maximal pain. Bowel movement disorders were measured by the number of stools passed during the 72 h prior to the visit, stool consistency (assessed on a scale of four, where 1 = hard, 2 = moderately hard, 3 = soft, and 4 = watery) and the absence/presence of mucus. The study patients and investigators also evaluated the therapeutic global response. The ranking of this response was determined by five categories: much improved, all symptoms subsided; improved, definitely well improved, but not eliminated; no change, remained similar; worse, bad compared to before treatment; and much worse, very severe compared to before treatment.

The primary efficacy endpoint was the changes of VAS score of IBS overall disorder and pain/discomfort-related symptoms after treatment at each visit. Other secondary outcome measures included changes in bowel movement disorders and bloating. The therapeutic global response was assessed by the patients and investigators, respectively, at each visit, as was drug safety.

Statistics

All values were expressed as mean and 95% confidence interval unless otherwise specified. Fisher's exact test, χ^2-test, ANOVA, and ANCOVA were used for the comparisons, and all tests were two-sided. The hypothesis was conducted at the 5% level of significance, thus a *P*-value less than 0.05 was considered significant.

Results

Population description

Overall, 104 patients (52 in each group, respectively) were eligibly enrolled in the study. Three patients (two in the DS group and one in the placebo group) withdrew their informed consent early, without administration of any study medication. Accordingly, 77 patients (37 in the group DS and 40 in the placebo group) finished the trial at week 8, while 86 patients (41 in the DS group and 45 in the placebo group) provided available efficacy data (Fig. 1). The reasons for early termination in the DS group were noncompliance of patient (one patient), patient's own decision to withdraw (seven patients), and side-effects related to the study (seven patients); whereas those in the placebo group were patient's own decision to withdraw (seven patients), treatment failure (one patient), and side-effects related to treatment (four patients; NS). Table 1 illustrates the demographic and clinical characteristics of patients divided into the two groups. There was no difference between the two groups, except that abdominal bloating was commonly presented among DS patients ($P < 0.01$). The total sachets used in the DS and placebo groups were 140.3 (126.7, 153.9) and 141.4 (128.9, 153.8), respectively, with a difference of −1.1 (−19.2, 17.0, NS). The total days of rescue agent consumption in the DS and placebo groups were 3.1 (1.3, 4.9) and 4.9 (1.6, 8.2), respectively, with a −1.8 (−5.6, 2.1, NS) group difference.

Efficacy results

Figure 2 illustrates the patients' self-evaluation of their IBS overall disorder throughout the whole study based on the VAS, with regards to the primary efficacy endpoint. Compared to the baseline, both treatments diminished the IBS overall disorder at each visit ($P < 0.01$). The diminished scores of DS and placebo treatment on day 28 were −1.92 (−2.6, −1.24) and −1.13 (−1.78, −0.48), respectively, with group difference at −0.79 (−0.17, 0.015) showing no difference between the group ($P = 0.0973$), whereas these scores on day 56 were −2.57 (3.27, 1.88) and −1.38 (−2.05, −0.071), respectively, with group difference at −1.19 (−2.16, −0.022) showing significant difference between the groups

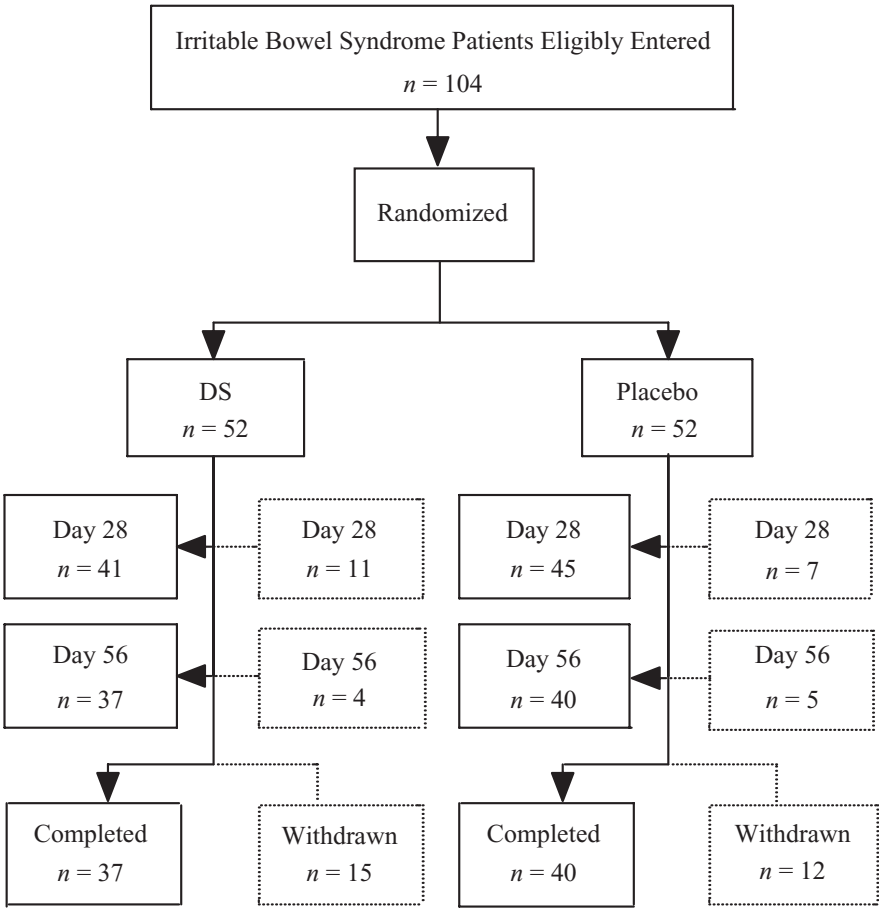

Figure 1 Flow chart showing trial overview among the 104 eligibly-enrolled, diarrhea-predominant irritable bowel syndrome patients. Dotted boxes represent number of patients lost on follow up.

Table 1 Demographic and clinical characteristics of diarrhea-predominant irritable bowel syndrome (IBS) patients

	DS ($n = 41$)	Placebo ($n = 45$)	*P*-value
Male (%)	23 (62.8)	31 (68.9)	0.267
Age (year)	53.8 (48.6, 59.0)	54.0 (49.0, 58.9)	0.969
Body weight; mean (kg)	63.1 (59.5, 66.6)	62.7 (59.3, 66.0)	0.872
Body height; mean (cm)	163.2 (160.6, 165.8)	165.6 (163.2, 168.1)	0.174
Duration of IBS (months)	88.6 (61.6, 115.5)	73.4 (47.6, 99.1)	0.419
Global IBS disorder, self evaluation (VAS, 0–10) Mean ± SE	4.19 ± 0.49	4.25 ± 0.47	0.912
Abdominal pain/discomfort (VAS, 0–100)	16.4 (9.2, 23.6)	17.2 (10.3, 24.0)	0.882
Abdominal bloating (%)	36 (87.8)	27 (60.0)	0.0065
Bowel movement disturbances			
No. in the last 3 days	7.7 (6.3, 9.0)	8.7 (7.4, 10.0)	0.272
Urgency (%)	34 (82.9)	38 (84.4)	1.0
Incomplete defecation (%)	35 (85.4)	35 (77.8)	0.416
Watery stool (%)	11 (26.8)	9 (20)	0.592
Mucus in stool (%)	17 (41.5)	14 (31.1)	0.372

Only patients finished 4-week trial with available efficacy data were compared; Results are mean and 95% confidence interval unless specified; VAS, visual analog scale; DS, Dioctahedral smectite.

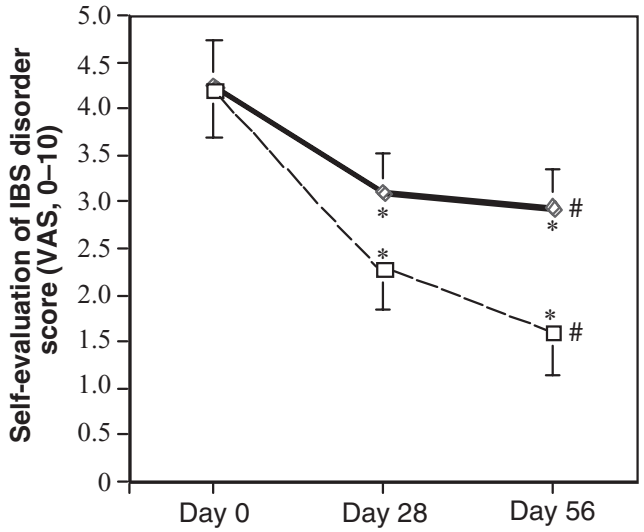

Figure 2 Primary efficacy endpoint showing change of patients' self-scored irritable bowel syndrome (IBS) overall disorder based on the visual analog scale (VAS, 0–10) at each visit. Vertical bars are mean ± SE. *, significant change from baseline, $P < 0.01$; #, group difference within the same visit, $P < 0.05$. (–□–), Dioctahedral smectite; (—◇—), Placebo.

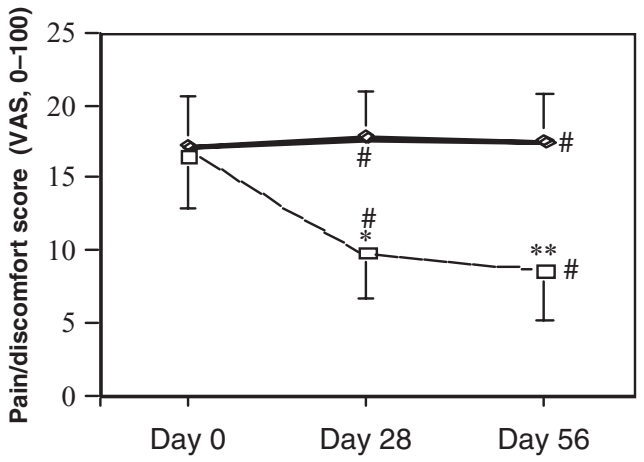

Figure 3 Change of pain/discomfort-related symptoms in study patients based on the visual analog scale (VAS, 0–100) at each visit. Vertical bars are mean ± SE. *, significant change from baseline, $P < 0.05$; **, significant change from baseline, $P < 0.01$; #, group difference within the same visit, $P < 0.05$. (–□–), Dioctahedral smectite; (—◇—), Placebo.

($P = 0.0167$). The change of the VAS score of abdominal pain/discomfort-related symptoms after treatment is illustrated in Figure 3. Placebo had no effect on the VAS score of present pain/discomfort at any visit, whereas DS obviously improved the scores (diminished pain/discomfort) on day 28 (−6.72 [−12.0, −1.41] versus 0.82 [−4.24, 5.88], with group difference at −7.54 [−14.87, 0.20], $P < 0.05$) and day 56 (−8.67 [−14.45, −2.89] versus −0.28 [−5.84, 5.28], with group difference at −8.39 [−16.42, −0.37], $P < 0.05$), respectively.

The analytic results of bowel movement disorder are presented in Table 2. Both DS and placebo treatment effectively diminished bowel movement frequency at each visit ($P < 0.001$). However, group differences were not found. Abdominal bloating was only improved by DS at each visit ($P < 0.01$). Other symptoms of urgency, incomplete defecation, and watery stools were markedly improved by both treatments at each visit, while their group differences were not significant. Improvement of mucus in stools was markedly increased after DS treatment, whereas this improvement was only found on day 28 in patients receiving placebo treatment ($P < 0.05$); the group difference remained insignificant.

Both patients and investigators revealed a greater number of DS- or placebo-related therapeutic global response (improved plus much improved) at each visit with insignificant differences (Table 3).

Safety results

The 101 patients who consumed at least one sachet of the study drug were included in the safety population. Neither serious drug-related adverse effects nor death were reported. However, three patients were hospitalized during the trial (two in the placebo group because of cellulitis and acute appendicitis; one in the DS group because of renal stone). Constipation was the most common effect related to DS treatment, but its occurrence was not different from placebo (Table 4). Other recorded effects, including nausea, abdominal pain, and dyspepsia were similar in both groups.

Discussion

The treatment of IBS is complex because the patient population is usually heterogeneous.[1] Until now, no single drug has been very effective in treating all IBS symptoms.[29] All our study patients met the symptom-based criteria for IBS diagnosis, particularly confined to diarrhea-predominant, as shown in Table 1.[1] Our results mainly indicated that DS appeared to be better than placebo in improving IBS overall disorder as well as abdominal pain/discomfort intensity after the 8-week treatment.

It has been recommended that the pharmacotherapy of IBS should be directed at a specific symptom with the rationale being either to modulate motility, sensitivity, or to treat associated psychiatric disorders.[1,3,30] In fact, abdominal pain/discomfort, the main IBS symptom defined by Rome criteria, is one of the most difficult symptoms to treat among IBS patients.[1] Jailwala *et al.*[31] pointed out that only smooth muscle relaxants could offer strong evidence to relieve predominantly painful IBS symptoms. Clinically, the description of pain in IBS patients has always been very subjective. This means that pain perception varies from individual to individual, while emotion, memory, culture, and psychosocial situation additionally modulates its perception, grading, and understanding.[32] Thus, the definition of pain may be markedly discrepant among the study designs. We attempted to evaluate this main IBS symptom subjectively with the patients themselves. On each visit, we found that DS treatment had better efficacy in the VAS score of pain index compared to placebo. This result most likely accounted for the superior efficacy of DS in relieving overall IBS disorder on day 58. Our study of better primary endpoint efficacy in reducing overall disorders as well as the pain intensity

Table 2 Therapeutic changes of bowel movement disorders in diarrhea predominant irritable bowel syndrome (IBS) patients at each visit

Category	DS	Placebo	Group difference	*P*-value
No. of stool during the last 3 days				
D 0	7.66 (6.29, 9.03)	8.71 (7.4, 10.02)		0.272
D 28	5.54 (4.67, 6.41)**	5.73 (4.9, 6.56)**		0.746
Change from baseline	–2.50 (–3.27, –1.73)	–2.63 (–3.36, –1.89)	0.13 (–0.94, 1.19)	0.816
D 56	5.59 (4.66, 6.53)**	5.10 (4.2, 6.0)**		0.45
Change from baseline	–2.35 (–3.2, –1.51)	–3.32 (–4.13, –2.51)	0.97 (–0.21, 2.15)	0.105
Abdominal bloating (%)				
D 0	36 (87.8)	27 (60.0)		0.0065
D 28	19 (46.3)**	26 (57.8)	–11.4% (–32.4, 9.6)	0.388
D 56	16 (43.2)**	10 (50.0)	–6.8% (–29.0, 15.5)	0.649
Urgency (%)				
D 0	34 (82.9)	38 (84.4)		1.000
D 28	22 (53.7)**	26 (57.8)**	–4.1% (–25.1, 16.9)	0.828
D 56	12 (32.4)**	21 (52.5)**	–20.1% (–41.7, 1.5)	0.107
Incomplete defecation (%)				
D 0	35 (85.4)	35 (77.8)		0.416
D 28	24 (58.5)**	20 (44.4)**	14.1% (–6.8, 35.0)	0.204
D 56	14 (37.8)**	22 (55.0)**	–17.2% (–39.1, 4.8)	0.172
Watery stool consistency (%)				
D 0	11 (26.8)	9 (20.0)		0.592
D 28	1 (2.4)**	1 (2.2)**	0.2% (–6.2, 6.6)	0.519
D 56	0 (0)**	1 (2.5)**	–2.5% (–7.3, 2.3)	0.36
Mucus in stool (%)				
D 0	17 (41.5)	14 (31.1)		0.372
D 28	10 (24.4)*	6 (13.3)*	11.1% (–5.4, 27.5)	0.268
D 56	9 (24.3)*	9 (22.5)	1.8% (–17.1, 20.8)	1.0

Data in parenthesis of group difference are 95% confidence interval; DS: Dioctahedral smectite; Numbers of IBS patients in DS and placebo on day 28 (D 28) were 41 and 45, on D 56 were 37 and 40, respectively; *: compared to D 0 within category, $P < 0.05$; **: compared to D 0 within category, $P < 0.01$.

may confirm that IBS disorder is mainly painful or discomforting in nature as defined by Rome criteria.[1,7]

Unlike 5-hydroxytryptamine receptor agonists or antagonists,[33] DS does not directly modulate the visceral sensory or motor pathway. It is of interest as to why DS can reduce the pain index among our IBS patients. DS is a non-systemic specific aluminomagnesium silicate with cytoprotective actions on gastrointestinal mucosa. Preliminary study data obtained from rat digestive tracts suggest that the content of mucus-producing cells could be affected by DS, even following short-term treatment.[34–36] This natural clay appears to enhance the intestinal barrier function leading to the prevention of mucosal damage.[37] An *in vitro* study also indicated that the apical effect of DS counteracts the disruption of the intestinal barrier induced by the release of pro-inflammatory cytokines, including tumor necrosis factor-α.[38] Based on the well-known observations of increased pro-inflammatory cytokines in D-IBS patients,[15,39,40] we are uncertain as to whether the reported preliminary *in vitro* data of protective mechanisms of this drug in the gut is likely to improve abdominal pain/discomfort among the D-IBS patients. Such results in favor of DS have been indicated by Opriu *et al*.[41] in IBS patients with accelerated bowel transit. Interestingly, beidellitic montmorillonite, another coating clay with the ability to adsorb gas, is only efficient in treating patients of constipation-predominant IBS rather than other subtypes. Its therapeutic mechanism is suggested to be due to the covering property leading to the modification of the sensory inputs elicited by luminal chemical changes.[42] Accordingly, this kind of putative mechanism owned by natural clays to treat IBS requires crucial future studies to confirm it.

Our results showed that apparent DS efficacy in treating abdominal bloating was most likely due to the higher occurrence of this symptom in the DS group, with regards to secondary outcome measures. Similarly in a double-blind, placebo-controlled study conducted on 350 patients with functional bowel disorders corresponding to the Manning criteria, Dapoigny *et al*.[43] illustrated that DS was an efficacious alternative to restrictive dietary advice for visible abdominal swelling or bloating. DS is initially indicated in treating acute diarrhea in adults[27,28,44,45] as well as children.[25] In addition, DS has been used with success as a symptomatic treatment for adults suffering from colonopathies with accelerated transit.[26] Unfortunately, the lack of difference between the two study medications (DS *vs* placebo) in the action on most bowel movement disorders at the end of the trial was found in our study. It is still unclear whether this absent efficacy was due to a type II error of the small analyzed sample size.[29,46] Alternatively, our result of no DS efficacy in reducing most bowel disorders in D-IBS patients suggests that these disorders are pathophysiologically different from that of acute diarrhea. Finally, the adverse events of DS were not apparent and its safety was acceptable by our study patients. In conclusion, DS seems acceptable in

Table 3 The therapeutic global response of trial efficacy on diarrhea predominant irritable bowel syndrome patients

	DS	Placebo	*P*-value
Subjective assessment by the patients on day 28 (%)			
	(*n* = 41)	(*n* = 45)	
Much worse	0 (0)	0 (0)	
Worse	1 (2.4)	0 (0)	
Unchanged	7 (17.1)	12 (26.7)	0.29
Improved	24 (58.5)	28 (62.2)	
Much improved	9 (22)	5 (11.1)	
Subjective assessment by the patients on day 56 (%)			
	(*n* = 37)	(*n* = 40)	
Much worse	0 (0)	1 (2.5)	
Worse	0 (0)	0 (0)	
Unchanged	6 (16.2)	5 (12.5)	0.97
Improved	22 (59.5)	25 (62.5)	
Much improved	9 (24.3)	9 (22.5)	
Objective assessment by the investigators on day 28 (%)			
	(*n* = 41)	(*n* = 45)	
Much worse	0 (0)	0 (0)	
Worse	3 (7.3)	2 (4.4)	
Unchanged	5 (12.2)	11 (24.4)	0.49
Improved	25 (61.0)	26 (57.8)	
Much improved	8 (19.5)	6 (13.3)	
Objective assessment by the investigators on day 56 (%)			
	(*n* = 37)	(*n* = 40)	
Much worse	0 (0)	0 (0)	
Worse	1 (2.7)	1 (2.5)	
Unchanged	5 (13.5)	8 (20.0)	0.87
Improved	22 (59.5)	21 (52.5)	
Much improved	9 (24.3)	10 (25.0)	

DS, Dioctahedral smectite. Data in parentheses are percentages.

Table 4 Adverse events of diarrhea-predominant irritable bowel syndrome patients undergoing dioctahedral smectite (DS) or placebo treatment

Events	DS (*n* = 50)	Placebo (*n* = 51)	*P*-value
Constipation (%)	5 (10)	2 (4)	0.269
Nausea (%)	4 (8)	2 (4)	0.436
Abdominal pain (%)	2 (4)	4 (8)	0.678
Dyspepsia (%)	2 (4)	0 (0)	0.243
Vomiting (%)	2 (4)	0 (0)	0.243
Dizziness (%)	1 (2)	1 (2)	1.0
Headache (%)	1 (2)	1 (2)	1.0
Malaise (%)	1 (2)	0 (0)	0.495
Insomnia (%)	1 (2)	0 (0)	0.495
Menstrual disorder (%)	1 (2)	0 (0)	0.495
Skin itching (%)	0 (0)	1 (2)	0.495

*Any patient administered the study drug was included in the safety analysis.

treating D-IBS patients, particularly in pain/discomfort-related disorders, whereas its efficacy in reducing bowel movement disorders is limited.

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References

1 Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002; **123**: 2108–31.
2 Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006; **130**: 1337–90.
3 Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480–91.
4 Lacy BE, Lee RD. Irritable bowel syndrome: a syndrome in evolution. *J. Clin. Gastrotenterol.* 2005; **39**: S230–42.
5 Xiong LS, Chen MH, Chen HX, Xu AG, Wang WA, Hu PJ. A population-based epidemiologic study of irritable bowel syndrome in South China: stratified randomized study by cluster sampling. *Aliment. Pharmacol. Ther.* 2004; **190**: 1217–14.
6 Chang FY, Lu CL. Irritable bowel syndrome in the 21st century: perspectives from Asia or Southeast Asia. *J. Gastroenterol. Hepatol* 2007; **22**: 4–12.
7 Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002; **360**: 555–64.
8 Lu CL, Chen CY, Lang HC *et al.* Current patterns of irritable bowel syndrome in Taiwan: the Rome II questionnaire on a Chinese population. *Aliment. Pharmachol. Ther.* 2003; **18**: 1159–69.
9 Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *Br. Med. J.* 1978; **2**: 653–4.
10 Lu CL, Chen CY, Chang FY, Lee SD. The characteristics of small bowel motility in irritable bowel syndrome patients and normal humans: an Oriental study. *Clin. Sci.* 1998; **95**: 165–9.
11 Sinhamahapatra P, Saha SP, Chowdhury A, Chakrabarti SK, Ghosh A, Maiti B. Visceral afferent hypersensitivity in irritable bowel syndrome-evaluation by cerebral evoked potential after rectal stimulation. *Am. J. Gastroenterol.* 2001; **96**: 2150–7.
12 Gupta V, Sheffield D, Verne GN. Evidence for autonomic dysregulation in the irritable bowel syndrome. *Dig. Dis. Sci.* 2002; **47**: 1716–22.
13 Lee CT, Chuang TY, Lu CL, Chen CY, Chang FY, Lee SD. Abnormal vagal cholinergic function and psychological behaviors in irritable bowel syndrome patients with predominant bowel symptoms: a hospital-based Oriental Study. *Dig. Dis. Sci.* 1998; **43**: 1794–9.
14 Wang LH, Fang XC, Pan GZ. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. *Gut* 2004; **53**: 1096–101.
15 Gwee KA, Collins SM, Read NW *et al.* Increased rectal mucosal expression of interleukin 1β in recently acquired pot-infectious irritable bowel syndrome. *Gut* 2003; **52**: 523–6.
16 Gwee KA, Leong YL, Graham C *et al.* The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999; **44**: 400–6.
17 Camilleri M, Heading RC, Thompson WG. Consensus report: clinical perspectives, mechanisms, diagnosis and management of irritable bowel syndrome. *Aliment. Pharmacol. Ther.* 2002; **16**: 1407–30.
18 Akehurst R, Kaltenthaler E. Treatment of irritable bowel syndrome: a review of randomised controlled trials. *Gut* 2001; **48**: 272–82.
19 Drossman DA. What dose the future hold for irritable bowel

syndrome and the functional gastrointestinal disorders? *J. Clin. Gastroenterol.* 2005; **39**: S251–6.
20 Lembo TJ, Fink RN. Clinical assessment of irritable bowel syndrome. *J. Clin. Gastroenterol.* 2002; **35**: S31–6.
21 Bueno L. Gastrointestinal pharmacology: irritable bowel syndrome. *Curr. Opin. Pharmacol.* 2005; **5**: 583–8.
22 Bensoussan A, Talley NJ, Hing M, Menzies R, Guo A, Ngu M. Treatment of irritable bowel syndrome with Chinese herbal medicine. *JAMA* 1998; **280**: 1585–9.
23 Bensoussan A. Establishing evidence for Chinese medicine: a case example of irritable bowel syndrome. *Chin. Med. J. (Taipei)* 2001; **64**: 487–92.
24 Floch MH. Use of diet and probiotic therapy in the irritable bowel syndrome, analysis of the literature. *J. Clin. Gastroenterol.* 2005; **39**: S243–6.
25 Madkour AA, Madina EM, El-Azouni OE, Amer MA, El-Walili TM, Abbass T. Smectite in acute diarrhea in children: a double-blind placebo-controlled trial. *J. Paediatr. Gastroenterol. Nutr.* 1993; **17**: 176–81.
26 Legré M, Andreotti D. Double-blind comparative study on dioctahedral smectite and actapulgite in treatment of colonopathies. *Gaz. Med. Fr.* 1980; **87**: 1–3.
27 Leber W. A new suspension form of smectite (liquid diasorb) for the treatment of acute diarrhea: a randomized comparative study. *Pharmatherapeutica* 1988; **5**: 256–60.
28 Van Maercke Y, Mallend M. Clinical trial to compare the efficacy and tolerance of Smecta (intestinal topic consisting of dioctahedral smectite) and loperamide in the treatment of acute diarrhea in adults. *TIJDSCHR Gastroenterology* 1987; **17**: 367–9.
29 Klein KB. Controlled treatment trials in the irritable bowel syndrome: a critique. *Gastroenterology* 1988; **95**: 232–41.
30 Pattee PL, Thompson WG. Drug treatment of the irritable bowel syndrome. *Drugs* 1992; **44**: 200–6.
31 Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann. Intern. Med.* 2000; **133**: 136–47.
32 Chang L, Toner BB, Fukudo S *et al.* Gender, age, society, culture, and the patient's perspective in the functional gastrointestinal disorders. *Gastroenterology* 2006; **130**: 1435–46.
33 Galligan JJ, Vanner S. Basic and clinical pharmacology of new motility promoting agents. *Neurogastroenterol. Motil.* 2005; **17**: 643–53.
34 Droy-Lefaix MT, Drouet Y, Schatz B. Sodium glycodeoxycholate and spinability of gastrointestinal mucus. protective effect of smectite. *Gastroenterology* 1985; **88**: 1369A.
35 Droy-Lefaix MT, Drouet Y, Geraud G. Protective effect of smectite on gastrointestinal biliary salts rat damage. *Gastronterol. Int.* 1988; **1** (Suppl. 1): 1076.
36 Moré J, Bénazet J, Fioramonti J, Droy-Lefaix MT. Effects of treatment with smectite on gastric and intestinal glycoproteins in the rat: a histochemical study. *Histochem. J.* 1987; **19**: 665–70.
37 Leonard AJ, Droy-Lefaix MT, Allen A. Pepsin damage in rat stomach in vivo: effect of smectite and dimethyl prostaglandin E2. *Gastroenterology* 1993; **104**: A132.
38 Mahraoui L, Heyman M, Plique O, Droy-Lefaix MT, Desjeux JF. Apical effect of diosmectite on damage to the intestinal barrier induced by basal tumour necrosis factor-alpha. *Gut* 1997; **40**: 339–43.
39 Spiller RC, Jenkins D, Thornley JP *et al.* Increased rectal mucosal enteroendocrine cells, T lymphocytes and increased gut permeability following acute *Campylobacter* enteritis and in post-dysenteric irritable bowel syndrome. *Gut* 2000; **47**: 804–11.
40 Collins SM, Barbara G. East meets west: infection, nerves, and mast cells in irritable bowel syndrome. *Gut* 2004; **53**: 1068–9.
41 Opriu AL, Diculescu M, Lov A *et al.* Enterocyte covering agent versus intestinal motility inhibitor in the irritable bowel. *Gut* 1996; **39** (Suppl.): A34.
42 Ducrotte P, Dapoigny M, Bonaz B, Siproudhis L. Symptomatic efficacy of beidellitic montmorillonite in irritable bowel syndrome: a randomized, controlled trial. *Aliment. Pharmacol. Ther.* 2005; **21**: 435–44.
43 Dapoigny M, Giral P, Plique O. Visible abdominal swelling and functional disorders of the intestine (FDI): should medical treatment be given along with dietary advice? *Gut* 1995; **37**: 1366.
44 De Sola Pool N, Loehle K, Radzik AJ, Kinsley J. A comparison of nonsystemic and systemic antidiarrheal agents in the treatment of acute non-specific diarrhea in adults. *Today's Ther. Trends* 1987; **5**: 31–8.
45 Wingate D, Phillip SF, Lewis SJ *et al.* Guidelines for adults on self-medication for the treatment of acute diarrhea. *Aliment. Pharmacol. Ther.* 2001; **15**: 773–82.
46 Irvine EJ, Whitehead WE, Chey WD *et al.* Design of treatment trials for functional gastrointestinal disorders. *Gastroenterology* 2006; **130**: 1538–51.