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Alimentary Tract

Comparative efficacy of dioctahedral smectite (Smecta®) and a probiotic preparation in chronic functional diarrhoea

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Abstract

The present study was designed to investigate the clinical efficacy and safety of dioctahedral smectite in Chinese patients with chronic functional diarrhoea and to compare this activity to a probiotic preparation.

Patients diagnosed with chronic functional diarrhoea (Rome II criteria), exclusion of blood, ova/parasites in the stool and a normal colonoscopy were included. After a 1-week period of baseline without any medication, they were prescribed three sachets of dioctahedral smectite 3 g, administered 1 h after the meals (Group A), or two capsules of Bifico 210 mg (Group B) for 28 consecutive days. Efficacy of the treatments was assessed on frequency of bowel movements and consistency of stool, as compared to baseline.

Four hundred and ten patients were included (258 males, 152 females; mean age 43.8 ± 13.9 years): 208 in Group A and 202 in Group B. In Group A, the mean number of stool per day decreased from 3.5 ± 1.0 at baseline to 2.0 ± 0.9 and from 3.3 ± 1.0 to 2.2 ± 0.9 in Group B (z = 2.699; P = 0.007). Decrease in stool number was significant with both treatments but more important with smectite at week 2 and remained significant throughout the treatment period. Stool consistency, assessed by the Bristol scale, also improved significantly over the treatment period, as compared to baseline (z = 3.310, P = 0.001).

Dioctahedral smectite appeared in this study to be an effective and safe treatment of chronic functional diarrhoea, its effect starting during the first week of treatment and consisting in a decrease in the frequency of daily bowel movements and improvement of stool consistency. Moreover, dioctahedral smectite displays a prolonged action after disruption of the treatment that may interfere with the natural course of the disease.

Keywords: Functional diarrhoea; Probiotic; Smecta

1. Introduction

Functional diarrhoea is defined by continuous or recurrent passage of loose or watery stool, without abdominal pain [1]. The condition is considered as chronic when it is present for at least 12 weeks over the last 12 months before the diagnosis and involves at least one-fourth of bowel movements. Functional diarrhoea must be distinguished from diarrhoea-predominant irritable bowel syndrome, which is characterised by the association of pain with diarrhoea. In a British study, its prevalence was estimated up to 4% of the adult population and it seems more common in patients over 50 [2]. In the Chinese population, functional chronic diarrhoea is almost as frequent, with a prevalence of 6.1% in the adult population [3].

Chronic diarrhoea is possibly curable if a cause can be found, but in the absence of a definite cause, functional diarrhoea often persists despite treatment attempts. Management is then mostly based upon the symptoms pattern and involves antidiarrhoeal drugs, among which probiotics have demonstrated some efficacy [4–6]. On the other hand, dioc-

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tahedral smectite has been shown to improve patients with chronic colonic disorders [7]. In acute diarrhoea, dioctahedral smectite was more effective than loperamide to reduce the number of days with diarrhoea [8,9]. Dioctahedral smectite is a clay derivative that has a protective effect on the intestinal mucosa by directly interacting with intestinal mucus [10,11].

However, the clinical efficacy of dioctahedral smectite has not been completely evaluated in patients with chronic functional diarrhoea. Therefore, the present study was designed to investigate the clinical efficacy of dioctahedral smectite in these patients, compared to a probiotic preparation, widely accepted as a treatment of this condition in China, where the study was conducted. Secondary objective was to assess the safety of dioctahedral smectite in this indication.

2. Patients and method

2.1. Patients selection

Patients diagnosed as having chronic functional diarrhoea were included in the study. Chronic functional diarrhoea was defined according to Rome II criteria [1]. Male and female patients aged between 20 and 70 years were included. All patients had undergone a standardised set of examinations prior to their entry in the study that included a normal blood cell count, a negative stool examination for blood and ova/parasites and a normal colonoscopy or barium enema within the last 6 months preceding inclusion.

Patients with significant heart, liver, renal or neurological dysfunction, a known malignant tumour, diabetes, proven inflammatory bowel disease and irritable bowel syndrome were excluded. Pregnant or lactating women were excluded. Patients with an identified cause of chronic diarrhoea, as diagnosed by the initial work-up, were also excluded.

2.2. Study design

After an initial consultation for verification of inclusion/exclusion criteria, patients were requested to stop all antidiarrhoeal medications. During 1 week, the number of bowel movements, consistency of stool and other digestive symptoms were monitored and recorded as baseline period.

At the end of the week, patients with an average of at least three bowel movements/day were randomised to one of the study treatments, after the inclusion/exclusion criteria and the patient's diary had been checked. Treatment was prescribed for 4 weeks (see here below), and stool frequency and consistency were daily reported on the diary. An intermediate visit was scheduled at 2 weeks of treatment. After 4 weeks of treatment, the medication was interrupted but the patients continued to record their symptoms for an additional 2-week follow-up.

2.3. Study treatments

Patients of the first group were prescribed three sachets of dioctahedral smectite 3 g, administered 1 h after the meals, for 28 consecutive days. Patients in the second group were administered two capsules of Bifico 210 mg (Xinyi Pharmaceutical LTD, Shanghai, China) before breakfast and dinner. Bifico is a mixture of probiotics containing the following strains: *Lactobacillus bifidus*, *acidophilic lactobacilli* and *Enterococcus* so that the number of living bacteria per capsule is not less than 10^7 colony-forming unit (CFU). During the treatment period, patients were allowed to stop the study medication for 3 days when they were constipated and had no bowel movement over three consecutive days.

2.4. Endpoints and data analysis

Primary endpoint to evaluate the efficacy of both treatments was the change in daily frequency of bowel movements, as recorded by the patient on the diary. Stool frequency was compared with the baseline period, at the end of each treatment week and over the whole treatment period. Secondary endpoints were the changes in stool consistency over the treatment period, as recorded daily by the patient with the help of the Bristol scale with drawings for assessment of stool consistency [12] and the tolerance of both treatments. Liquid stool was quoted 7 and mushy stool 6. Hard lumpy stool was quoted 1.

Based on the assumption that the most effective treatment would reduce the number of stools by 15%, and anticipating a standard deviation of the primary endpoint measurement of 1.7, according to previous studies in this population [12], 206 patients had to be included in each treatment arm, with an α risk of 5% and a β risk of 20%.

Data input was achieved on EPI-Info software (CDC, Atlanta, GA) and statistical analysis performed with the SAS software 6.12 (SAS Software, Cary, NC). Data on frequency of bowel movements were analysed with the paired *t*-test with Bonferroni's correction. Data on stool consistency were analysed with the chi-square test. Data are expressed as mean $\pm$ S.D. and *P* values lower than 5% were regarded as significant.

3. Results

3.1. Study population

Four hundred and ten patients were included in the study, from whom 208 were treated with dioctahedral smectite and 202 with Bifico. Patients were 258 males and 152 females, with a mean age of 43.8 ± 13.9 years (extremes: 19–70 years). There was no significant difference in the demographic and clinical characteristics of patients included in either of the treatment groups (Table 1).

From these patients, four were withdrawn from the study before randomisation, as they appeared not to meet the

Table 1
Demographic and clinical characteristics of included patients

	Group A (smectite)	Group B (probiotics)	Statistical value	*P* value
Age (years)	43.1 ± 14.9	44.6 ± 12.8	$t = 1.093$	0.275
Sex ratio (M/F)	1.89	1.53	$\chi^2 = 1.093$	0.296
Height (cm)	168.3 ± 7.7	167.6 ± 7.1	$t = 0.922$	0.357
Weight (kg)	64.1 ± 10.9	63.8 ± 9.9	$t = 0.305$	0.761
BMI (kg/m^2)	22.6 ± 3.0	22.7 ± 3.0	$t = 0.325$	0.745
Duration of diarrhoea (years)	5.6 ± 9.6	4.9 ± 5.4	$z = 0.075$	0.941

inclusion criteria. After randomisation, eight patients, four in each treatment group were excluded, mainly because of a lack of effect of the treatment (two in Group A—patients treated with dioctahedral smectite; and three in Group B—patients treated with probiotics). These patients were included in the analysis of the results and considered as failures of the treatment.

3.2. Effect of treatments on the frequency of bowel movements

Over the whole study, frequency of bowel movements were averaged over 1 week and compared between treatments and as changes over the baseline.

At baseline, the average number of daily bowel movements was not different between Groups A and B. In Group A, the mean number of stool was 3.5 ± 1.0 per day at baseline and 3.3 ± 1.0 per day in Group B ($z = -1.618$, NS). On treatment, the daily number of bowel movements decreased on both treatments. However, the weekly average number of stools was 2.0 ± 0.9 per day in the Group A compared to 2.2 ± 0.9 per day in patients of Group B. The difference between the two groups was statistically significant ($z = 2.699$, $P = 0.007$).

The difference between the groups appeared already significant after 2 weeks of treatment and maintained over the whole treatment period (Fig. 1). Moreover, during the follow-up period of 2 weeks after the disruption of the treatment, the difference between the treatment groups remained significant (Fig. 1).

3.3. Effect of treatments on the consistency of bowel movements

At baseline, consistency of stool was reported as mushy or liquid by almost all patients and the average Bristol score was not statistically different between Group A (5.84 ± 0.58) and Group B (5.78 ± 0.79). Over the whole treatment period, the consistency of stool quickly improved in both groups. The average Bristol score over the 28 days of treatment was significantly lower in Group A (4.64 ± 0.83) than in Group B (4.89 ± 0.83) ($z = 3.310$, $P = 0.001$).

Improvement in stool consistency was more pronounced in patients of Group A and the median of Bristol score was significantly lower in this group over the first 2 weeks of treatment than in patients of Group B (Fig. 2). The difference was also significant during the last 2 weeks of treatment.

During the follow-up after discontinuation of the treatment, stool consistency remained moderately improved as compared to baseline but the difference between treatments was no longer significant (Fig. 2).

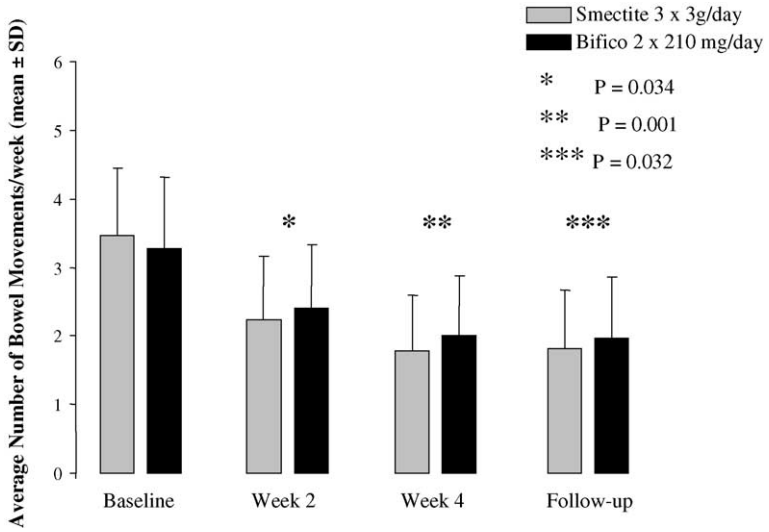

Fig. 1. Average number of bowel movements recorded daily by the patients during the baseline period, during the first 2 weeks of treatment, the last 2 ones and the 2 weeks follow-up. Statistical significance is shown for the difference between the treatment groups at weeks 2, 4 and at follow-up.

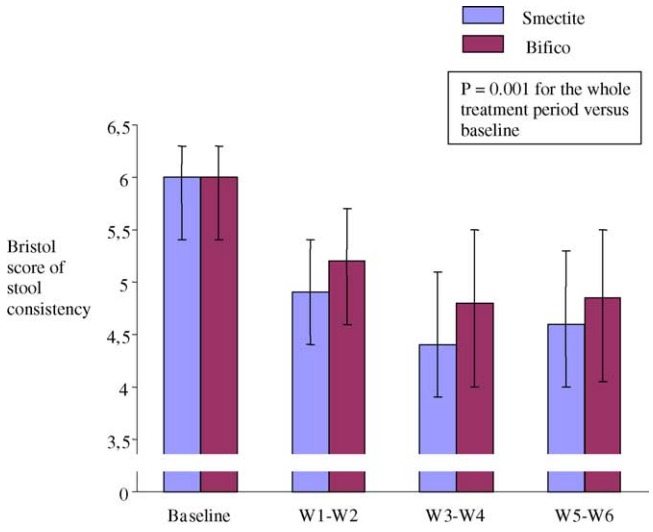

Fig. 2. Median of the score of stool consistency determined by the categories of the Bristol scale. Error bars represent the percentile 25 and 75.

3.4. Treatment safety

No serious adverse event was reported in any of the treatment groups. Adverse events reported were minor and non-specific, and their frequency was not different in the two groups.

Discontinuation of the medication after 2 days without a bowel movements was necessary in eight patients in Group A (3.8%) and five patients in Group B (2.5%) (χ^2 = 2.269, NS).

4. Discussion

The present results constitute the first study demonstrating that dioctahedral smectite is effective in improving stool frequency and consistency in patients with chronic functional diarrhoea. Moreover, dioctahedral smectite was more effective than the control treatment, which consisted of a mixture of probiotic strains, currently in use in China for the treatment of diarrhoea. The effect of dioctahedral smectite was observed since the first week of treatment and maintained over the 4 weeks. Moreover, after disruption of the treatment, the consistency of stool returned less frequently to baseline in patients treated with dioctahedral smectite than with Bifico.

This probiotic mixture was chosen as the comparator instead of placebo, because of its potential therapeutic effect, in order to decrease the withdrawal of patients from the control group, for inefficacy of the treatment. Chronic functional diarrhoea significantly impairs quality of life of patients [13] and may lead to larger dropouts in clinical studies on the condition. The therapeutic benefit of Bifico has been demonstrated in the treatment of acute diarrhoea [14,15]. On the other hand, dioctahedral smectite has been shown effective in patients with acute diarrhoea as it cures diarrhoea in more patients than loperamide [16]. In two other studies, dioctahedral smectite appeared as effective as loperamide to relieve acute diarrhoea [9,17]. In the present study, the effect of dioctahedral smectite was investigated in patients with chronic functional diarrhoea. Dioctahedral smectite rapidly and durably improved stool consistency and frequency in these patients, but its effect was also prolonged after disruption of the treatment as shown by the evolution of the patients over the 2-week follow-up. Indeed, the average frequency of bowel movements remained at the same level during the follow-up as it was during the last 2 weeks of treatment and the proportion of patients who relapsed during the follow-up was significantly lower in the dioctahedral smectite group than in the control group.

The therapeutic effect of dioctahedral smectite can be related to its interaction with the intestinal mucosa. Several studies have shown that dioctahedral smectite is able to aggregate with *Escherichia coli* in vitro [18] and in vivo [19]. In animals, dioctahedral smectite also protects the intestinal mucosa against injury induced by biliary salts [10]. The protective effect of smectite is related to its interaction with intestinal mucus [11]. These properties may explain not only the direct therapeutic effect of dioctahedral smectite but also its prolonged action after withdrawal. It could then act as a regulatory agent, interacting with the gut flora and regulating intestinal secretions. Finally, this prolonged effect might interfere with the natural course of chronic functional diarrhoea and needs to be further studied.

On the other hand, dioctahedral smectite did not induce constipation or any other significant adverse event. It can thus be used safely in these patients. Indeed, although patients were allowed to interrupt treatment after 2 days without bowel movement, only 3.8% of the patients in the group treated with dioctahedral smectite had to stop the medication and this proportion was not different from that of the control group. This observation indicates that the action of dioctahedral smectite on intestinal secretions does not increase the risk of constipation.

In conclusion, dioctahedral smectite appears to be an effective and safe treatment of chronic functional diarrhoea. Its effect starts during the first week of treatment and consists of a decrease in the frequency of daily bowel movements and in improvement of stool consistency. The effect of dioctahedral smectite appeared significantly more important than that of the probiotic preparation used as comparator in this study. Moreover, dioctahedral smectite displays a prolonged action after disruption of the treatment that may interfere with the natural course of the disease.

Conflict of interest statement

The support of Beaufour Ipsen was obtained for the logistics of the study in China, without any personal fee for the investigators.

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