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Oral Cimetropium Bromide, a New Antimuscarinic Drug, for Long-Term Treatment of Irritable Bowel Syndrome

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Most drugs are ineffective for the long-term treatment of irritable bowel syndrome (IBS). The beneficial effects of medical treatment of IBS are poor and last for only a relative short time. Over a period of 6 months, we investigated the effectiveness of cimetropium bromide, a new antimuscarinic compound, in patients with IBS. Forty-eight patients were treated at random and in double-blind fashion with cimetropium bromide (50 mg, tid) or placebo for 6 months. Personal diary cards and monthly check-ups guaranteed the monitoring of symptoms (mainly pain). In addition, personality patterns (MHQ–CBA tests) were obtained for the patients before and after therapy, both to detect possible psychoneurotic traits and to observe the changes in these traits in relation to the changes in pain symptoms. Three patients on placebo and one on cimetropium dropped out. At the end of therapy, pain scores had decreased an average of 16% in the placebo group and 87% in the cimetropium group ($p < 0.01$). Twenty patients (87%) on cimetropium *versus* five patients (24%) on placebo considered themselves to be globally improved ($p < 0.01$). The MHQ test showed significant improvement in the anxiety score in the cimetropium group only. The CBA test confirmed a significant decrease in anxiety state (STAI-X-1) after cimetropium treatment. Eleven patients (48%) on cimetropium reported side effects (mainly dry mouth and sleepiness), but none withdrew from the study. The results of this trial indicate that long-term treatment of IBS with cimetropium bromide significantly improves symptoms and associated psychological disorders.

INTRODUCTION

When the typical symptoms of irregular bowel habits, abdominal pain, distension, and a feeling of incomplete defecation are not associated with *other* gastrointestinal diseases, irritable bowel syndrome (IBS) is commonly diagnosed. This syndrome affects up to 15% of the population (1, 2) and accounts for about half of the referrals to gastrointestinal clinics (3). The pathogenesis of IBS is unknown, but abnormal gut motility (4–6) and psychological factors (7–9) have been implicated. Because its causes are multiple, there is no specific and consistently effective therapy for patients with this syndrome. Some will respond to a combination of antispasmodics and bulking agents and a sympathetic explanation of symptoms (4, 10). However, up to 25% of patients do not improve, and there has been no study (11) of the effectiveness of drugs in long-term treatment of symptoms. In effect, many patients improve at first with any drug treatment, but the beneficial effects of medical treatment soon disappear. The clearest benefit is in abdominal pain. The cumulative evidence of benefit has already justified a 6-wk trial of treatment with mebeverine (12, 13); however, evidence for its efficacy in the longer term is not available (11). Dicyclomine (14, 15) or mepenzolate (16) may help some patients, but unwanted effects limit their use (11).

The aims of this study were to see whether or not a new antimuscarinic compound, cimetropium bromide (17, 18), might be effective for long-term treatment of IBS and, during the trial, to look for possible psychoneurotic traits and to observe the changes in these traits in relation to changes in the pain.

MATERIALS AND METHODS

This was a double-blind, randomized, placebo-controlled, parallel-groups study. The trial included a 3-wk screening period and a 6-month test period, during which each patient was randomly assigned to drug or placebo. Patients, 18–65 years old, with clinical diagnoses of IBS based on one or more of the following criteria, qualified for admission to the study: *1*) abdominal pain, most severe after breakfast; *2*) persistent abdominal pain with accompanying urge to defecate; *3*) sharp, cramp-like lower quadrant pain, usually relieved by passing gas; *4*) straining at stool. Emphasis was placed on enrolling patients for whom pain and constipation were the predominant features of IBS, and for whom the disease had been diagnosed during the

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previous 5 yr. Diarrhea was defined as more frequent, loose-to-liquid stools without treatment. It was not defined as more than three stools per day. Constipation was defined as less frequent and harder stools, more straining, and an increased sense of incomplete emptying without intervention. Constipation was not defined as fewer than three stools a week, since the numerical frequency was usually of less concern to the patients than more subjective attributes. The patients were classified as either diarrhea- or constipation-predominant from the pattern that occurred most often and was most bothersome.

During the first week of the screening phase, a medical history was taken, a physical examination was given, and laboratory tests were completed, including CBC, SMA-12, serum electrolytes, urinalysis, and stool culture. To enter the study, patients had to have no clinically significant deviations from normal values. Sigmoidoscopy and barium enemas should have been performed within the last year. Barium studies or endoscopy of the upper gastrointestinal tract, cholecystograms, and ECG were optional. The second and third weeks of the screening phase were used to define baseline data: eligible patients were instructed to record their symptoms on a diary card. The following symptoms were recorded: *1*) number of days with bowel disturbances (constipation or diarrhea) per week, *2*) intensity of pain, rated on a four-point scale (Table 1), *3*) number of days with pain per week, *4*) retrospective global assessment since last visit (as better, same, worse).

Between January 1986 and June 1986, sixty-eight patients referring to our out-patient department were diagnosed as having IBS. Of these, 59 patients fit the inclusion criteria; of these 59, seven patients were excluded because they did not give informed consent and four because of poor compliance. The remaining forty-eight patients were randomly assigned to either the drug group or the placebo group. Dosage was one 50-mg tablet of cimetropium bromide three times a day before meals. During the treatment period, patients continued to record stool frequency, and frequency and intensity of abdominal pain. The patients were also asked monthly to fill out symptom questionnaires. At these visits, they submitted their diaries and were given new ones, new tablets were dispensed, and unused tablets were returned and counted. The Middlesex Hospital Questionnaire (MHQ) and the Cognitive Behavioural Assessment (CBA) were administered at the screening visit and at the end of treatment. At the end of the 6-month treatment period, the laboratory tests were repeated. Sedatives, hypnotics, tranquilizers, laxatives, antacids, anticholinergic drugs, and antispasmodic agents were not allowed. Informed oral consent was obtained. The study was approved by the Local Ethical Committee and was conducted according to the principles of the Helsinki Declaration.

TABLE 1
Pain Symptom Score

0	= None
1	= Mild (pain cannot be ignored, but does not influence daily activities)
2	= Moderate (pain influences concentration on daily activities)
3	= Severe (pain markedly influences daily activities except the most elementary)

The primary data were either frequencies or qualitative scores or counts. The frequencies were tested by χ^2 or Fisher's exact test. Qualitative scores were examined by Mann-Whitney, Wilcoxon, and Friedmann test. The counts after adequate transformation to obtain normalization were analyzed by analysis of variance for split-plot design. The rejection region was set at the 0.05 level, and two-tailed tests were used. Data were expressed as means ± standard errors of means or medians and ranges.

RESULTS

Four patients (one in the drug group, three in the placebo group) did not complete the study, three because of noncompliance and one because he moved away. The characteristics of the 41 remaining patients with respect to age, sex, duration of illness, bowel habits, smoking, and alcohol, coffee, and laxative consumption, are summarized in Table 2, and show that the drug and placebo group were not comparable for sex distribution.

Abdominal pain

The intensity and frequency of abdominal pain for the drug and placebo groups are shown in Figures 1

TABLE 2
Characteristics of the Patients

	Placebo	Cimetropium	*p*
Sex: men/women	6/15	16/7	<0.05
Age (yr)			
Median	32.0	33.5	NS
Range	18–65	18–54	
Duration of disease (yr)			
Median	5.0	3.0	NS
Range	1–30	1–20	
Bowel habits			
Diarrhea-predominant	7	9	NS
Constipation-predominant	14	14	
Habits			
Smoking (yes/no)	11/10	14/9	NS
Coffee (yes/no)	13/8	13/10	NS
Alcohol (yes/no)	16/5	21/2	NS
Laxative (yes/no)	14/7	12/11	NS

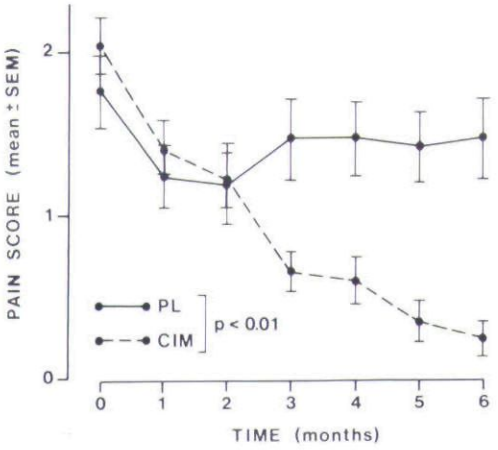

FIG. 1. Abdominal pain scores for placebo and cimetropium groups during the 6 months of treatment.

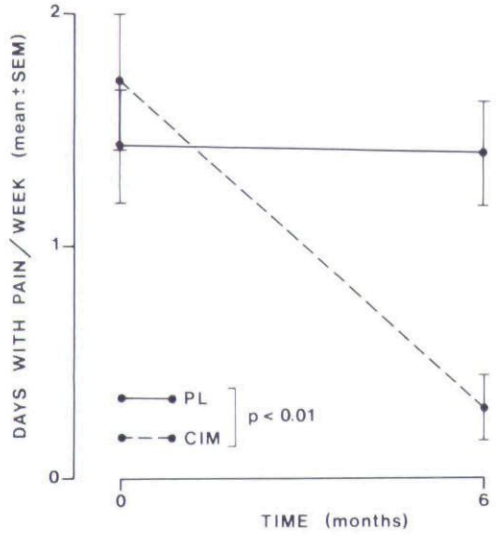

FIG. 2. Mean numbers of days per week with pain for the placebo and the cimetropium groups before and after 6 months of therapy.

and 2. The intensity of pain decreased over the entire period in the cimetropium-treated group ($p < 0.01$). In the placebo-treated group, there was a transient improvement of this symptom over 2 months, and after that the positive effects partially disappeared (NS). The mean number of days per week with pain also decreased significantly in the drug group from 1.7 ± 0.3 to 0.3 ± 0.1, whereas in the placebo group the effect was not significant in the 6th month. At the end of treatment, the pain scores had decreased an average of 16% in the placebo group and 87% in the cimetropium group ($p < 0.01$).

Bowel habits

The baseline numbers of days per week with bowel disturbances were 3.3 ± 0.4 for the drug group and 2.4 ± 0.3 for the placebo group (NS) (Fig. 3). After cimetropium, these figures decreased significantly to 1.2 ± 0.3, whereas there were no significant changes after placebo (1.9 ± 0.3).

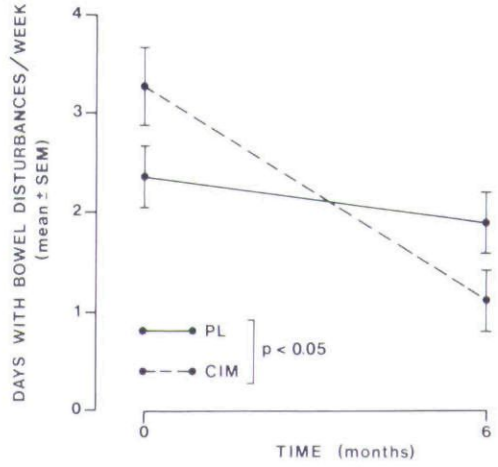

FIG. 3. Mean numbers of days per week with bowel disturbances for the placebo and the cimetropium groups before and after 6 months of therapy.

Patient self-assessment of treatment

The results of the patients' self-assessment are shown in Table 3. Eighty-seven percent of the drug-treated group who responded to the question regarding their general condition indicated that they were improved ($p < 0.01$).

Psychological assessment

Nineteen patients in the cimetropium group and 18 patients in the placebo group could be evaluated from the MHQ and CBA. Table 4 shows the results of the MHQ before and after treatment in the placebo and drug groups. At the beginning of treatment, the median scores were within the normal range for all the variables analyzed except anxiety. The median evaluation of anxiety was moderate (12.0) for the cimetropium group and mild (8.5) for the placebo group, but the difference between the two base-line anxiety scores was not significant ($p = 0.12$). After 6 months of treatment, there was a significant decrease in the anxiety score to mild (9.0) in the cimetropium-treated group. Somatization also decreased in the drug group, although the median value (6.0) remained unchanged. There were no other significant changes in the other components in either group. On the other hand, none of the median values of these psychoneurotic traits can be considered pathological, even before treatment. The CBA showed that, at the end of the treatment, there were significantly more patients with decreased anxiety state (STAI-X-1) in the cimetropium group (74%) than in the placebo group (39%), whereas the anxiety trait (STAI-X-2) did not change in most patients of both groups (Table 5).

Laboratory results

Hemoglobin, hematocrit, white blood count, differential, SMA-12 battery, serum electrolytes, and urinalysis were done for each patient before and after the trial. No clinically significant changes in any of these

TABLE 3
Patients Self-assessments at the End of Study, Compared with Baseline

	Placebo	Cimetropium
Better	5 (24%)	20 (87%)
Same	7 (33%)	2 (9%)
Worse	9 (43%)	1 (4%)
	$p < 0.01$	

TABLE 4
Scores for the Personality Traits Evaluated by MHQ

	Placebo		Cimetropium	
	Before	After	Before	After
Anxiety				
Median	8.5	8.0	12.0	9.0
Range	5–15	5–15	5–16	4–14
p	NS		$p < 0.01$	
Depression				
Median	5.0	6.0	6.0	6.0
Range	4–13	5–14	4–10	4–11
p	NS		NS	
Somatization				
Median	6.0	5.5	6.0	6.0
Range	4–12	4–13	4–13	4–12
p	NS		$p < 0.05$	
Obsession				
Median	5.0	5.0	5.0	6.0
Range	3–13	3–14	2–12	3–11
p	NS		NS	
Phobia				
Median	4.5	4.0	4.0	4.0
Range	2–6	2–6	2–11	2–12
p	NS		NS	
Hysteria				
Median	5.0	5.0	4.0	4.0
Range	1–12	1–12	2–13	2–12
p	NS		NS	

TABLE 5
Anxiety Pattern Evaluated by CBA

	Placebo	Cimetropium
Anxiety state (STAI-X-1)		
Unchanged	11	5
Decreased	7	14
	$p < 0.05$	
Anxiety trait (STAI-X-2)		
Unchanged	16	14
Decreased	2	5
	NS	

laboratory values were seen in either the drug or placebo group.

Adverse reactions

All of the patients who completed the double-blind treatment phase of the study (23 drug and 21 placebo) were evaluated for adverse reactions. Eighteen unwanted effects were reported by 11 of the 23 (48%) patients while taking drug, and seven unwanted effects were complained of by six of the 21 (29%) placebo-treated patients. The most frequently reported adverse effects associated with the drug were dry mouth and sleepiness (Table 6). These effects are considered to be typical anticholinergic manifestations of cimetropium bromide. None of the 11 drug-treated patients reporting adverse effects withdrew from the study or required dosage reduction.

TABLE 6
Unwanted Effects

	Placebo	Cimetropium
Dry mouth	1	11
Sleepiness	1	5
Epigastric fullness	2	1
Pyrosis	1	
Dizziness		1
Insomnia	1	
Nausea	1	
Total	7	18

DISCUSSION

The results of this study show, first, that an anticholinergic agent is significantly more effective than placebo for long-term therapy of IBS. At 6 months, and even at 3 months, there was a clearly significant difference in favor of the patients who took cimetropium bromide. This was true for global patient self-evaluation, as well as for abdominal pain and bowel disfunction. Not surprisingly, the early evaluations (1st and 2nd month) showed improvement in both groups, suggesting a placebo effect, but later the placebo group had worsened, whereas the cimetropium group continued to improve.

The patients were well-matched except for sex distribution, the cimetropium-treated group having fewer women. The prevalence of men in the treatment group does not agree with the general experience of western clinics, who report ratios of females to males ranging from 2:1 to 4:1 (1). The ratio is reversed in other geographical areas, in which women are discouraged from seeking medical help, suggesting that cultural factors influence which sex is more likely to report symptoms to a doctor (19). In this study, we found no statistically significant differences between the responses to treatment in men and women. Consequently, we felt this imbalance should not greatly influence the results, although it might, perhaps, have been involved in the poorer effect in the placebo group.

Patients taking antimuscarinics who recognize side effects may come to recognize whether they are taking an active drug or placebo. This is a general problem in all placebo-controlled trials with patients who are familiar with the possible side-effects of the active drug.

Symptoms of abdominal pain, bloating, changeable

bowel habits, constipation, or diarrhea are produced by abnormal motor activity of the intestinal tract, whether due to an inherent abnormality of the smooth muscle of the gut or of its neurohumoral control mechanisms (6, 20) or the effect of a faulty diet. Finally, the condition might be due to an altered perception of normal physiology. Anticholinergics are given for IBS because they reduce excessive colonic motility. Cimetropium bromide given intravenously (5 and 10 mg) has been shown to reduce the motor responses to food in both the sigmoid and transverse colons of healthy volunteers (21) and in the sigmoid colon of IBS patients (22). Although the drug is poorly absorbed (1–4% of the administered dose) (23), it accumulates after repeated oral doses (24) because of its long terminal half-life (29 h) and, hence, reaches sufficient levels in the body for the pharmacological effects. Indeed, when the drug is given orally for 1 month, it accelerates intestinal transit time in patients with pain and constipation (25).

The presence of psychological and emotional disorders in patients with IBS has been observed by several investigators (4, 8, 26–28). In fact, it has been proposed that the colon is a target organ for stress (29). The results of this study indicate that psychoneurotic indices appeared to improve in parallel with the improvement in symptoms. It would seem that improvement in pain control removed one of the factors aggravating reactions to stress. This explanation would appear to be corroborated by the change in anxiety-state scores but not the anxiety-trait scores.

In conclusion, the results of this study indicate that cimetropium bromide is very effective for long-term treatment of symptoms of IBS, especially pain. The favorable results of this trial are supported by those of previous double-blind placebo-controlled studies (30, 31). Finally, our findings are consistent with the hypothesis that in IBS there is a considerable relationship between psychological disorders and pain symptoms.

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