Trimebutine maleate in the treatment of irritable bowel syndrome: Canadian clinical experience

ABSTRACT: An open multicentre study was conducted at 18 Canadian centres in patients diagnosed as suffering from irritable bowel syndrome (IBS). One hundred and thirty-one (72% female and 28% male) patients, mean age 44 years, were treated with 200 mg tid trimebutine maleate (Modulon; Jouveinal) for periods of four weeks. Frequency and severity of pain, constipation and diarrhea were analyzed, as were stool frequency and consistency. A statistically significant reduction of frequency and severity was discerned in all symptoms (pain, constipation, diarrhea). Stool frequency fell within normal range (three per week to three per day) in close to 90% of patients as compared to 66% prior to the study. Similarly, stool consistency was normal in over 40% more patients at the end of the study than before treatment. Global evaluation by physicians and patients showed that approximately 70% of patients felt better at the end of the treatment than before the study. Side effects such as nausea, headaches and fatigue were reported in 14 patients, leading to discontinuation of therapy in seven. In conclusion, trimebutine maleate was effective in reducing the frequency and severity of the major symptoms of IBS as well as in normalizing transit disturbances as measured by stool frequency. **Can J Gastroenterol 1987;1(1):23-27**

Key Words: *Constipation, Diarrhea, Irritable bowel syndrome, Pain, Trimebutine maleate*

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THE GREAT MAJORITY OF PATIENTS with irritable bowel syndrome (IBS) present with a multitude of symptoms, all of which are often not responsive to a single agent such as anticholinergics or antispasmodics which are prescribed for pain, antidiarrheal agents, dietary fibre for transit disturbances and antidepressants/anxiolytics for patients with associated psychological problems. Rather, a combination of several agents must often be prescribed. Thus, agents capable of controlling the entire symptom complex under monotherapy would offer an obvious advantage.

Trimebutine maleate (maleate salt of 2-dimethyl-amino-2-phenylbutyl 3,4,5 trimethoxy benzoate) was shown to stimulate motility in the small intestine and to modulate it in the colon, and to possess nonspecific spasmolytic activity associated with local anesthetic properties. Its stimulant activity appears to be related mostly to peripheral μ enkephalinergic agonist activity, while the inhibitory effect is mediated by its interaction with κ receptors (1). In preclinical studies, it was shown to exert regularizing effect on abnormal contractility in vitro, as well as in vivo, where it induced phase III activity in dog intestine (2). In human intestine, it induces phase III activity (3), accelerates duodenal transit (4) and stim-

ulates spike potential activity (5). These effects have been found useful in accelerating the resolution of postoperative paralytic ileus (5,6). In the colon, the drug seems to exhibit bivalent action, as was demonstrated in studies where it reduced abnormally elevated and stimulated abnormally diminished colonic motor and electromyogenic activities (7-9). It appears to exert no effect on normal colonic activity (3,7,8). Frexinos (10) showed that the drug is active in both constipated and diarrheic patients in that it reduces colonic long spike burst electromyogenic activity. All these parameters seem to be related to the drug's ability to reduce clinical symptoms of IBS.

Numerous controlled clinical trials evaluating the effect of trimebutine maleate in the treatment of IBS have been completed (12-14). Short to medium term studies (three days to four weeks) comparing the drug to placebo showed that it is significantly more effective than placebo, particularly in relieving pain and constipation. Unpublished reports indicate that it also reduces diarrhea. Single stool transit time was significantly reduced in constipated patients with spastic colon (13). In a six month study, no significant differences in global assessment were found between the drug and placebo in patients treated concomitantly with high fibre diet, although colon tenderness was significantly reduced at three months (15). Studies comparing trimebutine to mebeverine (16,17), anticholinergics such as pinaverium bromide (18) and clidinium bromide/chlordiazepoxide combination (19), showed equivalent efficacy in all treatment groups.

A post marketing open multicentre study was conducted in order to observe the effect of trimebutine maleate in the treatment of IBS and its various subgroups within the scope of routine gastroenterology practice.

MATERIALS AND METHODS

Eighteen Canadian centres participated in the study. Patient selection criteria included presence of chronic abdominal pain and/or transit disturbances such as constipation, diarrhea and alternation of the two. Patients must have had no evidence of organic gastrointestinal disease as demonstrated by barium enema, sigmoidoscopy, hemogram, blood biochemistry and/or lactose tolerance test. Only patients symptomatic at the time of entry into the study were to be included.

Patients were treated with two 100 mg trimebutine maleate tablets three times a day (30 mins before meals) during four weeks, with follow-up every two weeks. Other medications for IBS were continued throughout the study with the exception of anticholinergics which were discontinued in all but two patients, starting at least 48 h prior to entry into the study. Although these two patients would have been excluded in a double-blind study analysis, they were included in this case.

During the trial, patients completed daily diary cards summarizing their intestinal habits and intensity of symptoms.

TABLE 1
Demographic data of patients with irritable bowel syndrome at 18 Canadian centres

Total entered	146
Total analyzed	131*
Female	72%
Male	27%
Age (years) (mean ± SEM)	44 ± 1.3
Duration of disease (years) (mean ± SEM)	7 ± 10.2
Initial classification by symptoms	
Pain	89%
Constipation	33%
Diarrhea	25%
Alternating constipation/diarrhea	33%
Initial overall severity of IBS	
Mild	17%
Moderate	53%
Severe	22%
Very severe	2%
Concomitant diseases	
Cardiovascular	8%
Endocrine	11%
Immunological/allergic	13%
Gastrointestinal	14%
Other	4%
Concomitant IBS medications	
Laxatives/bulk forming agents	13%
Anxiolytics	14%
Antispasmodics	3%
Antidiarrheals	3%
Antidepressants	3%
Analgesics	6%
Combination drugs	2%
GI motility modifying agents	1%

*15 lost to follow-up

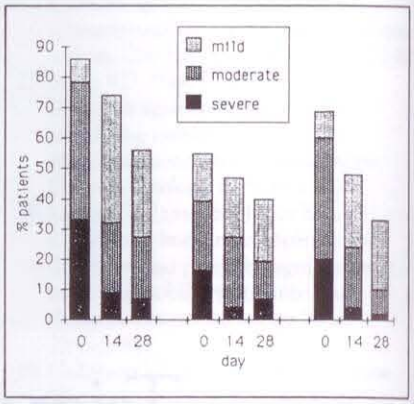

Figure 1) *Severity of symptoms, all patients combined. Symptoms (from left to right) pain; constipation; diarrhea*

At each visit, the investigators assessed the patients' clinical status, based on physical examination, review of daily diary cards and personal interviews. Severity of symptoms was assessed using a five point rating scale: 1 absent, 2 slight (present but not bothersome), 3 moderate (occasionally bothersome), 4 severe (bothersome most of the time), 5 very severe (incapacitating).

At the end of the four week period, both patients and investigators performed a global evaluation of the effect of the drug on the patients' condition. Change of symptom severity scores was evaluated for all patients and separately by symptom subgroups, as defined by investigators at time of patient enrollment (pain, constipation, diarrhea, alternation of constipation/diarrhea). Friedman's analysis over time was used to evaluate statistically changes relative to day 0.

Study sample: Twenty-one investigators entered 146 patients at 18 centres throughout Canada. Fifteen patients failed to return after their initial consultation and were excluded from the study. Another 11 discontinued due to lack of improvement (four) or side effects (seven). The initial demographic data are summarized in Table 1. The usual spectrum of the syndrome was well represented in the study sample.

RESULTS

Symptom severity: A statistically significant reduction of severity was observed in all symptoms (pain, constipation, diarrhea) (Table 2, Figure 1).

At the start of the study, 91% of pa-

TABLE 2
Symptom frequency and severity during treatment with trimebutine maleate (all patients combined)

Symptom	Day 0	Day 14	Day 28	P ‡
Pain				
Patients affected (%)*	91	77	59	<0.005
Mean severity score (± SEM)†	3.1±0.1	2.2±0.1	2.0±0.1	<0.001
Patients improved (%)		63	72	
Number of days per week with pain	4.9±0.2	3.4±0.3	2.6±0.3	<0.001
Constipation				
Patients affected (%)*	56	47	39	
Mean severity score (± SEM)†	2.1±0.1	1.8±0.1	1.6±0.1	<0.001
Patients improved (%)		37	39	
Number of stools per day (± SEM)	2.4±0.2	1.6±0.1	1.4±0.1	<0.001
Diarrhea				
Patients affected (%)*	70	48	35	
Mean severity score (± SEM)†	2.5±0.1	1.8±0.1	1.5±0.1	<0.001
Patients improved (%)		55	56	
Number of stools per day (± SEM)	4.4±0.3	1.4±0.1	1.2±0.1	<0.001

** Missing data excluded; † 1 Absent; 2 Slight; 3 Moderate; 4 Severe; 5 Incapacitating; ‡ Difference between day 0 and day 28*

tients suffered from pain; at the end of four weeks treatment, it was present in 59% and the mean pain severity score diminished from 3.1 to 2.0. Similarly, while 56% of patients presented with constipation (with or without alternating diarrhea) at entry into the study, only 39% reported it at the end of the study and the mean severity score fell from 2.1 to 1.6. As for diarrhea, 70% of the patients had this symptom (with or without alternating constipation) at the start of the study and 35% at the conclusion. The mean diarrhea severity score was reduced from 2.5 to 1.5.

These results were confirmed when the data were re-analyzed by symptom subgroups, (Table 3, Figure 2) based on classification presented at the onset of the study (pain, constipation and diarrhea).

In patients with alternating constipation and diarrhea, 58% and 65% no longer had constipation or diarrhea at the end of the study, respectively (as compared to 24% and 6%, respectively prior to the study). The mean constipation severity score was reduced from 2.3 to 1.6 and diarrhea severity from 3.0 to 1.4 (Table 4).

Symptom improvement: After four weeks treatment, pain improved by at least one score level in 78% of patients in the pain subgroup, constipation in 65% and diarrhea in 74% of patients in the respective symptom subgroups. Over 80% of patients with alternating bowel habit showed improvement (Table 3). The mean severity score was reduced by 1.3 in all the subgroups.

TABLE 3
Symptom frequency and severity during treatment with trimebutine maleate (by initial symptom subgroup classification)

Subgroup	Symptom	Day 0	Day 14	Day 28	P‡
Pain	Pain				
	Patients affected (%)*	99	83	62	<0.005
	Mean severity score (± SEM)†	3.3±0.1	2.3±0.1	2.0±0.1	<0.001
	Patients improved (%)		69	78	
	Number of days per week with pain	5.2±0.2	3.6± 0.3	2.7±0.4	<0.001
Constipation	Constipation				
	Patients affected (%)*	94	84	66	
	Mean severity score (± SEM)†	3.4±0.2	2.5±0.2	2.1±0.2	<0.001
	Patients improved (%)		55	65	
Diarrhea	Diarrhea				
	Patients affected (%)*	100	70	59	
	Mean severity score (± SEM)†	3.2±0.1	2.1±0.2	1.9±0.2	<0.001
	Patients improved (%)		64	74	
Alternating bowel habit					
	Constipation				
	Patients affected (%)*	76	48	42	
	Mean severity score (± SEM)†	2.3±0.2	1.8±0.2	1.6±0.2	<0.001
	Patients improved (%)		52	80	
	Diarrhea				
	Patients affected (%)*	94	60	35	
	Mean severity score (± SEM)†	3.0±0.1	1.7±0.1	1.4±0.1	<0.001
	Patients improved (%)		52	84	

** Missing data excluded; † 1 Absent; 2 Slight; 3 Moderate; 4 Severe; 5 Incapacitating; ‡ Difference between day 0 and day 28*

TABLE 4
Stool frequency during treatment with trimebutine maleate

Subgroup	Number of stools per day		
	Day 0	Day 14	Day 28*
Constipation	0.8±0.1	1.1±0.2	1.1±0.2
Diarrhea	4.7±0.6	2.7±0.3	2.5±0.2
Alternating bowel habit	4.4±0.3	1.4±0.1	1.2±0.1

** P<0.001 compared to day 0*

Incidence of pain: In the pain subgroup, incidence of pain was significantly reduced from a mean of 5.2 to 2.7 days per week and the percentage of patients reporting pain decreased from 99 to 62% (Table 3).

Bowel habit: The number of patients with stool frequency within the normal range (three per day to three per week) increased significantly from 64 to 85% following treatment (Table 4, Figure 3).

Stool consistency became significantly ($P<0.0001$) more frequently normal in the entire study sample. Abnormal stool consistency (watery or hard) was reported 76% of the time prior to and 34% following treatment.

Global evaluation: Overall condition was assessed as better than before treatment in about 70% of the patients. Only six patients considered their condition worse (Table 5).

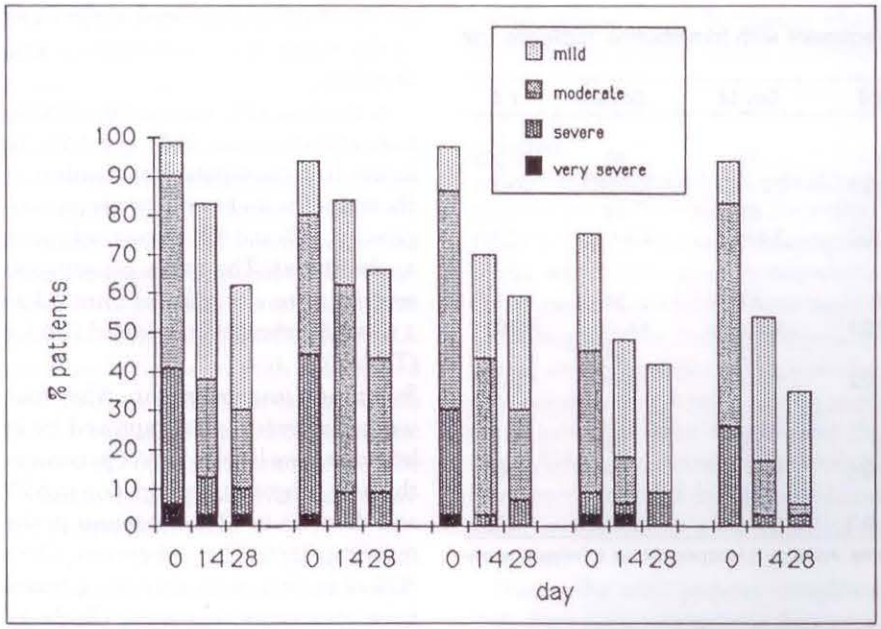

Figure 2) *Severity of symptoms, separate symptom subgroups. Subgroups (from left to right) pain; constipation; diarrhea; constipation (with or without alternating diarrhea); diarrhea (with or without alternating constipation)*

Side effects: Fourteen patients (11%) reported side effects (Table 6). These lead to discontinuation of therapy in seven patients. Some of these reactions may have been related to the condition (eg, nausea) rather than to the drug.

DISCUSSION

Studies of effect of drugs on IBS typically pool all patient subgroups in their analysis. Separating the various symptom subgroups, as defined prior to therapy, refines the data analysis. This makes it possible to assess better the effect of a treatment on a particular symptom by including mostly symptomatic patients and excluding those suffering from symptoms that are at opposite extremes from each other (eg, constipation/diarrhea).

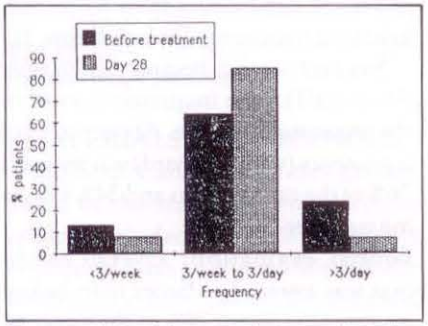

Figure 3) *Stool frequency before and 28 days after treatment. Three per week to three per day is considered normal*

TABLE 5
Global evaluation: Patient's overall condition at the end of treatment

	Better	No change	Worse
Physician's assessment	89 (69%)	39 (30%)	1 (1%)
Patient's assessment	84 (71%)	29 (24%)	6 (5%)

TABLE 6
Side effects of trimebutine

Side effect	Number of patients affected
Nausea	4
Headache	3
Fatigue	1
Foul smell/taste	2
Cutaneous rash/pruritus	1
Blurred vision	1*
Dizziness + swelling of hands	1†
Muscular pains	1
Total	14

** Concomitant glaucoma; † Not thought to be drug related*

Trimebutine maleate was shown to significantly reduce the frequency and severity of the major symptoms of IBS. Each of the symptoms improved in 65 to 80% of the patients reported to suffer from them. The trial confirmed results obtained in preclinical and clinical studies in that it exerts a bivalent action on gastrointestinal transit by normalizing stool frequency and consistency, regardless of the initial type of transit disturbance. This may be explained by trimebutine maleate's activity which may differ according to the different sites of the gastrointestinal tract (1) and/or the different activity states of the colon (3). Abdominal pain improved in over 80% of patients and disappeared in over 40%.

Symptom improvement obtained with trimebutine maleate occurred within the first two weeks of treatment and was sustained or continued up to the end of the study. Patients continuing treatment beyond the duration of the study report continued long term benefit. It appears that, in certain patients, the efficacy of the drug increases with continued treatment. The drug was generally well tolerated and offers a viable all round therapeutic alternative in the treatment of IBS.

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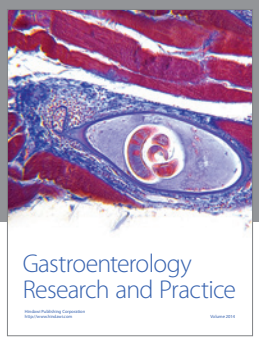

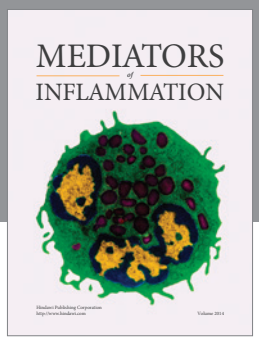

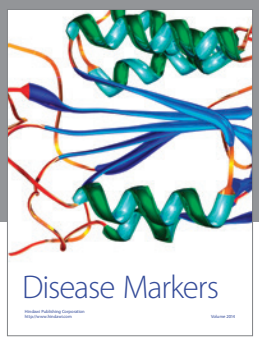

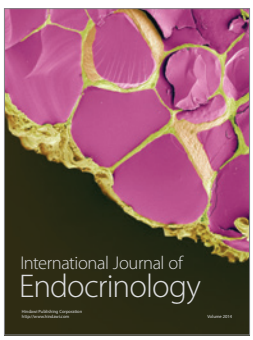

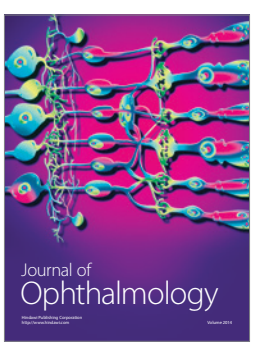

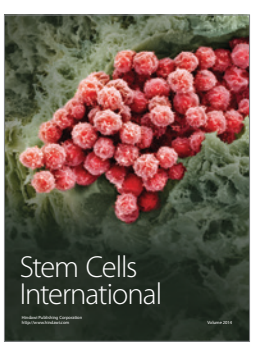

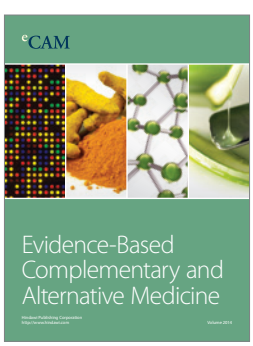

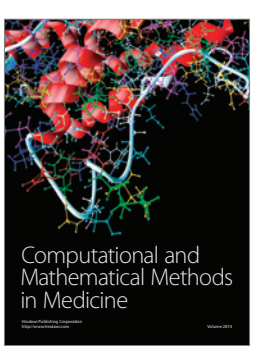

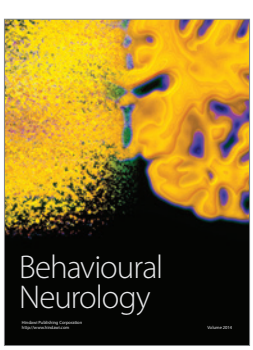

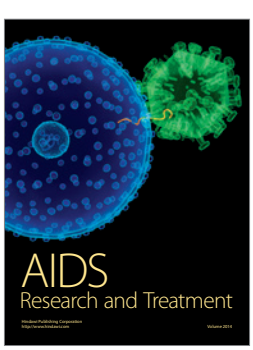

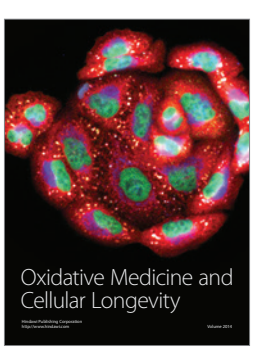

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