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Effects of oral pinaverium bromide on colonic response to food in irritable bowel syndrome patients

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Summary – We have recently developed a simple method to investigate the colonic response to food (CRF). This study describes the modifications of CRF induced by treatment with oral pinaverium bromide in irritable bowel syndrome (IBS) patients.
Thirty healthy subjects and 43 patients suffering from IBS were studied. Colonic transit time (CTT) was measured in fasting conditions and after eating a standard test meal. Colonic response to food was quantified by calculating the variation in number of markers in each zone of interest of the large bowel between the X-ray films of the abdomen taken before and after eating.
CRF is characterized by caudal propulsion of colonic contents in the two groups. In controls, there is emptying of the caecum-ascending colon region and filling of the rectosigmoid. In IBS patients, only the left transverse colon and the splenic flexure empty. Pinaverium bromide exerts no effect in controls but reverses the CRF of the right colon in IBS patients by inhibiting right colon emptying.
These results suggest that the inhibitory action of pinaverium bromide on CRF may support the clinical efficacy of this calcium channel blocker in the treatment of IBS. © 2000 Éditions scientifiques et médicales Elsevier SAS

drug evaluation / meal / placebo effect / transit

Pinaverium bromide is a spasmolytic agent with powerful muscolotropic action and a very weak neurotropic component [12]. The spasmolytic action of this quaternary ammonium derivative [4-(6-bromoveratyl)-4{2-[2-(6,6-dimethyl-2-norpinyl)-ethoxyl]-ethyl}-morpholinium hydroxyde] has been related to a calcium channel blocking action similar to that of verapamil [7, 19]. These properties explain the decrease in colonic motility observed in conscious dogs [26] and in men after eating [23], and its clinical efficacy to treat IBS observed in several double-blind studies [38].

Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain is associated with change of bowel habit and abdominal distension [41]. The recognition of clusters of symptoms provides an IBS diagnosis with reasonable reliability. This approach has led to a wide recognition and adoption of Manning's criteria [27] and more recently, of the Rome criteria [41].

IBS patients have altered colonic motility and are often hypersensitive to various stimuli, such as stress, food or distension [28]. The nature of colonic motility response to food nevertheless is the subject of controversy: it has been found to be increased [30], delayed [40], or decreased [18, 23]. The colonic response to food (CRF) is an integrated function of the colon, characterized by an increase in magnitude and frequency of colonic contractions [17]. Neural or hormonal pathways have been implicated but no clear mechanism of food action has been described [17]. We have recently described a simple and low-cost method of estimating CRF based on propagation of radiopaque markers [10].

The aim of the present study is to compare the effect of oral pinaverium bromide on colonic transit and colonic response to food in healthy controls and IBS patients.

PATIENTS AND METHODS

Subjects

Studies were performed in 30 control subjects (19 females and 11 males, 19–36 years old) and 43 IBS subjects (38 females and five males, 19–68 years old). Informed consent was obtained from all subjects.

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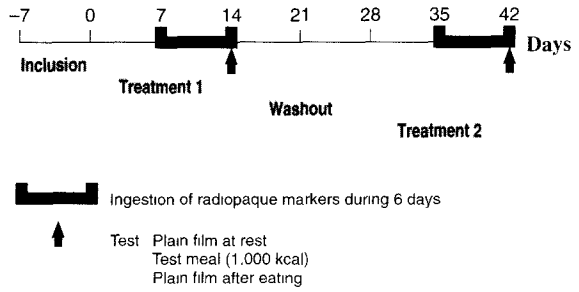

Figure 1. Schedule of the study. For every subject, two tests were performed after 14 days of each treatment. Each test was composed of two measurements of colonic transit time, one at rest and one 30 minutes after ingestion of a standard test-meal

All patients had been referred to the laboratory of digestive physiology at the Laennec hospital with IBS symptoms as defined by the Manning [27] and Rome criteria [41]. These symptoms lasted for more than two years (M ± SD 18 ± 13 years; range 2 to 60 years). Lactase deficiency was excluded by history. Organic, infectious and parasitic diseases were excluded by colonoscopic examination, barium enema, anorectal manometry, laboratory tests, stool examination and culture.

Experimental procedure

The local ethics committee (CCPRB, Ile-de-France–Paris Saint-Antoine, #92022), approved the protocol for the study. The experimental design *(figure 1)* included two randomized studies (placebo and drug studies) of colonic transit time with films taken at rest and after eating a standard test meal, in every subject. An interval of 14 days separated the two studies in the same patient.

Colonic transit was measured with a previously described technique [9]. Briefly, 24 radiopaque markers within a gelatin capsule were ingested from day 1 to day 6 at 9:00 a.m. A plain film of the abdomen was taken on the seventh day, at 9:00 a.m., at rest. Thereafter a standard test-meal (1,000 kcal, proteins: 32 g, lipids: 47 g, glucides: 112 g) was ingested, and a second plain film (postprandial film) was taken at 11:00 a.m.

Data analysis

Markers were localized and counted in the different segments of the large bowel according to bony landmarks and gaseous outlines, as classically described [9]. The spinal column served to separate the right from the left colon; the pelvic inlet was taken to separate the rectosigmoid area from the left colon. The colon was also divided into seven

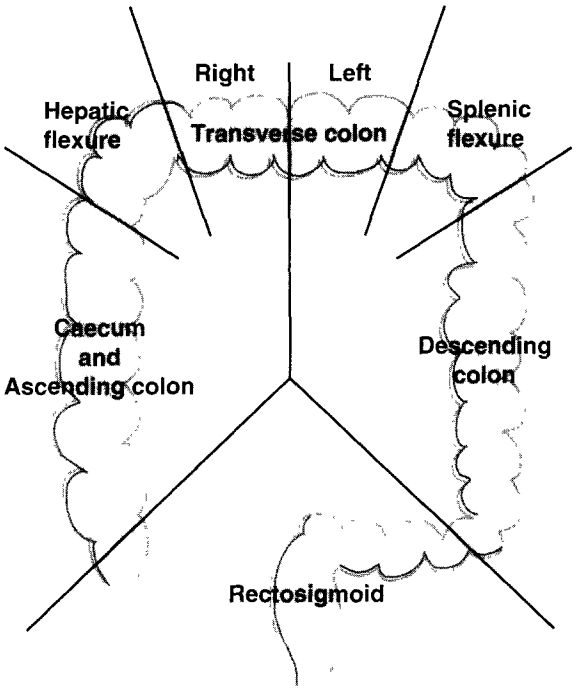

Figure 2. The abdomen was divided into seven zones according to bony landmarks and gaseous outlines: caecum and ascending colon, hepatic flexure, right transverse colon, left transverse colon, splenic flexure, descending colon, rectosigmoid segment

zones to order to have a better description of the movements of markers [10] *(figure 2)*.

Segmental and total colorectal transit times (CTT) were calculated according to the distribution of the markers in the different segments of bowel. This was done, using the equation $CTT = \frac{\Delta T}{N} . n$, where: ΔT is the time between two ingestion of markers, N is the number of markers ingested at each intake, and n is the number of markers in the zone of interest. According to the values used in the present study (N = 24 radiopaque markers, T = 24 hours):

$$\mathrm{CTT} = \frac{24}{24} n = n.$$

Colonic transit response to food

The colonic transit response to food was quantified by determining the variation in number of markers in each zone of interest between the film taken after eating and that before eating. The response was negative when a decrease in number of markers was found (i.e., emptying of the zone) and positive when an increase was found (i.e., filling of the zone).

Statistical analysis

Analysis was performed by using ANOVA for repeated measures using Bonferoni adjustments (FOVEA, 3 bis, chemin de la Jonchère, 92500 Rueil Malmaison, France). Parameters to analyse were the differences between healthy controls and IBS patients, the change in number of markers induced by the meal and the differences between the placebo and the drug study. Differences between the two groups were compared by the Wilcoxon test.

RESULTS

Placebo study

Colonic transit time during fasting conditions

Total CTT was increased in IBS patients by comparison with the healthy controls, (74.3 ± 6.1 h vs 46.4 ± 4.5 h; $P = 0.0006$). This was related to a delay in the right and left part of the colon *(table I)*. The main difference was found in the transit time through the descending colon (18.2 ± 2.4 h vs 8.3 ± 1.3 h; $P = 0.0006$).

Colonic transit time after eating

After eating, similar results were found. IBS patients have a delayed transit in the right ($P = 0.0204$) and left colon ($P = 0.0005$) *(table II)*. Transit of the rectosigmoid area was not significantly different.

Colonic transit response to food

The test-meal induced caudal propulsion of colonic contents both in healthy controls and in IBS patients *(table III)*. In healthy controls, after eating, a significant emptying of the right colon occurred ($P = 0.0142$), due to emptying of the caecum-ascending colon zone ($P = 0.0256$) and filling of the rectosigmoid ($P = 0.0047$). In contrast, in IBS patients, emptying of the right colon was not significant and limited to emptying of its proximal portion ($P = 0.0102$). Filling of the rectosigmoid was not significant either. Significant changes were found only in the left part of the colon, consisting in net emptying of the left colon ($P = 0.0102$) because of emptying of the left transverse colon ($P = 0.0249$) and the splenic flexure ($P = 0.0024$). These results are summarized in *figure 3*.

Because of the great variation of the colonic response found in the left colon, no significant difference between IBS patients and healthy subjects was found in intensity of colonic response to food.

Action of pinaverium bromide *(figure 4)*

Colonic transit time during fasting conditions

Pinaverium bromide did not modify segmental or total CTT either in healthy controls or in IBS patients *(table I)*.

Colonic transit time after eating

Pinaverium bromide had no effect either on colonic transit time after meal, and this both in healthy controls and in IBS patients *(table II)*.

Colonic transit response to food

Ingestion of the test meal, under the influence of pinaverium bromide, results in caudal propulsion of colonic contents in the two groups *(table III)*. In healthy controls, after meal, there was no effect of the medication: just as under placebo, significant emptying of the

Table I. Total and segmental colonic transit time (M ± SEM) during fasting conditions.

	Placebo			*Pinaverium bromide*			*Pinaverium bromide vs Placebo*	
	Group		*Controls vs IBS*	*Group*		*Controls vs IBS*	*Controls*	*IBS*
Segment	*Controls (N = 30)*	*IBS (N = 43)*	P-*value*	*Controls (N = 30)*	*IBS (N = 43)*	P-*value*	P-*value*	P-*value*
Caecum and ascending colon	14.0 ± 1.4	18.5 ± 2.1	NS	15.0 ± 1.9	20.9 ± 2.1	0.00379	NS	NS
Hepatic flexure	1.7 ± 0.5	1.9 ± 0.5	NS	1.2 ± 0.4	1.5 ± 0.6	NS	NS	NS
Right transverse colon	4.0 ± 1.2	6.3 ± 1.1	NS	2.5 ± 0.5	6.8 ± 1.2	0.0020	NS	NS
Right colon	19 7 ± 1.8	26.7 ± 2.8	0.0362	18.7 ± 2.2	29.2 ± 2.8	0.0051	NS	NS
Left transverse colon	3.3 ± 0.9	7.2 ± 1.5	0.0241	3 4 ± 1.0	5.8 ± 1.0	NS	NS	NS
Splenic flexure	2.6 ± 0.8	3.7 ± 0.7	NS	1.7 ± 0.6	3.0 ± 0.9	NS	NS	NS
Descending colon	8.4 ± 1.3	18.2 ± 2.4	0.0006	7.1 ± 1.2	20.7 ± 2.2	< 0.0001	NS	NS
Left colon	14.3 ± 2.4	29.1 ± 3.0	0.0002	12.2 ± 1 9	29.5 ± 3.0	< 0.0001	NS	NS
Rectosigmoid area	12.4 ± 2.2	18.5 ± 2.7	NS	13.9 ± 2.3	16.3 ± 1.9	NS	NS	NS
Total colonic transit	46.4 ± 4.5	74.3 ± 6.3	0.0006	44.8 ± 3.9	75.0 ± 5 7	0.0001	NS	NS

Table II. Total and segmental colonic transit time (M ± SEM) after meal.

	Placebo			*Pinaverium bromide*			*Pinaverium bromide vs Placebo*	
	Group		*Controls vs IBS*	*Group*		*Controls vs IBS*	*Controls*	*IBS*
Segment	*Controls (N = 30)*	*IBS (N = 43)*	P-*value*	*Controls (N = 30)*	*IBS (N = 43)*	P-*value*	P-*value*	P-*value*
Caecum and ascending colon	12.0 ± 1.5	16.4 ± 1 9	NS	12.1 ± 1.5	20 3 ± 2.2	0.0031	NS	NS
Hepatic flexure	1 9 ± 0.6	2.4 ± 1.0	NS	1.6 ± 0.3	2.2 ± 0 6	NS	NS	NS
Right transverse colon	3.9 ± 1 1	7.3 ± 1.3	NS	2.6 ± 0.8	7.7 ± 1 4	0.0014	NS	NS
Right colon	17.8 ± 1.9	26.1 ± 2.9	0.0204	16.3 ± 1.8	30.2 ± 2.9	0.0002	NS	NS
Left transverse colon	3.5 ± 0.9	5.4 ± 1 0	NS	2 50.8	5.2 ± 1.0	0 0322	NS	NS
Splenic flexure	1.7 ± 0.6	2.2 ± 0.6	NS	2.3 ± 0 9	1.9 ± 0.8	NS	NS	NS
Descending colon	8.1 ± 1.6	19.4 ± 2.4	0 0002	5.8 ± 1.1	19.0 ± 2.2	< 0.0001	NS	NS
Left colon	13.3 ± 2 3	27 0 ± 2.8	0.0005	10.6 ± 1 9	26.1 ± 2.8	< 0.0001	NS	NS
Rectosigmoid area	15.3 ± 2.3	21 2 ± 3.1	NS	17.9 ± 2.4	18.7 ± 2.1	NS	NS	NS
Total colonic transit	46 4 ± 4.5	74.3 ± 6.3	0.0006	44.8 ± 3 9	75.0 ± 5.7	0.0001	NS	NS

Table III. Colonic transit response to food (M ± SEM).

	Healthy controls (N = 30)					*IBS patients (N = 43)*				
	Placebo		*Pinaverium bromide (PB)*		*PB vs Placebo*	*Placebo*		*Pinaverium bromide*		*PB vs Placebo*
Segment		P-*value (vs no action)*		P-*value (vs no action)*	P-*value*		P-*value (vs no action)*		P-*value (vs no action)*	P-*value*
Caecum and ascending colon	–2.0 ± 0.8	0.0256	–2.9 ± 1.0	0.008	NS	–2.1 ± 0.8	0 0102	–0.6 ± 0.7	NS	NS
Hepatic flexure	0 2 ± 0.6	NS	0.4 ± 0.3	NS	NS	0.5 ± 0.9	NS	0.7 ± 0.7	NS	NS
Right transverse colon	–0 1 ± 0.6	NS	0.1 ± 0.4	NS	NS	1.0 ± 0.7	NS	0.9 ± 0 6	NS	NS
Right colon	–1.9 ± 0.7	0.0142	–2.4 ± 1.1	0.023	NS	–0.6 ± 0.9	NS	1.0 ± 1.0	NS	NS
Left Transverse colon	0.2 ± 0.9	NS	–0 9 ± 0.5	NS	NS	–1 8 ± 1.0	0.025	–0.6 ± 0.7	NS	NS
Splenic flexure	–0.9 ± 0.5	NS	0.6 ± 0.7	NS	NS	–1.5 ± 0.5	0.002	–1.1 ± 0.8	NS	NS
Descending colon	–0.3 ± 0.9	NS	–1.3 ± 0.9	NS	NS	1.2 ± 1.1	NS	–1.7 ± 0.8	0.0477	0.048
Left colon	–1.0 ± 1.0	NS	–1.6 ± 1 3	NS	NS	–2.1 ± 1.6	0.010	–3.4 ± 0.8	0.0022	NS
Rectosigmoid area	2.9 ± 0.9	0.0047	4.0 ± 1 6	0.028	NS	2.7 ± 1.8	NS	2.4 ± 0.7	0 0023	NS

right colon ($P = 0.0228$) occurred, as a result of emptying of the caecum-ascending colon area ($P = 0.0084$), and filling of the rectosigmoid ($P = 0.0281$). In contrast, under treatment, in IBS patients, there was no significant emptying of any zone of the right colon *(table III)*. There was emptying of the left colon ($P = 0.0022$), because of emptying of the descending colon ($P = 0.0477$). In addition, there was significant filling of the rectosigmoid ($P = 0.0023$).

Under treatment, the statistical comparison of the intensity of the colonic response to food in the two groups showed only one significant difference *(figure 4)*: the response of the right colon ($P = 0.0159$). In healthy controls, there was emptying of this area (–2.4 ± 1.1), and in IBS patients, filling (1.0 ± 1.0).

DISCUSSION

The use of radiopaque markers permits the measurement of colonic transit time and the analysis of the colonic response to food as an expression of transit (i.e., propulsion of the bolus induced by the food intake). We applied this technique to the study of the action of pinaverium bromide on CRF. Our results indicate that pinaverium bromide inhibits the colonic response to food only in IBS patients. It decreases significantly the emptying of the right colon. A previous study has shown that pinaverium bromide suppresses the increase of electromyographic activity [23]. These results may explain the clinical efficacy of this drug in the treatment of IBS by its action on the colonic response to food [16, 33].

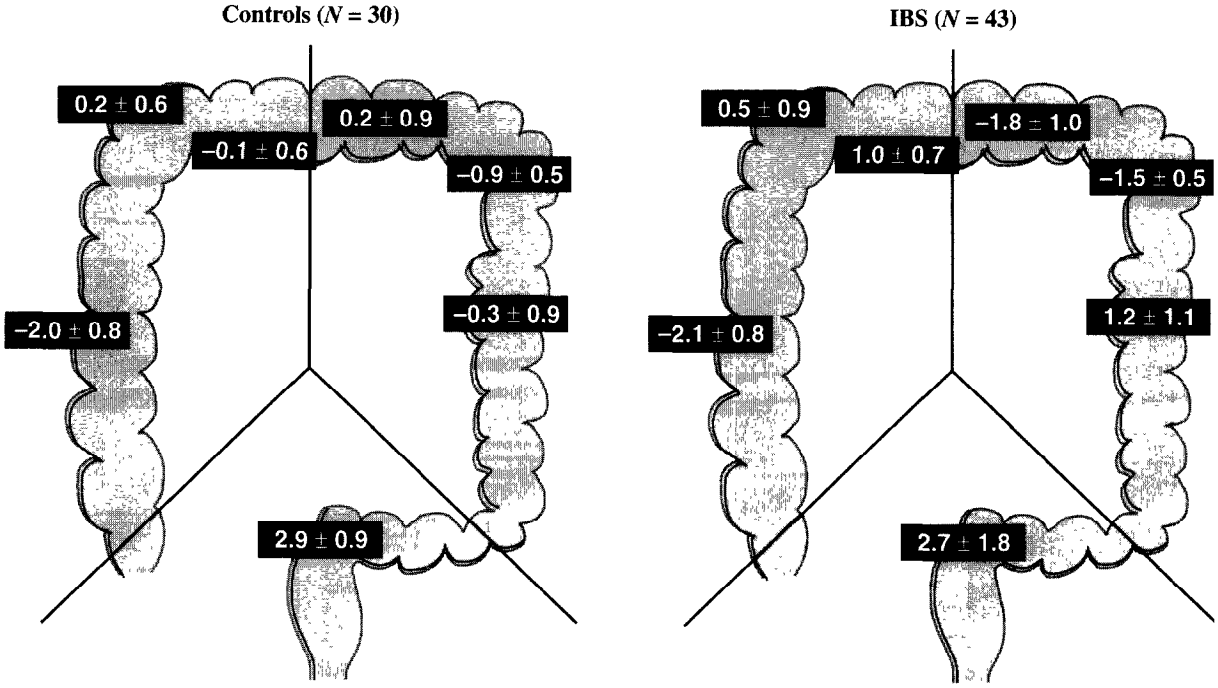

Figure 3. Movement of radiopaque markers after ingestion of a test meal in control subjects and IBS patients. In the two groups, there is emptying of the first part of the colon and filling of the terminal intestine. However, in IBS patients, abnormal emptying of the left transverse colon is associated to filling of the right transverse colon (retrograde mass movement) and filling of the descending colon (anterograde mass movement).

In humans, the changes in colonic motility after meal have been studied by several techniques. Manometry [8, 30, 36, 43], electromyography [6, 18], scintigraphy [15, 32], and telemetry [42] have been used alone or in association to describe meal-induced changes in motor activity. These techniques are not of practical use in the clinical evaluation of outpatients. This explain why the postprandial rhythmic modulation of gastrointestinal motility, so important a physiological phenomenon, is not used to define the subtypes of functional bowel disorders [20]. The technique used in the present study is simple, cheap and easily practicable in the evaluation of outpatients.

In IBS patients, pain is often related to meals [14, 39]. Thus, it is not surprising that their colonic myoelectric and motor response to meals is different from that in healthy controls [40]. The most commonly found abnormality is a prolonged colonic motor response to food [28]. The importance of meal composition in the genesis of colonic response to food has been emphasized; thus, low-fat or high-protein diets have been recommended to inhibit the colonic response to food [34, 43]. In our test meal, fat constituted 43% of the caloric intake. Nevertheless, no abdominal pain was reported during the test.

In IBS patients, anticholinergic medications inhibit the late colonic response to food [25, 37, 40]. A lot of interest has been addressed to the potential effects of calcium antagonists on colonic motility disorders [2, 11, 21, 35, 38]. Pinaverium bromide is a calcium antagonist, which is poorly absorbed and acts locally. This drug has no cardiovascular or systemic effect [12]. In two previous studies, pinaverium bromide was found to accelerate the transit of radiopaque markers through the colon [4, 24], in contrast to nifedipine and verapamil, which induce constipation [5, 13, 29, 30]. In the present study, in the fasting state, pinaverium bromide did not influence total or segmental transit time either in controls or IBS patients. This could be due to the dose which was used (100 mg 3 times per day in the present study vs 50 mg 3 times per day in the previous studies), or to timing of the measurements as related to meals: using fasting conditions in the present study, but not defined in the previous ones.

Calcium channel blockers, such as nifedipine [5, 30], octylonium bromide [3, 31], nicardipine [33, 42, 43], and pinaverium bromide [1, 23] decrease the colonic response to food. The clinical efficacy of these drugs is related to this postprandial inhibition of myoelectric spike activity [1, 23, 26]. Our study shows that after

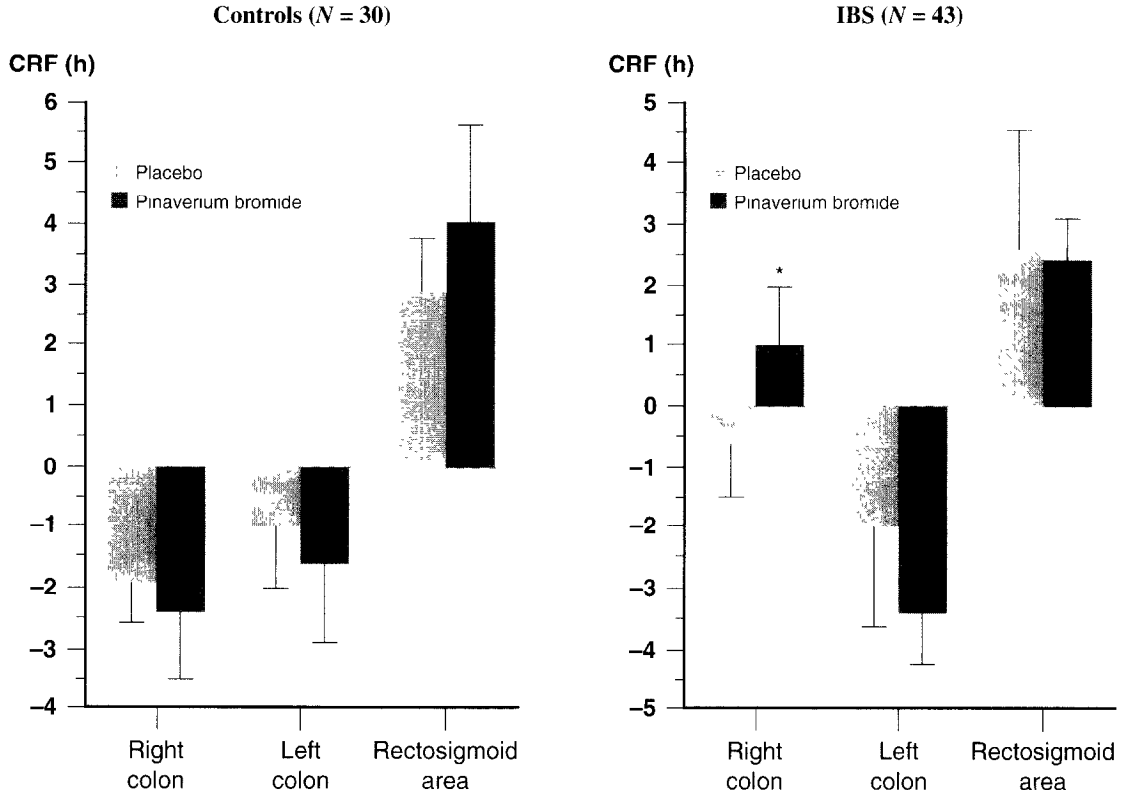

Figure 4. Modification of the colonic transit response to eating after pinaverium bromide treatment in healthy controls and IBS patients. Pinaverium bromide reverses the colonic transit response to eating in the right colon (*. $P = 0.0159$).

eating, pinaverium bromide reverses, in IBS patients, the normal response to food of the ascending colon. In contrast, in healthy controls, similar movements of markers were found during the period of drug or placebo ingestion. This result confirms the action of pinaverium bromide on the colonic response to food in IBS patients and adds some precision on its site of action. The mechanism of action of pinaverium bromide on the colonic response to food has been recently clarified. It reduces the contractions induced by CCK on isolated muscular cells that inhibit the CCK component of the colonic response to food [22].

In conclusion, pinaverium bromide decreases the colonic transit response to food in IBS patients.

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