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INHIBITION OF THE COLONIC MOTOR RESPONSE TO EATING BY PINAVERIUM BROMIDE IN IRRITABLE BOWEL SYNDROME PATIENTS

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Summary – The effect of pinaverium bromide on the colonic motor response to eating was investigated in 10 irritable bowel syndrome patients, by means of an intraluminal probe supporting 8 groups of electrodes. At each site examined from transverse to sigmoid colon, the electromyograms exhibited 2 kinds of spike bursts: short spike bursts (SSB) localized at one electrode, and long spike bursts (LSB), isolated, propagated orally or aborally over a few centimeters, or aborally propagated over the whole length of the colon investigated (migrating long spike bursts, MLSB). Recordings were continuously performed over 24 hr. Each patient received at 7.00 p.m. on day 1 and at noon on day 2 an 800-1000 Kcal meal preceded by IV administration of pinaverium bromide (4 mg) or placebo.

After placebo administration, the duration of LSB activity and the number of MLSB were significantly increased over 3 postprandial hr by comparison with the 2 hr preceding the meal. After pinaverium injection no significant postprandial change in LSB and MLSB activity was noted. The SSB activity was not modified after the meals preceded by placebo or pinaverium injection.

These results suggest that the inhibitory action of pinaverium bromide on postprandial colonic motility may support the clinical efficacy of this agent in the treatment of the irritable bowel syndrome.

colonic motility / pinaverium bromide / irritable bowel syndrome / calcium channel blockers

Introduction

The quaternary ammonium derivative 4-(6-bromoveratyl)-4{2-[2-(6,6-dimethyl-2-norpinyl)-ethoxyl]-ethyl}-morpholinium hydroxide, or pinaverium bromide, is a spasmolytic agent with powerful musculotropic action and a very weak neurotropic component (Baronnet *et al.*, 1974). In the guinea pig ileum *in vitro*, the spasmolytic action of pinaverium bromide is approximately 10 times greater than that of papaverine and its anticholinergic action corresponds to 1/400 to 1/1000 that of atropine (Bretaudeau *et al.*, 1975). Its spasmolytic action has been found to be mediated through an effect on calcium channels similar to that of verapamil (Droogmans *et al.*, 1983; Baumgartner *et al.*, 1985).

These properties correspond to an inhibitory action on gastrointestinal and colonic motility, shown in conscious animals (Itoh and Takahashi, 1978). On the other hand, several double-blind clinical studies point to a significant effect of this compound on the irritable colon (Dubarry and Quinton, 1977; Levy *et al.*, 1977; Del-

mont, 1981). However, as far as we know, no study on the effect of pinaverium bromide on colonic motility has been performed in humans.

This study, using an electromyographic technique, was undertaken to determine whether pinaverium bromide inhibits colonic motility in irritable bowel syndrome (IBS) patients. According to the great diurnal fluctuations of colonic motility associated with meals and sleep (Frexinos *et al.*, 1985) the study was focused on the effect of the compound on the colonic motor response to eating.

Method

Patients

The protocol for the study was approved by the Ethical Committee of the Medical Faculty of the University of Toulouse (25 November 1985). Colonic myoelectrical activity was recorded in 10 patients with functional colonic disorders: 3 women and 7 men aged 31–68 yr (Table I). The absence of overt colonic lesions was confirmed endoscopically.

Patients presented abdominal pain either associated with chronic diarrhea or constipation, or without disturbance of bowel habits. Symptoms had lasted longer than 6 months.

Recording system

Colonic myoelectrical activity was recorded by use of a probe made of a polyvinyl tube, 0.5 cm in diameter and 150 cm in length, supporting 8 groups of 3 annular electrodes at 17-cm intervals, with the first group located 10 cm from the tip (Fioramonti *et al.*, 1980). Each electrode consisted of a ring of nickel-chrome wire fixed around the probe in groups of 3 at 4-mm intervals. A 180-cm-long thread was attached to the tip of the tube. Bipolar recordings were made with an 8-channel electroencephalograph (Minihuit Alvar, Paris) with a short time constant (0.03 s).

Table I. Patients and colonic area investigated.

Case No.	Sex	Age	Symptoms	Colonic location of the tip of the probe
1	M	57	Pain, chronic diarrhea	Transverse
2	M	43	Pain, distension, without disturbances of bowel habits	Descending
3	M	68	Moderate pain, chronic diarrhea	Descending
4	M	58	Pain, distension, without disturbances of bowel habits	Transverse
5	M	62	Pain, constipation	Descending
6	F	62	Pain, constipation, melanosis coli	Descending
7	F	57	Pain, without disturbances of bowel habits	Descending
8	M	43	Pain, constipation	Transverse
9	F	31	Pain, without disturbances of bowel habits	Transverse
10	M	53	Pain, constipation	Descending

Recording session

All subjects fasted for at least 14 hr before introduction of the probe, and careful bowel cleansing (tap water enema) was performed 24 hr and 12 hr before the probe was introduced into the colon by means of a flexible colonoscope (Olympus, CF1BW). The thread attached to the tip of the probe was introduced into the operator channel of the colonoscope and the 2 tubes were pushed together to reach the caecum. The colonoscope was then withdrawn and the position of the probe was noted under fluoroscopy. During colonoscopy, IV injections of fentanyl (0.1 mg, Janssen Lab., Paris) and diazepam (10 mg, Roche S.A., Neuilly) were given if necessary. They were followed by injection of naloxone (0.4 mg, Winthrop Lab., Clichy) at the end of the colonoscopy. To avoid any possible effect of colonoscopy, air insufflation, enemas, and medication, recording sessions began only at 5.00 p.m., *i.e.* 7–8 hr later, and lasted 24 hr. A meal was given at noon, 5 hr before the beginning of the recording session. An 800–1000 Kcal meal was then given at 7.00 p.m. on day 1. On day 2 a continental breakfast (< 300 Kcal) was given at 8.00 a.m. and a second meal (800–1000 Kcal) at noon. The position of the probe was radiographically confirmed 15 hr after the beginning of recording. The subjects remained in bed throughout the recording session.

In 4 patients colonic myoelectrical activity was recorded from the transverse to the sigmoid colon, and in the other 6, from the descending to the sigmoid colon.

Each patient received under double-blind conditions 15 min before the 7.00 p.m. meal either pinaverium bromide (Dicetel ND, a gift from LTM Laboratoires, 92 Suresnes, France) or placebo. The patient received placebo 15 min before the noon meal on the following day if pinaverium bromide had been given on day 1, or pinaverium bromide if he had already received placebo. Pinaverium bromide (4 mg dissolved in 10 ml saline) or placebo (10 ml saline) was slowly given IV. Decoding of administrations (pinaverium bromide or placebo) was performed at the end of the experimentation after analysis of the electromyograms.

Analysis of signals

The signals arising from 4 electrode sites were quantitatively analyzed by means of a microcomputer Epson HX 20 (Hachet *et al.*, 1985). Briefly, we distinguished 2 kinds of colonic spike bursts (Fioramonti and Buéno, 1980; Buéno *et al.*, 1980) on the electromyogram. The computing system recognized each kind of burst on the basis of its duration and gave the time occupied by each kind of burst every 60 min for each channel. Moreover, the number of spike bursts propagated over the whole length of the colon investigated was measured by visual inspection of the 8-channel records.

The postprandial changes in spiking activity, expressed as the time of recording occupied by each kind of spike burst, under placebo or pinaverium, were determined by comparing values obtained for 2 hr before, and 1, 2, or 3 hr after the meals (*t*-Wilcoxon test). For each patient, the value given corresponds to the mean activity of 4 electrode sites from the transverse or the descending colon to the rectosigmoid junction, according to the location of the tip of the probe (Table I).

Results

In all patients the 2 kinds of colonic spiking activity previously described in healthy subjects, as well as in IBS patients (Buéno *et al.*, 1980), were observed (Fig. 1). The first kind consisted of short spike bursts (SSB) lasting 3.1 ± 0.4 s and usually appearing rhythmically at an average rate of 10.3 ± 0.4 per min. These bursts were always localized at one electrode site and were not propagated to an adjacent group of electrodes. The second kind of spike activity consisted of long spike bursts (LSB) lasting

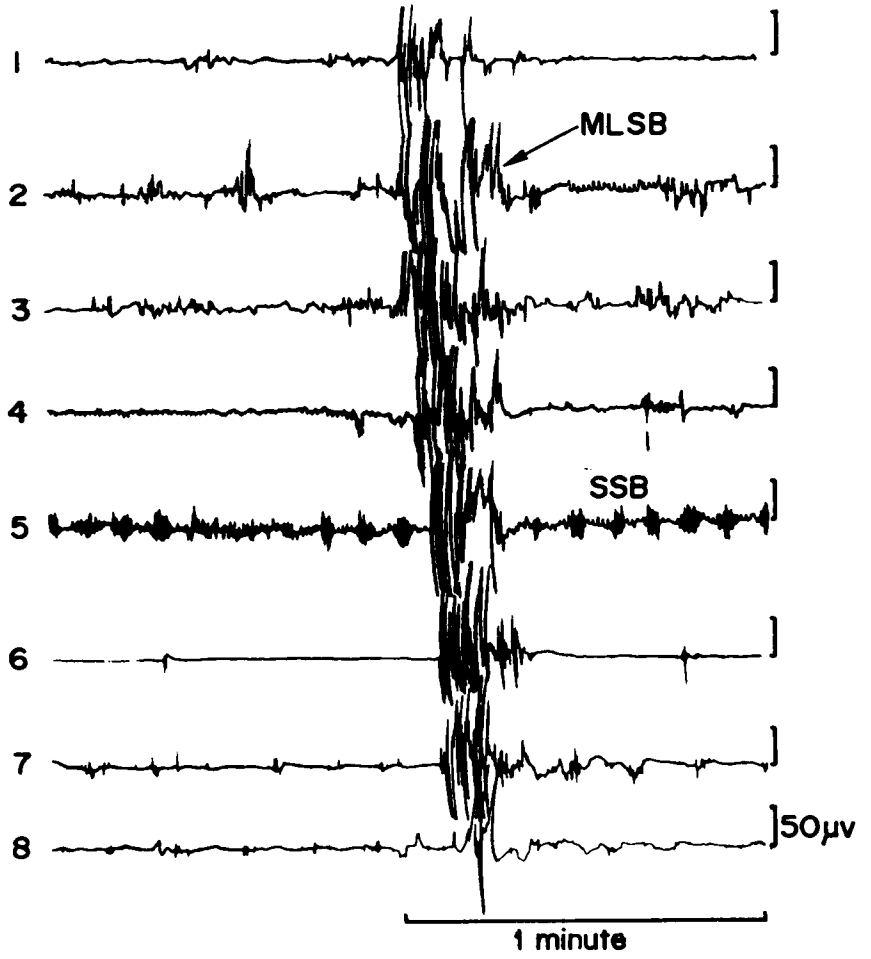

Fig. 1. Representative electromyogram obtained from the transverse colon (1) to the rectosigmoid junction (8). On the 5th channel a series of short spike bursts (SSB) appeared at a frequency of 11/min. A migrating long spike burst (MLSB) rapidly propagated over the whole length of the colon investigated.

10.3 ± 3.6 s and could appear in any of 3 patterns: (*a*) localized at one electrode site; (*b*) propagated over few centimeters in aboral or oral directions; (*c*) propagated in the aboral direction over the whole length of the colon investigated (migrating long spike bursts, MLSB). SSB have been found to be associated with contractions of small amplitude and probably correspond to tonic activity of the colonic wall, whereas it has been shown that LSB correspond to large-amplitude contractions responsible for mixing and propulsion of digested food (Buéno *et al.*, 1980).

Basal values of SSB and LSB activity during the 2 hr preceding the meal associated with pinaverium administration did not differ significantly ($P > 0.05$) from those

observed before the meal associated with placebo administration. Similarly, the number of MLSB observed before the meals with placebo and pinaverium was not significantly different (see Table III).

After administration of placebo or pinaverium and in comparison with values observed during the 2 hr before the meals, no significant ($P>0.05$) change in SSB activity appeared during the 3 hr following the meals. When placebo was administered before the meal, only 3 patients exhibited a clearcut postprandial increase in LSB activity (Fig. 2). However, the mean values of LSB activity for the 10 patients were significantly increased during the 3 hr following the meal (Table II). After pinaverium administration no significant postprandial increase in LSB activity was noted (Fig. 2, Table II).

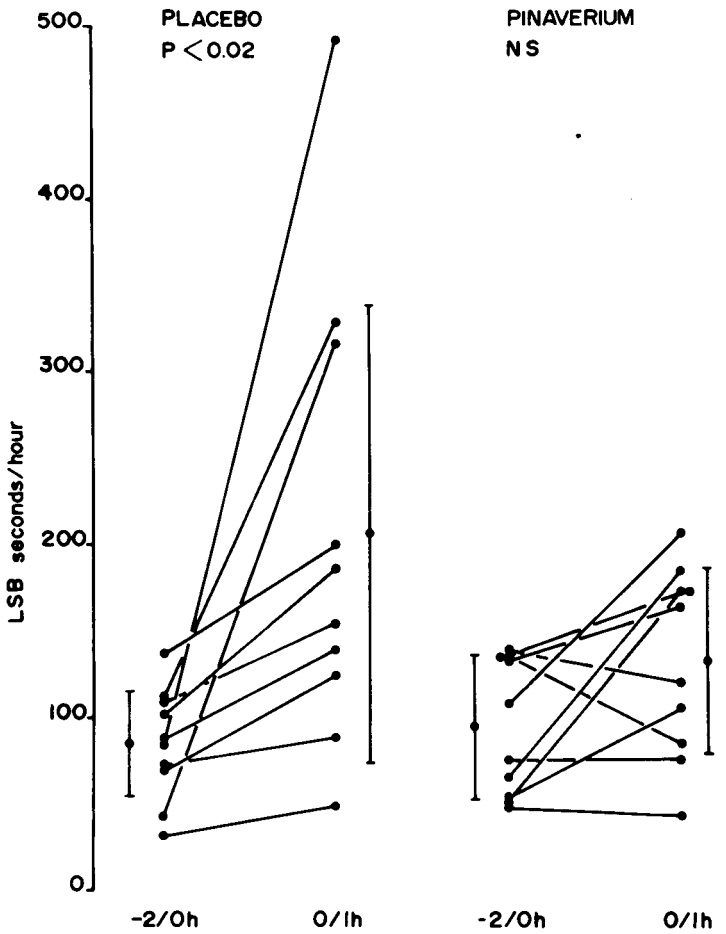

Fig. 2. Postprandial changes in long spike burst (LSB) activity in the 10 patients receiving placebo or pinaverium bromide (4 mg IV) 15 min before the meal. The significant ($P<0.02$) increase in LSB activity appearing during the Ist hr after a meal (placebo) was abolished by pinaverium administration.

Table II. Postprandial changes in SSB, LSB, and MLSB activity after placebo or pinaverium bromide (4 mg IV) administration (mean ± SD, $N = 10$).

Time after meal		−2/0 hr	0/1 hr	0/2 hr	0/3 hr
SSB	Placebo	17 ± 21	19 ± 27	24 ± 30	20 ± 25
(s/hr)	Pinaverium	22 ± 26	16 ± 19	23 ± 27	26 ± 31
LSB	Placebo	85 ± 31	207 ± 133[b]	163 ± 91[c]	143 ± 59[b]
(s/hr)	Pinaverium	94 ± 39	132 ± 54	103 ± 44	91 ± 39
MLSB	Placebo	4.7 ± 3.1	10.0 ± 6.8[a]	7.7 ± 4.3[a]	6.4 ± 3.5[c]
(No./hr)	Pinaverium	4.3 ± 2.4	6.6 ± 4.3	4.9 ± 2.1	4.5 ± 2.4

SSB, short spike burst; LSB, long spike burst; MLSB, migrating long spike burst.
a, b, c: significantly different (*a*, $P < 0.01$; *b*, $P < 0.02$; *c*, $P < 0.05$) from values observed during the 2 hr preceding the meal.

The number of MLSB observed during the 2 hr before the meal associated with placebo administration ranged between 0 and 10.5/hr and did not differ ($P > 0.05$) from the number observed before the meal preceded by pinaverium administration. After placebo administration the number of MLSB was significantly increased during the 3 postprandial hr, whereas no significant change appeared after the meals preceded by pinaverium administration (Fig. 3, Table II).

Discussion

Our results indicate that pinaverium bromide inhibits the colonic motor response to eating. This pharmacological action may support the agent's clinical efficacy in the treatment of the irritable bowel syndrome (IBS) (Dubarry and Quinton, 1977; Levy *et al.*, 1977; Delmont, 1981). Such a relationship between clinical efficacy and reduction of the postprandial colonic motor response has been already found for anticholinergic drugs (Murney and Winship, 1982; Sullivan *et al.*, 1978).

Disturbances of the colonic motor response to eating seem to be a major abnormality of colonic motility in IBS patients. However, controversial data have been reported. The colonic motor response to eating in IBS has been described as exaggerated (Narducci *et al.*, 1986), delayed (Sullivan *et al.*, 1978), or attenuated (Dapoigny *et al.*, 1985). These discrepancies may be attributed to the heterogeneity of the patients involved in these studies, but also to differences in the techniques used and the colonic area investigated. With a similar electromyographic technique, the colonic motor response to eating has been found reduced in IBS patients (Dapoigny *et al.*, 1985) compared with healthy subjects (Frexinos *et al.*, 1985) except in a subgroup of IBS patients characterized by painless diarrhea, for whom postprandial colonic motility was enhanced (Frexinos *et al.*, 1987). In our study the postprandial increase

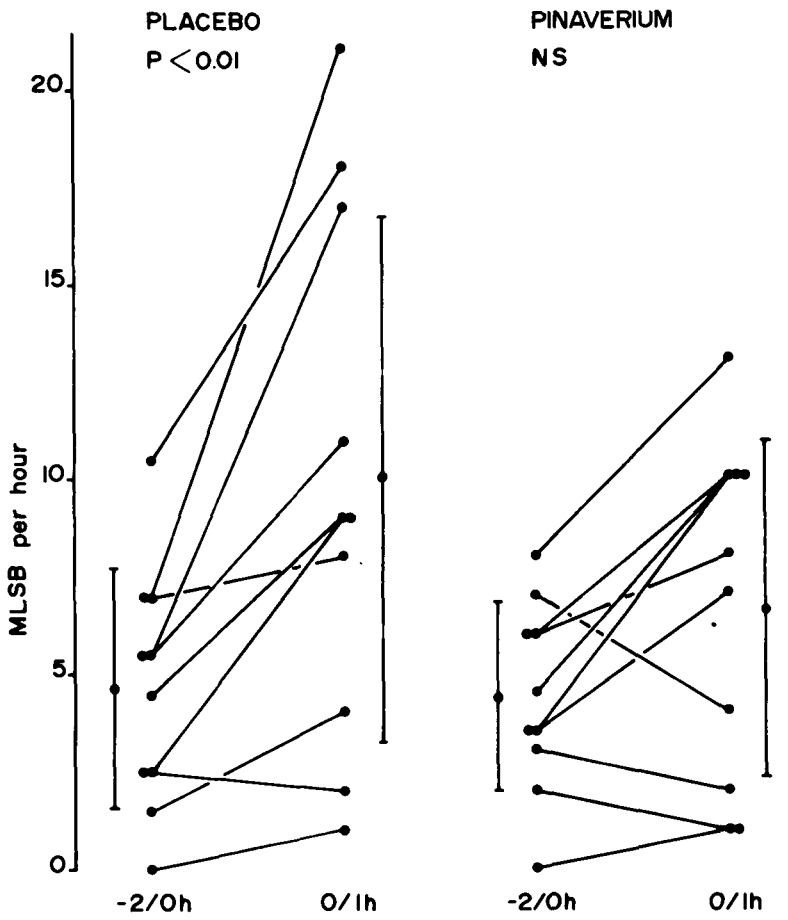

Fig. 3. Postprandial changes in the number of migrating long spike bursts (MLSB) in the 10 patients receiving placebo or pinaverium bromide (4 mg IV) 15 min before the meal. A significant ($P<0.01$) increase appeared after placebo but not after pinaverium administration.

in LSB activity was very low after placebo administration except in 3 patients, confirming the data of Dapoigny *et al.* (1985). However, in most of the patients the postprandial number of MLSB that corresponded to peristaltic contractions was in the same range as, or even higher than, that observed in healthy subjects (Frexinos *et al.*, 1985).

The suppression of this postprandial change in colonic motility by pinaverium bromide is in agreement with the agent's properties as a calcium channel blocker. *In vitro,* the mechanical activity of human or animal colonic smooth muscle has been found to be inhibited in the absence of calcium ions (Duthie and Kirk, 1978; Snape, 1982), but also by verapamil (Baumgartner *et al.*, 1985). *In vivo,* calcium channel

blockers are known to reduce lower esophageal sphincter pressure and their efficacy in the treatment of achalasia has been shown (Bortolotti and Labo, 1981). It has also been shown that nifedipine reduces the response to eating of the rectosigmoid (Narducci *et al.*, 1985) and such inhibition has been reproduced by octylonium bromide (Narducci *et al.*, 1986), a drug that interferes with calcium ion mobilization (Maggi *et al.*, 1983). Moreover, pinaverium and octylonium have both been found efficacious in the treatment of IBS, with a greater improvement of symptoms with pinaverium (Galeone *et al.*, 1986).

Pinaverium did not induce any change in SSB activity, which corresponds to tonic contractions of the colonic wall (Buéno *et al.*, 1980). However, no conclusion can be drawn about the action of pinaverium on this tonic activity, since the recording time occupied by the SSB was very low in comparison to data obtained in healthy subjects or IBS patients (Frexinos *et al.*, 1985; Buéno *et al.*, 1980). This initial low level of activity does not permit disclosure of a possible inhibitory effect of pinaverium.

In conclusion, according to the importance of the disturbances of the colonic response to eating in the irritable bowel syndrome, our data indicate that the clinical efficacy of pinaverium in the treatment of this syndrome may be correlated with its pharmacologic inhibitory action on postprandial colonic motility. Such an action has been found for other calcium channel blockers and is probably due to interference with calcium ion mobilization.

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