Effects of an Intestinal Smooth Muscle Calcium Channel Blocker (Pinaverium Bromide) on Colonic Transit Time in Humans

E. Froguel,* S. Chaussade,* H. Roche,* M. Fallet,† D. Couturier,* and J. Guerre*

*Department of Gastroenterology, Hôpital Cochin, Paris, France; and †Latema Laboratories, Suresnes, France

Pinaverium bromide, a calcium channel blocker, is often used in the treatment of the irritable bowel syndrome. Colonic transit time (CTT) was evaluated by a simplified method using radiopaque markers in 19 healthy volunteers during 2 weeks of treatment with pinaverium bromide (50 mg three times a day) or placebo according to a double-blind crossover design. Pinaverium bromide significantly ($p < .05$) accelerated total CTT (30.2 ± 4.6 h, mean ± SE) compared with the placebo (38.2 ± 3.7 h). The decrease in CTT was related to accelerated transit in the descending and rectosigmoid areas of the colon (21 ± 4.5 vs. 30 ± 3.9 h, $p < .05$). CTT in the ascending colon was not significantly modified (9.2 ± 2.7 as compared with 9.5 ± 2.3 h). Stool frequency was not significantly increased by pinaverium bromide. These results suggest that pinaverium bromide might be effective in idiopathic constipation with slow CTT in the descending or rectosigmoid areas of the large bowel. The measurement of CTT is an easy and useful method for investigating the effects of drugs on colonic motility. (Journal of Gastrointestinal Motility 1990; 2(3):176–179)

Key Words: calcium channel blockers; gastrointestinal motility; colonic transit time.

Introduction

Pinaverium bromide (4-(6-bromoveratryl)-4 {2-(2-(6.6-diméthyl-2-norpinyl)-éthoxyl)-éthyl}-morpholinium hydroxide) is a musculotropic spasmolytic drug virtually devoid of anticholinergic action (1,2). Its mechanism of action involves blocking the calcium channels of the intestinal smooth muscle cells (3–7). In vitro, its spasmolytic action is approximately 10 times greater than that of papaverine (2). In the conscious dog, a high intravenous dose of pinaverium bromide inhibits gastrointestinal and colonic motility (8). In humans, its effectiveness in the treatment of irritable bowel syndrome is well established (9,10). By contrast, its effects on colonic transit are less well known.

The aim of the present study was to evaluate the effect of orally administered pinaverium bromide on total and segmental colonic transmit time (CTT), using a simplified technique in healthy volunteers.

Address correspondence to: Docteur Chaussade, Service de Gastroenterologie, Hôpital Cochin, Achard 9, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France.

Paper received November 6, 1989; accepted January 9, 1990.

Material and Methods

SUBJECTS

Nineteen healthy volunteers were studied (11 women, eight men; mean age ± SE = 25.7 ± 2 years). These subjects had no gastrointestinal transit disturbance, had no digestive tract symptomatology, and were receiving no treatment of any sort. Women included in the trial were using some method of contraception intrauterine device or oral contraceptive). Written consent was obtained in all cases.

MEASUREMENT OF CTT

The method used has been described elsewhere (12–14). Briefly, 20 radiopaque markers were ingested at a fixed time on three consecutive days. A plain x-ray of the abdomen using ultrasensitive film (estimated surface exposure = 0.08 mrad per film) was obtained at the same time as the pellets were ingested on the fourth day, and on the seventh day if more than 40 markers were present on the fourth-day film. If the number of radiopaque markers was less than 40, we assumed that the 20 markers given on day 1 had

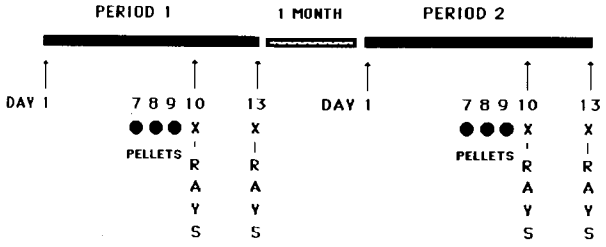

Figure 1. Experimental protocol.

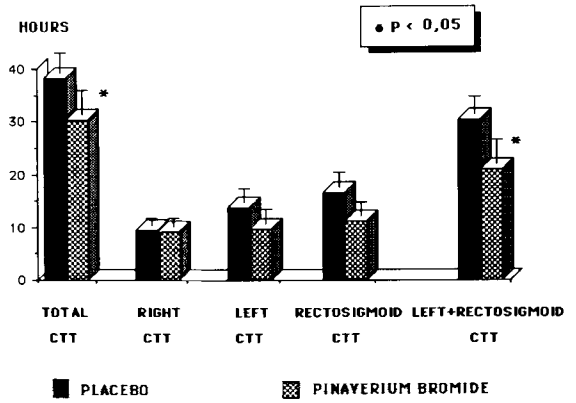

Figure 2. Effect of placebo and pinaverium bromide on total and segmental colonic transit time in 19 healthy subjects.

been eliminated in the stool and that the colonic transit time was less than 72 hours (which is the upper limit of the CTT measured with a single x-ray). On the x-ray, the projection zones of right colon, left colon, and rectosigmoid were delimited by the bony landmarks as described by Arhan et al. (15). The markers were identified and counted, and transit time in each segment was obtained using the following formula: $T = 1.2 \Sigma ni$, where ni was the total number of markers present on a given film sector on day 4 or day 7 (12,14).

EXPERIMENTAL PROTOCOL

The treatment phase of the study lasted 14 days and was randomized, double-blind, and placebo-controlled. Pinaverium bromide was administered at a dosage of 50 mg twice a day, with meals, for 14 days. During this period, a self-evaluation diary card was filled out by the subjects to determine the frequency of stools and any possible side effects. Radiopaque markers were ingested between day 7 and day 9, and x-rays were obtained on day 10 and, if necessary, on day 13. Each study period was separated by a 1-month interval (Fig. 1). Informed written consent was obtained from all subjects.

STATISTICAL ANALYSIS

Statistical analysis involved a Student's test for paired data. Results were expressed as mean ± standard error.

Results

Weekly stool frequency was not significantly modified by pinaverium bromide (7.3 ± 0.6/wk) in comparison with the placebo (6.8 ± 0.6/wk). By contrast (Fig. 2), overall CTT decreased significantly from 38.2 ± 3.7 hours with placebo to 30.2 ± 4.6 hours with pinaverium bromide ($p < .05$). This decrease was due to a decrease in CTT in the descending colon and rectosigmoid area (30.2 ± 3.5 h vs. 21 ± 4.5 h, $p < .05$). Taken separately, CTTs in the descending colon and the rectosigmoid were decreased by pinaverium bromide, but this difference was not significant. CTT in the ascending colon was not significantly modified (9.2 ± 2.7 h as compared with 9.5 ± 2.3 h). Epigastric cramps and flatulence occurred on one occasion in the placebo group.

Discussion

This study showed that pinaverium bromide is able to accelerate CTT in healthy subjects. This acceleration in CTT was due to an action in the descending colon and rectosigmoid while CTT in the ascending colon was unaffected. These results emphasize the value of techniques of measurement of overall and segmental CTTs using radiopaque markers. CTT measurement seemed to be a more sensitive method for drug evaluation in humans since stool frequency was not modified while overall CTT was decreased by approximately 8 hours.

Measurement of segmental CTT showed that the action of pinaverium bromide differed according to the colonic segment considered. These results were similar to those of Barbara et al. (11), who showed by a radioisotopic method that pinaverium bromide accelerated the rectosigmoid CTT in eight patients suffering from idiopathic chronic constipation. This acceleration of CTT appears paradoxical, since it has been suggested that the use of calcium channel blockers like nifedipine or verapamil can be complicated by constipation as a side effect. However, this side effect seems to be infrequent, and the effect of nifedipine on CTT is not known.

The mechanism of action of pinaverium bromide on colonic motility would appear to be complex. In humans, rectosigmoid manometric studies have shown that pinaverium bromide decreased motility index in patients with an irritable bowel syndrome (11), but these studies provided no precise information about the effects of the drug on propulsive and nonpropulsive movements of the colon. Fioramonti et

al. (16) studied the effect of intravenously administered pinaverum bromide on the electrical activity of the entire colon of patients with irritable bowel syndrome. These authors showed that pinaverium bromide, administered intravenously before a meal, significantly decreased the number of migrating long-spike bursts while short-spike burst activity was decreased in a nonsignificant manner. As short-spike bursts are thought to reflect a contraction localized at the electrode site (17), it has been suggested that short-spike bursts may indicate a pressure barrier opposing the propulsive effect of migrating long-spike bursts (16). From this study, it could be expected that pinaverium bromide slowed CTT since the number of migrating long-spike bursts decreased after a meal. It is thus possible that chronic administration of pinaverium bromide intravenous injection would have different effects than intravenous injection. During oral administration, it could then preferentially inhibit short-spike burst activity and thus accelerate colonic transit. Further investigations of colonic motility during oral administration of pinaverium bromide are needed to explain the acceleration of CTT in the left and rectosigmoid colon. The possibility of a different effect according to the route of administration is not surprising given the low level of digestive absorption (less than 8%) of pinaverium bromide (18). So a local action of the drug could explain the difference in action of oral pinaverium bromide compared with the intravenous dose on colonic motility.

The reason for the preferential action of oral pinaverium bromide on the descending colon and rectosigmoid area remains unknown since the numbers of short-spike bursts have been found to be identical in the ascending and descending colon (19). A selective action on the rectosigmoid junction is possible since this area is characterized by the existence of permanent day and night short-spike burst activity (20). Inhibition of colonic contractions results from an effect of pinaverium bromide on intestinal smooth muscle (6). It has been shown in vitro that the action of pinaverium bromide is similar to that of calcium channel blockers such as verapamil, nifedipine, nicarpidine, or D600 (4,5,21). These are believed to act essentially by blocking voltage-dependent calcium channels while receptor-dependent channels and intracellular calcium stores are relatively insensitive to these drugs.

In conclusion, our results show that pinaverium bromide is able to accelerate CTT in the descending and rectosigmoid areas of the colon. This action could partially explain the beneficial effect of pinaverium bromide seen in patients suffering from idiopathic constipation, especially in those with left or rectosigmoid stasis (22).

References

1. Baronnet R, Foussard-Blanpin O, Bretaudeau J, Hubert F. Synthèse et étude pharmacodynamique comparée d'ammoniums quaternaires dérivés du diméthyl-6, 6 norpinane: leur action spasmolytique. Eur J Med Chem Chim Ther 1974;9:182–87.
2. Bretaudeau J, Foussard-Blanpin O, Baronnet R, Desprairies R. Etude pharmacodynamique des propriétés spasmolytiques du bromure de pinaverium. Therapie 1975;30:919–30.
3. Bretaudeau J, Foussard-Blanpin O. Recherche sur le mécanisme d'action du bromure de pinaverium. J Pharmacol 1980;11:233–43.
4. Droogmans G, Himpens B, Casteels R. Effect of pinaverium bromide on electrical and mechanical activity of smooth muscle cells: Ca^{++} entry blocking properties. Naunyn Schmiedebergs Arch Pharmacol 1983;323:72–77.
5. Mironneau J, Lalanne C, Mironneau C, Savineau JP, Lovie JL. Comparison of pinaverium bromide, manganese chloride and D600 effects on electrical and mechanical activities in rat uterine smooth muscle. Eur J Pharmacol 1984;98:99–107.
6. Baumgartner A, Drack E, Halter F, Scheurer U. Effects of pinaverium bromide and verapamil on the motility of the rat isolated colon. Br J Pharmacol 1985;86:89–94.
7. Wuytack F, De Schutter G, Casteels A. Action of pinaverium bromide on calmodulin-regulated functions. Eur J Pharmacol 1985;114:85–88.
8. Itoh Z., Takahashi I. Inhibitory effect of pinaverium bromide on gastrointestinal contractile activity in conscious dogs. Arzneim Helforschung 1981;31: 1450–53.
9. Corazza GR, Valra D, Milletti S, Vanzini S, Gasbarrini G. Controlled clinical evaluation of pinaverium bromide and trimebutine in functional disorders of the colon. Acta Therapeutica 1983;9:383–89.
10. Galeone EM, Stock F, Molse G, Cociolli RN, Toll L, Megevand J. Pinaverium bromide versus otilonium bromide in patients with irritable bowel syndrome. Curr Ther Res 1986;39:613–24.
11. Barbara L, Corinaldesi R, Baldi F, et al. Effects of pinaverium bromide on intestinal transit time and sigmoid contractile activity in patients with chronic idiopathic constipation. Farm Ter 1984;1:43–46.
12. Chaussade S, Roche H, Khyari A, Couturier D, Guerre J. Mesure du temps de transit colique (TTC): description et validation d'une nouvelle technique. Gastroenterol Clin Biol 1986;10:385–89.
13. Chaussade S, Guerre J, Couturier D. Measurement of transit time (letter). Gastroenterology 1987;92:2053.
14. Metcalf AM, Phillips SF, Zinsmeiter RA, Mac Carty RL, Beart RW, Wolff BG. Simplified assessment of segmental colonic transit. Gastroenterology 1987; 92:40–47.

15. Arhan P, Devroede G, Jehannin B, et al. Segmental colonic transit time. Dis Colon Rectum 1981;24:625–29.
16. Fioramonti J, Frexinos J, Bueno L, Coulom P. Evaluation of colonic myoelectrical activity in health and functional disorders. Gut 1980;21:480–85.
17. Bueno L, Fioramonti J, Ruckebusch Y, Frexinos, J. Coulom. P. Inhibition of the colonic motor response to eating by pinaverium bromide in irritable bowel syndrome. Fundam Clin Pharmacol 1988;2:19–27.
18. Jacquot C, Rapin J, Lambrey B, Baronnet R, Pichat L. ^{14}C pinaverium bromide synthesis and pharmacokinetics study in the rat. Eur J Med Chem Chim Ther 1978;13:61–66.
19. Dapoigny M, Trollese JF, Bommelaer G, Tournut R. Réponse colique au repas du colon droit, du colon gauche, du rectosigmoide et de la charnière rectosigmoidienne chez le sujet présentant des troubles fonctionnels intestinaux. Gastroenterol Clin Biol 1988;12:361–67.
20. Frexinos J, Bueno L, Fioramonti J. Diurnal changes in myoelectric spiking activity of the human colon. Gastroenterology 1985;88:1104–10.
21. Golenhofen K, Hermstein N. Differentiation of calcium activation mechanisms in vascular smooth muscle by selective suppression with verapamil and D600. Blood Vessels 1975;12:21–37.
22. Chaussade S, Khyari A, Roche H, et al. Determination of total and segmental colonic transit time in constipated patients: results in 91 patients with a new simplified method. Dig Dis Sci 1989;34:1168–72.