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Original article

Effect of pinaverium bromide on jejunal motility and colonic transit time in healthy humans

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Summary – Pinaverium bromide is a specific calcium channel blocker used in the treatment of irritable bowel syndrome (IBS) for its spasmolytic activity. The aim of the present study was to evaluate the effect of orally administered pinaverium bromide on jejunal motility and total and segmental colonic transit time in control subjects. Gastrointestinal studies were performed in 10 healthy volunteers (30 ± 3 years), before and after a treatment phase of 14 days (150 mg/d). Jejunal motility was measured by prolonged manometry (14 h) and colonic transit time by a multiple ingestion, single marker technique. No significant modification of phase III of the migrating motor complexes was demonstrated. On the contrary, a significant ($p < 0.01$) but weak decrease of the frequency of contraction was found. Unlike previous studies, no decrease of total or segmental colonic transit time was demonstrated.

jejunum, colon / motility / calcium-channel antagonist

Résumé – Effet du bromure de pinaverium sur la motricité jéjunale et le temps de transit colique chez l'homme sain. *Le bromure de pinaverium est un antagoniste spécifique des canaux calciques utilisé dans le traitement du colon irritable. Le but de cette étude est d'étudier l'effet de cette drogue administrée par voie orale sur la motricité jéjunale et le temps de transit colique total et segmentaire chez l'homme sain. L'étude a été réalisée chez 10 volontaires âgés de 30 ± 3 ans, avant et après 14 jours de traitement (150 mg/24 h). La motricité jéjunale a été étudiée par une manométrie longue (14 heures) et le temps de transit colique par une étude à l'aide de marqueurs radioopaques. Aucune variation de la phase III des complexes moteurs migrants n'a été démontrée; par contre, il existait une diminution légère mais significative ($p < 0.01$ de la fréquence des contractions. Aucune variation significative du temps de transit colique total et segmentaire n'a été mise en évidence, contrairement à des travaux antérieurs.*

jejunum, colon / motricité / bromure de pinaverium

Introduction

An increase of intracellular concentration of calcium ions [Ca^{2+}] activates many biologic processes, *eg* enzymatic reactions, activation of excitable cells and coupling of electrical activation to cellular secretion. Muscle contraction is a classic example. The generation of force utilizes ATP and involves the interaction of myosin and actin filaments, a Ca^{++} dependent process [14]. Calcium channel blockers have been found to be useful in treating a wide variety of cardiovascular disorders [27] and are now used in the treatment of digestive diseases [11, 27].

The quaternary ammonium derivative 4-(6-bromoveratyl)-4{2-[2-(6,6-dimethyl-2-norpinyl) -ethoxyl]-ethyl}-morpholinium hydroxide, or pinaverium bromide (Dicetel®), is a spasmolytic agent with powerful musculotroic action and a very weak anticholinergic action [3]. Its action is due to inhibition of transmenbrane calcium movements, by blockage of voltage-dependant Ca^{2+}-channels [4, 12, 21, 31], which are only one of several types of Ca^{2+}-channel. *In vitro*, it induces

smooth muscle relaxation in the presence of known antagonists [10]. *In vivo*, in conscious dogs, pinaverium bromide has an inhibitory effect on gastrointestinal contractions [19]. In man, its clinical effectiveness in the treatment of irritable bowel syndrome [9, 16] and its physiological action on colonic activity [2, 13] are well documented. By contrast, its effects on jejunal motility are less well known and have only been studied in dogs [19], and its action on colonic transit time [2, 15] is disputed.

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

Materials and methods

Subjects

The healthy volunteers were studied (6 women, 4 men; mean age ± SE: 30 ± 3 years). These subjects were asymptomatic and had a completely negative physical examination. They had always been in good health. Women included in the trial were using contraceptives. Written consent was obtained in all cases.

Jejunal motility

The jejunal manometric study was carried out after an overnight fast using a four-lumen perfusion tube introduced through the nose at 9 00 am. The perfusion assembly was fluorscopically placed in a jejunal position at 12 00 noon. Two standard test meals were given at 1 00 pm and 7 00 pm. They contained 51 g protein (35 and 26 g respectively, for each meal), 80 g lipids (40, 40) and 185 g glucose (82, 103). Each catheter of the manometric tube was perfused with distilled water through a low compliance, pneumohydrolic pump (perfusion rate 0.1 ml.min^{-1}; perfusion pressure 12 psi). Each opening was 5 cm apart from the next one. Manometric recording, tramsitted to a computer (Copaq computer) at a sampling rate of 5 Hz per channel, was carried out during a 14–hour period from 7 00 pm to 9 00 am the following day.

The records were analyzed by calculating the number of Phase III episodes, their duration, the frequency of their contractions and the migration velocity. A specific program was written (Turbo C, Borland Ed) to calculate the frequency of contractions during each recording [5].

Measurement of colonic transit time

Segmental and total CTT were measured according to a previously described method [7]. Subjects ingested 10 radiopaque markers during a period of 6 consecutive days at 9 00 am. A plain film of the abdomen using ultrasensitive film (surface exposure 0.1 mrad per film) was obtained on the 7th d at 9 00 am.

Measurement of CTT was made by counting the radiopaque markers on the abdominal plain film. CTT was determined by: (1) $CTT = n\ DT/N$ where: CTT is the colonic transit time, expressed in hours; n is the number of markers on the film, in the studied zone: right colon, left colon, rectosigmoid area or total colorectal area; DT is the time between the intake of markers, *ie* in this case 24 hours; N is the number of markers ingested each time, in this case 10. CTT was then express as: (2) $CTT = 1.2\ n$.

Experimental protocol

Subjects were studied before and after a treatment phase of 14 d (150 mg pinaverium bromide/d). During this period, a self evaluation diary-card was filled out by the subjects to determine any possible side-effects.

Statistical analysis

Data analysis was performed with the Wilcoxon paired-test using SAS 5.16 Software (SAS Institute Inc, Cary, NC, USA).

Results

Jejunal motility

In three out of the 20 records, no phase III was found. No significant differences was found following intake of pinaverium bromide with regard to the number of regular activity phases (2.4 ± 0.8 *vs* 3.1 ± 0.9), their duration (8.7 ± 1.4 min *vs* 8.4 ± 1.2 min), the speed of migration of phases III (3.8 ± 0.6 cm.min^{-1} *vs* 3.7 ± 0.7 cm.min^{-1}) or the frequency of contractions during this phase (11.7 ± 0.7 min^{-1} *vs* 11.3 ± 0.2 min^{-1}). In contrast, the frequency of contractions during the recording decreased significantly following intake of pinaverium bromide (3.3 ± 0.5 min^{-1} *vs* 3.1 ± 0.5 min^{-1}; $p < 0.01$) (fig 1).

Colonic transit time

After ingestion of pinaverium bromide, we found no significant decrease of total (42.6 ± 8.1 *vs* 41.6 ± 5.9 hours) or segmental colonic transit time (14.8 ± 3.8 *vs* 15.5 ± 3.8 h in the ascending colon; 10.0 ± 4.1 *vs* 13.8 ± 3.3 hours in the left colon, 17.8 ± 4.7 *vs* 12.3 ± 3.2 h in the rectosigmoid area) (fig 2).

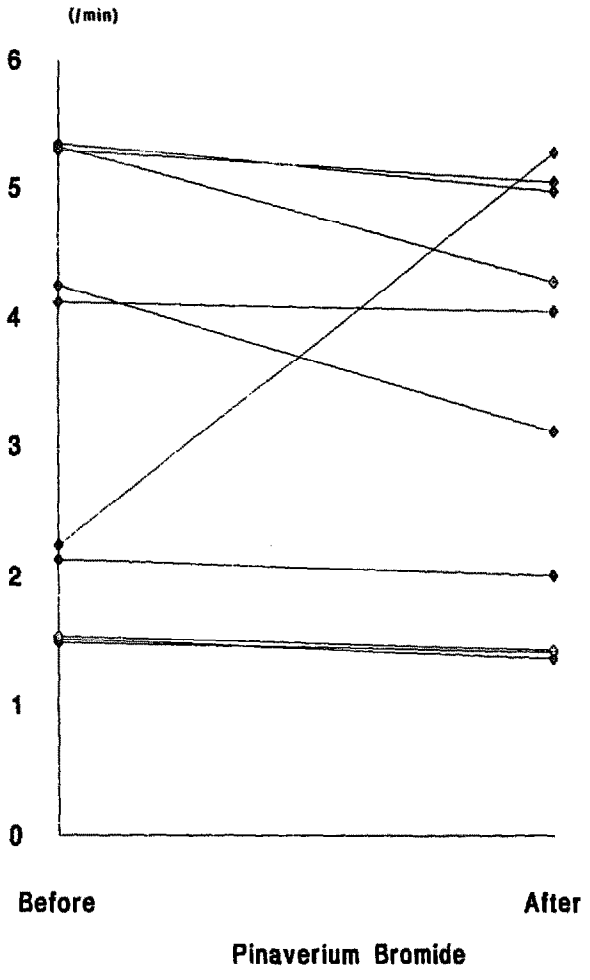

Fig 1. Frequency of jejunal contractions. In contrast with the absence of modification of the regular activity (phase III) of the migrating motor complex, a significant decrease ($p < 0.01$) of the frequency of jejunal contractions was demonstrated after 14 d of oral ingestion pinaverium bromide (150 mg/d).

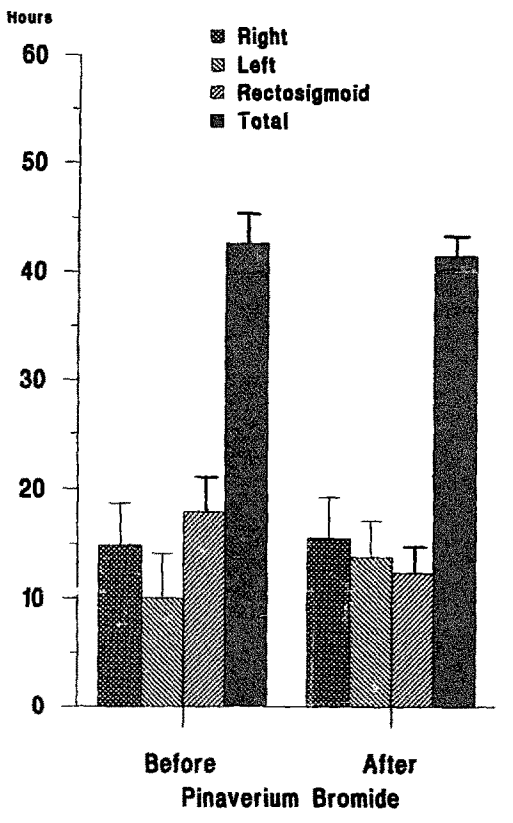

Fig 2. Total and segmental colonic transfer time. Transit time (h) in total colon and in individual colonic segments before and after treatment with 300 mg/d of pinaverium bromide for 14 d in 10 healthy subjects. No statistically significant variation was observed.

Discussion

The spasmolytic effect of nifedipine, a calcium channel blocker, has been demonstrated in the treatment of nut-cracker oesophagus [23] or achalasia [6, 17]. The irritable bowel syndrome (IBS), the most common gastrointestinal disorder [24], is a functional disease mainly related to an alteration of intestinal motility in the fed state or after meal ingestion [29], psychological stress [1] or rectal distension [30]. The use of spasmolytic drugs would be useful in order to attenuate the abdominal pain which is one of the most common complaints. Use of a calcium channel blocker was thus logical in this situation. Nifedipine has only been used sporadically in IBS [26], like verapamil [8]. For these two drugs, no optimum dose has been established in dose ranging/dose regimen studies. Moreover, nifedipine and verapamil are known to delay gastrointestinal transit time and to lead to constipation as a side-effect.

Altered small bowel motility has been demonstrated in IBS [20]. Manometric recordings showed a pattern consisting of regular bursts of contractile activity or an abnormal preponderance of giant migrating contractions in the ileum associated with abdominal pain. Our study showed that pinaverium bromide did not alter the temporal organization of small bowel motility, but did significantly decrease the frequency of jejunal

contractions. Similar results were found in dogs by intestinal electromyography. Contrary to our study, it was found that pinaverium bromide increased the duration and decreased the frequency of myoelectric complexes. These results were obtained with a high dose (10 mg.kg^{-1} *per os*) which is four times the human therapeutic dose used in our study. This pharmacological action can be explained by inhibition of voltage-dependant Ca^{2+}-channels in smooth muscle cells. In fact, there was a striking parallelism between the concentrations at which the mechanical activity, *ie* frequency and amplitude of contractions of smooth muscle of guinea pig ileum, was inhibited and those at which the electrical activity was inhibited [12].

Pinaverium bromide at doses of 150 mg/d did not modify transit time measurement in man [2, 28]. Paradoxically, some studies have found a reduction of colonic transit time in descending colon and rectosigmoid area in control subjects [15] and in chronically constipated patients at a dose of 50 mg per d [2]. Moreover, overdosage with pinaverium bromide at single oral doses of 700 mg or more induced diarrhea dose-dependently in volunteers [10]. Our results show no modification of total or segmental colonic transit time after ingestion of 150 mg pinaverium bromide per day, even when transit time in the descending colon and recto sigmoid area are added. The mechanism of action of pinaverium bromide on colonic motility could result from its pharmacological action on smooth muscle. It suppressed the gastrocolonic electromyographic response to a test meal after intravenous injection (4 mg) in man [13] as effectively as sublingual nifedipine [22] did in patients with IBS. It decreased the motor index in the sigmoid after a test meal or after neotigmine stimulation [2].

No cardiovascular effect of pinaverium bromide was observed in our study, in contrast to a previous specific study [18]. Nevertheless, this drug has, as is also the case for other calcium channel blockers like verapamil or nifedipine, a specific inhibitory action on cardiac muscle and aortic smooth muscle, namely a decrease of the contractile response to calcium and the inotropic effect. Nevertheless, the kinetic profile of this drug explains why it has only a local effect in the gastrointestinal tract when taken orally and why it is devoid of any adverse systemic effects by this route of administration. Pinaverium bromide is poorly absorbed (< 10%) and is metabolized rapidly and extensively. This is in contrast to other calcium antagonists used for their cardiovascular effects with significant absorption and sytemic bioavailability. Moreover, regional selectivity of calcium blockers at different intestinal sites has been observed [25]. In the rat intestine, significant regional differences exist in Ca^{2+} pools mobilized by different activating stimuli and in sensitivity to the blocking action of drugs which interfere with calcium mobilization from either intra- or extracellular Ca^{2+} pools. Finally, the role of calcium antagonists on the intrinsic nervous system has been poorly studied, despite the fact that this system is at the source of gastrointestinal motility and that nervous cells possess calcium channels.

The present study showed that ingestion of pinaverium bromide, a calcium channel blocker did not significantly modify the characteristics of the jejunal phase III but did significantly decrease the frequency of jejunal contractions.

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