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Pirenzepine versus scopolamine methyl bromide in double-contrast barium enema study of large bowel

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Abstract
To evaluate the usefulness of pirenzepine for diagnostic double-contrast barium enema study of the large bowel, pirenzepine and scopolamine methyl bromide (SMB) were compared in a single, blind, randomized trial. Sixty consecutive patients were enrolled in the study. Quantitative analysis of bowel distention was done by measuring the maximum diameter of the transverse colon before and after drug administration. Four independent observers blindly evaluated distention and mucosal coating of the large bowel and global quality of the images. No differences were found in the diagnostic performance between the two drugs. However, pirenzepine induced a slight but significantly larger distention of the large bowel (68 ± 12 vs. 65 ± 8 mm, $p = 0.02$). Heart rate and rhythm during the study were recorded by ECG. SMB induced tachycardia in all patients (from 72 ± 15 to 98 ± 24 beats/min, $p < 0.01$), whereas pirenzepine did not (from 76 ± 13 to 78 ± 20, p = NS). After SMB, one-patient exhibited faintness, and some patients complained of visual accommodation defects, dryness of the mouth, and dizziness. Pirenzepine had a diagnostic performance similar to SMB in avoiding adverse effects elicited by SMB.

Key words: Large bowel—Double-contrast studies—Barium enema—Colon—Pirenzepine—Scopolamine methyl bromide.

A double-contrast study of large bowel tract requires pretreatment with a hypotonic agent to avoid smooth muscle contraction. Scopolamine methyl bromide (buscopan) is commonly used [1].

Buscopan cannot be used in patients with glaucoma and benign prostatic hypertrophy, because it frequently induces hypotension and tachycardia, thus being potentially harmful in patients with cerebral and cardiac disease.

Pirenzepine, a pyridobenzodiazepine, is a selective M1 antimuscarinic agent commonly used for the treatment of peptic diseases such as gastritis, duodenitis, and ulcers, inducing a relaxation of enteric smooth muscle [2–14]. Pirenzepine was used as alternative hypotonic agent in a double-contrast study of the upper gastrointestinal tract; it had a good diagnostic performance without inducing tachycardia and significant collateral effects [15]. This study evaluated the use of pirenzepine as a hypotonic agent for double-contrast barium enema of the large bowel study in comparison with scopolamine methyl bromide (SMB).

Materials and Methods

Patients

Sixty consecutive patients (40 women, 20 men; mean age-59 years old, range-29–82 years) underwent double-contrast study of colon. The reasons for submission were altered bowel habits (32 patients), fecal occult blood (8 patients), rectal bleeding (3 patients), and abdominal pain (27 patients). All the patients gave their informed consent to participate in this study.

Study Protocol

In all patients, the double-contrast studies were carried out with a barium sulphate suspension (Prontobario Colon Bracco™ 100% W/

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V, 400 g) and air. Air infusion was stopped as soon as the patient had colon discomfort.

Pirenzepine or SMB (Gastrozepin® and Buscopan®, both manufactured by Boehringer Ingelheim; 0.1 mg/kg and 20 mg, respectively), was intravenously administered as a hypotonic agent. The single-blind trial and the sequence of drug randomization were coupled.

During each study the operator took care to note secondary or adverse drug reactions, which were treated promptly when necessary.

An electrocardiographic lead was recorded before and 5 min after drug administration and at the end of the double-contrast examination with an event ECG tape recorder (Cardiobip Esaote Biomedica™) and transmitted by phone to the Cardiology Department. The study did not receive financial support from any pharmaceutical company.

Evaluation of Images and Electrocardiograms

The colon diameter was blindly measured in three abdominal films of each double-contrast enema study of the large bowel. The radiographs examined were a PA prone film before and a PA prone and an AP supine films after drug administration. The maximum transverse colon diameter was measured. The geometric magnification error was computed using a metallic calliper as reference.

Four experienced radiologists examined double-contrast enema studies to evaluate qualitatively distention and mucosal coating of the large bowel and performance of the radiological diagnosis with a score scale (1–4).

Off-line, two cardiologists blindly evaluated heart rate and cardiac rhythm on electrocardiograms.

Statistical Analysis

Two-way analysis of variance was used for weighting the differences in drug effects and observers' evaluations. Probability values greater than or equal to 0.05 were considered statistically significant. Data are shown as means and standard deviations.

Results

In five patients, who suffered from cardiovascular diseases, buscopan was contraindicated, and pirenzepine was administered instead. For this reason an additional five patients who were to receive pirenzepine were also excluded from the randomized study. Therefore, five sets of patients were excluded from the randomized study, but data from all 60 patients were also analyzed.

Double-Contrast Diagnostic Study of Colon

The results of randomized patients (25 pairs) and total population of treated patients are reported in Tables 1 and 2.

Good double-contrast images of the large bowel were obtained with both hypotonic agents; however, better distention of the transverse colon resulted from pirenzepine (diameter in AP supine film: 68 ± 12 vs. 65 ± 8 mm, $p = 0.02$), and, in addition, observer scores for the global large bowel distention was higher for pirenzepine studies (3.5 ± 0.6 vs. 3.0 ± 0.7, $p < 0.01$).

Table 1. Distention, mucosal coating, and diagnostic performance (mean ± SD) of 25 randomized patient pairs

	Buscopan	Pirenzepine	*p*
Transverse colon diameter in PA prone films, before drug	44.2 ± 8.7	46.2 ± 9.7	NS
Transverse colon diameter in PA prone films, after drug	56.8 ± 8	60.2 ± 9.3	<0.01
AP supine film transverse colon diameter after drug	64.8 ± 8.5	69.9 ± 12.3	<0.01
Distention (qualitative)	3.0 ± 0.7	3.5 ± 0.6	<0.01
Mucosal coating	2.9 ± 0.6	3.0 ± 0.7	NS
Diagnostic performance	3.0 ± 0.6	3.1 ± 0.6	NS

Table 2. Distention, mucosal coating, and diagnostic performance (mean ± SD) in the examined population

	Buscopan (25 pts)	Pirenzepine (35 pts)	*p*
Transverse colon diameter in PA prone films, before drug	44.2 ± 8.7	45.2 ± 9.9	NS
Transverse colon diameter in PA prone films, after drug	56.8 ± 8	59.1 ± 9.8	<0.05
AP supine film transverse colon diameter after drug	64.8 ± 8.5	68 ± 12	=0.02
Distention (qualitative)	3.0 ± 0.7	3.4 ± 0.6	<0.01
Mucosal coating	2.9 ± 0.6	3.0 ± 0.7	NS
Diagnostic performance	3.0 ± 0.6	3.1 ± 0.6	NS

No differences were found for mucosal coating and diagnostic performance. The frequency of distal ileal filling was lower in the pirenzepine group (6/25 vs. 9/25 pts).

These results were independent of the observers' evaluations, which were homogeneous as documented by two-way analysis of variance.

Diagnostic results of double-contrast studies are reported in Table 3.

Effects on Heart Rate and Cardiac Rhythm

The quality of phone-transmitted electrocardiograms was always sufficient for the evaluation of heart rate in all but four cases; evaluations of PR interval were possible in only 46 patients. The behavior of heart rate before and after drug administration is shown in Table 4 for the 25 randomized pairs and in Table 5 for the total treated population. Under buscopan, heart rate rose from

Table 3. Diagnostic results of the examined population

Diagnosis	Buscopan (25 pts)[a]	Pirenzepine (35 pts)[b]	Total (60 pts)[c]
Paracolic abscess	—	1	1
Ulcerative colitis	—	1	1
Crohn disease	—	1	1
Rectal cancer	—	1	1
Polyps	1	1	2
Diverticular disease	5	4	9
Dolichocolon	2	1	3
Irritable bowel syndrome	6	5	11
Negative	11	20	31

[a] Nineteen women and six men; age: mean = 56 years old, range = 29–73 years old
[b] Twenty-one women and 14 men; age: mean = 60 years old, range = 32–82 years old
[c] Forty women and 20 men; age: mean = 58 years old, range = 29–82 years old

71.8 ± 14.6 beats/min to 97.8 ± 24.4, with an increment of 23 ± 24.2 beats/min.

Conversely, pirenzepine did not induce any tachycardic effect, heart rate being unchanged from baseline (76.2 ± 13 vs. 77.6 ± 19.6, p = NS). Both drugs had no effect on atrioventricular conduction (PR interval).

Other Side Effects

Buscopan did not induce any serious side effect that required medical intervention and interruption of the study; however, one patient complained of faintness at the end of the study. The majority of patients complained of visual accommodation defects and dryness of the mouth. Five patients had dizziness. With pirenzepine, no side effects were reported (Table 6).

Discussion

The radiological study of the colon is an important step in the diagnostic process of inflammatory and neoplastic diseases. A good double-contrast series of colon images is a prerequisite for a correct and predictive study and requires distention and hypokinesis of parietal musculature. Usually, smooth muscle hypotonia is obtained by intravenous administration of SMB (buscopan).

In this study, pirenzepine induced a slight but significant improvement in distention of the large bowel. This was obtained without any of the side effects that frequently occur with SMB, although we observed fewer side effects as compared with upper gastrointestinal studies [15], probably due to the supine position

Table 4. Heart rate (beats/min) in the 25 randomized pairs

	Buscopan (23 pts)	Pirenzepine (23 pts)	p
Heart rate before drug administration	71.8 ± 14.6	76.2 ± 13	NS
Heart rate 5 min after drug administration	97.8 ± 24.4	77.6 ± 19.6	<0.01
Heart rate at the end of DC exam	91.0 ± 18.8	79.3 ± 21.9	=0.059
Heart rate change	23 ± 24.2	1.3 ± 11.2	<0.01

Table 5. Heart rate (beats/min) in the examined population

	Buscopan (24 pts)	Pirenzepine (32 pts)	p
Heart rate before drug administration	72.2 ± 14.4	77.3 ± 12.8	NS
Heart rate 5 min after drug administration	97.1 ± 24.1	78.1 ± 18	<0.01
Heart rate at the end of DC exam	91.0 ± 18.8	80.8 ± 21.3	=0.072
Heart rate change	22.2 ± 24.1	0.7 ± 9.9	<0.01

Table 6. Side effects (in points) of buscopan and pirenzepine observed in the patient population

	Faintness	Visual accomodation defects	Dryness of the mouth	Dizziness
Scopolamine methyl bromide	1	8	18	5
Pirenzepine	—	—	—	—

of the patients during the large bowel exams. This study, however, confirms the data reported in our recent paper concerning the safety of pirenzepine is suspected or known cardiac patients [15]. In the case of the colon examination, pirenzepine gave good technical results. No differences in mucosal coating and diagnostic performance were observed between the two hypotonic drugs. Figure 1 shows some cases of observed pathologies studied with pirenzepine to judge the diagnostic performance.

Pirenzepine is not contraindicated in patients with glaucoma and benign prostatic hypertrophy. Buscopan was found to be possibly harmful in heart disease patients because of its marked tachycardic effect, and in this study it was not administered in five patients who suffered from cardiovascular diseases.

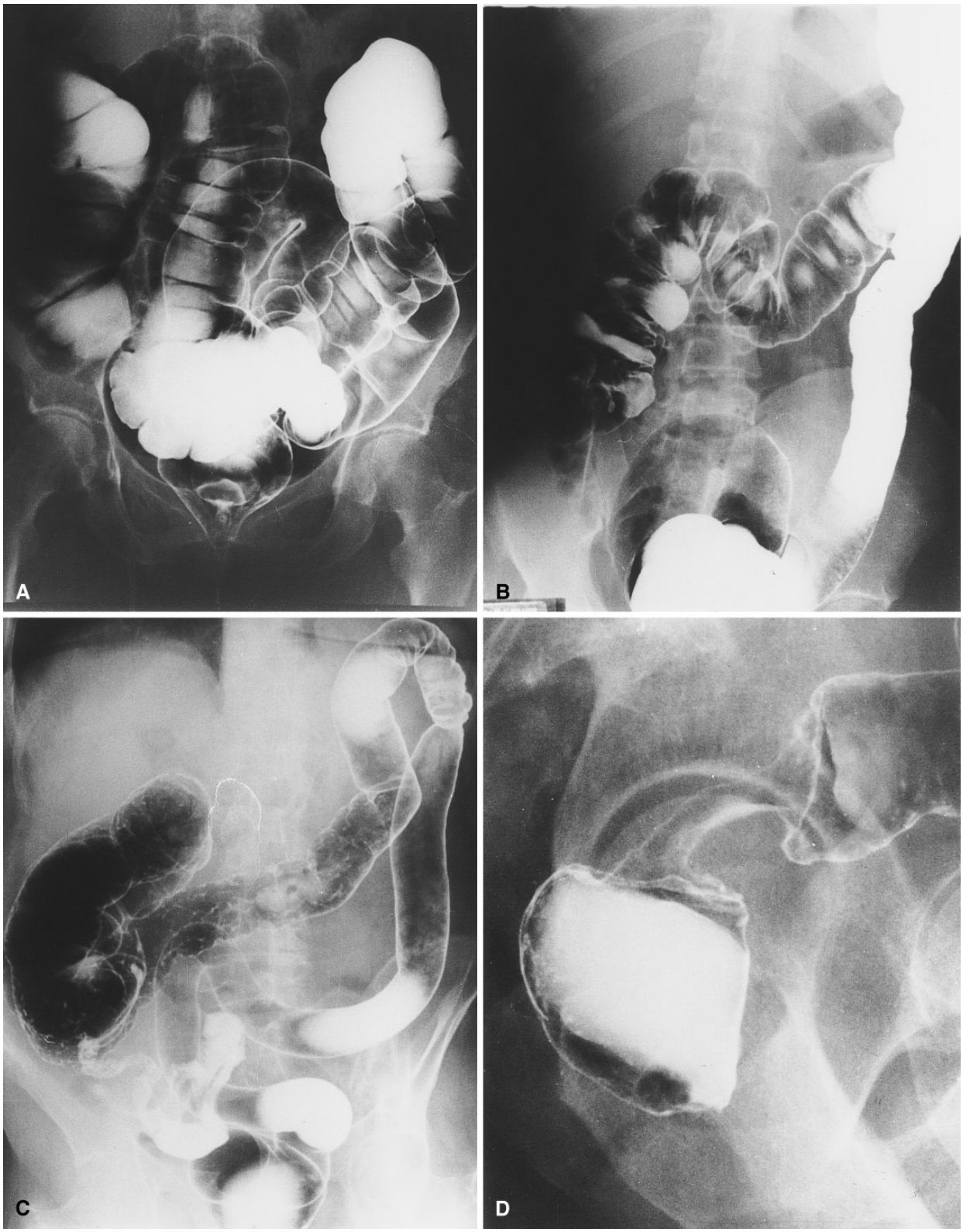

Fig. 1. Four examples of observed pathologies after using pirenzepine. **A** Dolichocolon. **B** Initial ulcerative colitis: a fine granularity of blurred mucosal line is shown in the sigmoid colon. **C** Crohn disease: the combination of aphthoid ulcers, linear ulcerations, and mucosal edema of the right colon and haustral loss are clearly demonstrated. **D** Carcinoma of the rectum.

Conclusions

Pirenzepine, at the dose of 0.1 mg/kg, is to be considered to be the first-choice hypotonic agent for double-contrast study of large bowel. In fact, a good diagnostic performance is obtained by avoiding the side effects induced by unselective antimuscarinic agents. In particular, pirenzepine appears to be safe in cardiac patients.

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