Effects of oral cyclopropium bromide, hyoscine N-butylbromide and placebo on gastric emptying and antral motor activity in healthy man

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SUMMARY Cyclopropium bromide, a new antimuscarinic agent, inhibits gastrointestinal motility in animals at lower doses than those required to inhibit gastric acid secretion and salivation. In man, cyclopropium bromide suppresses fasting and meal stimulated colonic motility. This study investigated the effects of single oral doses of 60 mg cyclopropium bromide, 60 mg hyoscine N-butylbromide and placebo on gastric emptying and on antral motor activity. Twenty four healthy men (mean age 25 years) participated in three experiments one week apart. The drugs were administered, in random double blind fashion, 30 minutes before the ingestion of a semisolid test meal labelled with 74 MBq (2 mCi) ^{99m}Tc sulphur colloid. A gamma camera coupled to a computer monitored gastric emptying together with amplitude, frequency, and propagation velocity of antral contractions. Cyclopropium bromide and, to a lesser degree, hyoscine N-butylbromide delayed gastric emptying and reduced contraction amplitude, but did not affect frequency and propagation velocity of antral contractions. Cyclopropium bromide was significantly more active than hyoscine N-butylbromide; the effects of hyoscine N-butylbromide differed significantly from placebo. Antral contractile activity was present all the time. After cyclopropium bromide, there was a significant correlation between antral contraction amplitude and gastric emptying. No adverse side effects occurred with any one treatment. In conclusion, cyclopropium bromide markedly inhibits gastric emptying and reduces antral contraction amplitude.

Cyclopropium bromide (CTB; Helopharm, Berlin) is a quaternary ammonium compound exhibiting differential activities at muscarinic receptor sites. In that rat, cyclopropium bromide administered subcutaneously or intraduodenally is 10 times less active in reducing gastric acid secretion than atropine, whereas its antagonistic effect on acetylcholine induced spasms of the guinea pig rectum is 7.3 times and the effect against pilocarpine induced spasms 2.8 times stronger than that of atropine. Tachycardia, mydriasis, and inhibition of salivary secretion occur only at high dosages (Helopharm, Berlin, unpublished data). In man it has been shown that a single oral dose of 60 mg cyclopropium bromide inhibits fasting and meal stimulated colonic

motility significantly without inducing any other antimuscarinic effects.¹ The present study was carried out to investigate, in healthy human subjects, the effects of the same dose of cyclopropium bromide on gastric emptying of a semisolid test meal and on the contractile activity of the gastric antrum, and to compare its effects with those of an established anticholinergic drug, hyoscine N-butylbromide (HBB; Buscopan®, Boehringer-Ingelheim), and of placebo.

Methods

SUBJECTS

Studies were performed in 24 healthy men aged between 20 and 39 years with a mean age of 25.3 years. None had any history of gastrointestinal disease or previous abdominal surgery, or were taking any drugs at the time of the investigation.

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The subjects were given a short explanation of the purpose of the research and a description of the procedures to be followed. They were also given a description of any reasonably foreseeable risks or discomforts and informed about the radiation hazard to be expected. Written consent was obtained from each subject. Before it was initiated, the investigation was approved by the Institutional Committee on Studies Involving Human Subjects.

EXPERIMENTAL DESIGN AND PROCEDURE

Each subject took part in three experimental sessions separated by one week intervals. The subjects were instructed to have their usual meal on the evening preceding the experiment but to refrain from eating after 22.00 hours and to eat and drink nothing before coming to the laboratory on the experimental day. All studies were carried out between 08.00 and 10.30 hours. On their arrival at the laboratory, the subjects received, under double blind conditions, either (1) 60 mg cyclotropium bromide, (2) 60 mg hyoscine N-butylbromide, or (3) placebo in dragées of identical size and shape together with 50 ml of water. The sequence, in which the subjects received the three treatments on the different days, was randomised according to a design with eight 3×3 Latin squares.

MEASUREMENT OF GASTRIC EMPTYING AND ANTRAL CONTRACTILE ACTIVITY

Gastric emptying and antral motility were recorded by means of an isotope technique.²⁻⁴ A semisolid test meal labelled with a dose of 74 MBq (2 mCi) 99m-Technetium sulphur colloid diluted in isotonic saline (0.15 M) was used. The ingredients of the meal were 250 ml whole milk (8.75 g protein, 8.75 g fat, 12.5 g carbohydrates), 15 g sugar, 14 g maize starch (Maizena®, Knorr, Wels, Austria; 11.9 g carbohydrates), and, for flavouring, cinnamon. The meal was cooked slowly under continuous stirring until a semisolid consistency was reached. After cooling to a temperature at which it could be ingested, it was mixed thoroughly with the radioisotope by means of an electric mixer. The subjects were seated in an armchair tilted at an angle of 60 degrees backwards to avoid possible overprojection of the stomach and the small intestine. Thirty minutes after drug administration, the subjects sucked the test meal through a wide lumen polyethylene tube. A large field of view gamma scintillation camera coupled to a computer system (Digital Equipments Corporation, System Gamma-11) was brought in an anterior position, in which the stomach appeared in the centre of the field of an

oscilloscope display. Immediately thereafter, recording of the radioactivity over the stomach and over the remaining abdomen was begun and continued for 50 minutes. In minutes 7 to 10, 27 to 30, and 47 to 50 after the start of recording, data were acquired in frame mode with 80 serial images over three seconds each and in the remaining time with serial images of one minute frame time. The one minute frames were used for the generation of the gastric emptying curves. Background activity was calculated and subtracted from the total, so that a falling count rate was representative of the rate of gastric emptying. The radioactivity count 10, 15, 20, 25, 30, 35, 40, 45, and 50 minutes after the start of recording was calculated as a percentage of the activity count at five minutes after the start of recording. In addition, the half emptying time ($T_{1/2}$) was calculated from the regression line of the count rate plotted on a logarithmic scale against time on a linear scale.⁵ The three second frames were used for measuring antral motility, which was quantified by recording the variations of radioactivity in three small regions of interest positioned at right angles to the axis of the antrum by means of a joystick-type computer program. The more or less sinusoidal variations of activity in each of these regions were high pass filtered by transforming the curve into the Fourier space, applying a filter with a lower frequency cut-off at 1.5 Hertz (Hz), and back transformation. The algorithm of the fast Fourier transform was used for these computations. From the resulting curve the modulation depth of the curve, which corresponds to the amplitude of antral contractions, was calculated.² After this procedure, the curve was low-pass filtered with an upper cut-off frequency of 5.5 Hz using the method described above. Then the autocorrelation function as well as the power spectrum of the curve were computed, both of which were used to determine the frequency of antral contractions. Based on this frequency, a 'gated' study⁶ was generated by adding all images of the three second frames belonging to the same state of concentration of the antral wall. An amplitude as well as a phase image were obtained by applying a Fourier analysis of the first component – that is, by fitting only the first sinusoid of the Fourier expansion to the time activity curve for each pixel of the gated study. As in the phase image regions of equal phase appear in the same colour, the distances between points of equal contraction state could be calculated. These distances were used, together with the contraction period, to compute the propagation velocity of antral contractions.

Side effects as reported spontaneously by the subjects were recorded together with the experimenters' observations.

STATISTICAL ANALYSIS

The data were subjected to an analysis of variance for repeated measures.⁷ The influences of the fixed factors 'treatment' (one to three), 'day' (experimental days one to three), 'time' (periods of measurement), and of the random factor 'subjects' (1 to 24) were studied. Differences between treatment effects were evaluated by comparisons based on the analysis of variance. In addition, correlations between the mean values over time of the measured variables were calculated.

Results

1 GASTRIC EMPTYING

The percentage gastric emptying was slowed by both drugs, cyclotropium bromide being more active than hyoscine N-butybromide (Fig. 1). The analysis revealed that the treatment effects differed significantly ($F(2,396)=34.24$, $p<0.001$). The emptying rate was significantly slower after administration of cyclotropium bromide than after both placebo ($F(1,396)=64.46$, $p<0.001$) and hyoscine N-butybromide ($F(1,396)=32.05$, $p<0.001$). Although hyoscine N-butybromide delayed emptying only slightly, this effect differed statistically from that of placebo ($F(1,396)=5.61$, $p<0.025$).

Half emptying time: the mean $T_{1/2}$ after placebo administration was 52.9 minutes ± 4.3 SEM as compared with 64.2 ± 7.1 minutes after hyoscine N-butybromide and 102.9 ± 16.3 minutes after cyclotropium bromide (Fig. 2). The effects of hyoscine N-butybromide on $T_{1/2}$ did not differ statistically from those of placebo, whereas the mean $T_{1/2}$ after administration of cyclotropium bromide was significantly longer than the mean $T_{1/2}$

Fig. 1 Mean per cent rate $\pm$ SEM of gastric emptying after administration of cyclotropium bromide (—), hyoscine N-butybromide (---), and placebo (.....).

Fig. 2 Half emptying time, in minutes, of the isotopically labelled test meal in the 24 subjects after the administration of placebo, hyoscine N-butybromide, and cyclotropium bromide. Horizontal lines indicate mean times.

after placebo ($F(1,44)=13.36$, $p<0.001$) and after hyoscine N-butybromide ($F(1,44)=8.00$, $p<0.01$), respectively.

2 ANTRAL MOTOR ACTIVITY

Regular antral contractions were present all the time and no 'silent' phases were observed in any subject. The analysis revealed that the sequence in which the subjects received the treatments on the three experimental days had no significant influence on the variables measured.

The amplitude of antral contractions was reduced by both drugs, cyclotropium bromide being markedly more active than hyoscine N-butybromide (Fig. 3). The analysis revealed significantly differing treatment effects ($F(2,132)=9.00$, $p<0.001$). The effect of cyclotropium bromide differed significantly from both placebo ($F(1,132)=18.00$, $p<0.001$) and hyoscine N-butybromide ($F(1,132)=4.87$, $p<0.05$). Hyoscine N-butybromide was significantly more active than placebo ($F(1,132)=4.15$, $p<0.05$). Regardless of what treatment had been administered, the amplitude tended to increase from relatively low levels immediately after the start of recording to higher levels at the end of the experimental time. This was reflected in the analysis by a significant F-value for the time-factor ($F(2,132)=8.80$, $p<0.001$).

Frequency of antral contractions: cyclotropium bromide, hyoscine N-butybromide, and placebo had no differential effects. With all three treatments, the contraction frequency decreased to about the same degree from a mean of 3.10 ± 0.06 cycles

Fig. 3 Antral contraction amplitude in per cent $\pm$ SEM in periods 7 to 10 minutes, 27 to 30 minutes, and 47 to 50 minutes after the start of recording. Cyclotropium bromide (—), hyoscine N-butylbromide (- - -), and placebo (· · · ·).

per min (cpm) in minutes 7 to 10 after the start of recording to 3.03 ± 0.03 cpm in minutes 27 to 30, and 2.98 ± 0.03 cpm in minutes 47 to 50, respectively. This effect was reflected by a significant F-value for the time-factor ($F(2,132) = 11.46$, $p < 0.001$).

Propagation velocity of antral contractions: the propagation velocity was not altered by any one of the treatments. There was a slight slowing from a mean velocity of 2.96 ± 0.07 mm/s in minutes 7 to 10 after the start of recording to 2.80 ± 0.05 mm/s in minutes 27 to 30, and to 2.77 ± 0.06 mm/s in minutes 47 to 50. This deceleration over time was significant ($F(2,132) = 3.99$, $p < 0.025$). No retroulsive contraction waves could be detected.

3 RELATIONSHIPS BETWEEN ANTRAL MOTILITY AND GASTRIC EMPTYING

The percentage gastric emptying tended to decrease with decreasing antral contraction amplitude. Whereas after administration of placebo and of hyoscine N-butylbromide there were statistically only indications for such a tendency, the correlation between emptying rate and antral contraction amplitude was significant after cyclotropium bromide ($r(22) = 0.475$, $p < 0.02$). Amplitude and frequency of antral contractions showed an inverse relationship: the frequency increased with decreasing amplitude ($r(70) = 0.553$, $p < 0.0001$). This relationship was significant after administration of all of the three treatments ($p < 0.015$). After cyclotropium bromide but not after hyoscine N-butylbromide and placebo there was a significant positive correlation between the propagation velocity and the amplitude of antral contractions: low velocities prevailed when the amplitudes were low, and higher velocities when the amplitudes were

high ($r(22) = 0.491$, $p < 0.015$). After cyclotropium bromide there was also an indication that higher propulsion velocities resulted in speedier gastric emptying ($r(22) = 0.341$, $p < 0.1$).

4 SIDE EFFECTS

No side effects whatsoever were reported or observed after the administration of any one treatment.

Discussion

The results of the present study show that cyclotropium bromide 60 mg significantly delayed gastric emptying and reduced the contraction amplitude of the gastric antrum, while it did not affect the frequency and the propagation velocity of antral contractions or cause any side effects. Cyclotropium bromide was markedly more active than hyoscine N-butylbromide, which had a significant inhibitory effect on antral contraction amplitude and on per cent emptying rate but not on T_4 . These findings are consistent with those from an earlier investigation, in which cyclotropium bromide was found to inhibit fasting and meal-stimulated contractile activity of the human colon significantly more than did hyoscine N-butylbromide.¹ The comparatively weak effect of oral hyoscine N-butylbromide on gastric emptying and motility is reflected by discordant reports in the literature. While some authors reported that hyoscine N-butylbromide produced, even at doses as high as 240 and 480 mg, only weak⁸ or no effects on gastric emptying,⁹ others found intraduodenal doses from 80 to 320 mg hyoscine N-butylbromide to reduce antral motor activity,¹⁰ and oral and rectal doses from 50 to 400 mg to decrease the number of gastric type II-waves.¹¹⁻¹³ Both, the modest effect on gastric emptying and the low incidence of anticholinergic side effects caused by hyoscine N-butylbromide have been ascribed to the fact that this drug, like all quaternary ammonium compounds, is poorly absorbed from the intestine.^{14, 15} Cyclotropium bromide, by contrast, is absorbed relatively well (Helopharm, unpublished data), a fact which seems to contribute crucially to its superiority over hyoscine N-butylbromide in inhibiting gastrointestinal motility.

The results also show that there was a positive correlation between antral contraction amplitude and gastric emptying. This observation confirms earlier findings from studies in dogs^{16, 17} but is inconsistent with the concept that emptying of liquids^{18, 19} or of homogenised food²⁰ occurs independently of antral contractile activity or that the latter is only of minor importance in such conditions. As a regular contractile activity of the

antrum was present all the time in each of the subjects of our study, the complete absence of antral pressure changes reported to have prevailed during the emptying of a homogenised meal in one paper²⁰ apparently can not be ascribed to a real absence of contractions but to the absence of a method sensitive enough to reliably monitor such contractions. Our observation indicates that antral contractile activity is involved not only with the grinding and the dispersion of solids²⁰ but also with the propulsion and emptying of semisolid or homogenised gastric contents. The steady increase of amplitude and the simultaneous decrease of frequency and propagation velocity of antral contractions, which continued in a more or less linear fashion throughout the entire recording time, was not influenced by the administration of the two anticholinergic drugs. This suggests that cholinergic nervous activity is not responsible for these effects, which also do not seem to be related to changes in gastric emptying rate as the latter showed a regular linear pattern after all of the three treatments. The fact that there was no evidence for retropulsive contraction waves does not preclude that there was no retropulsion of antral contents into more proximal parts of the stomach,²¹ because the method used in the present study did not allow quantification of this retropulsion. It is concluded that cyclotropium bromide clearly inhibits gastric emptying and antral contractile activity in healthy man and may, after appropriate testing, find a use in the treatment of accelerated gastric emptying and of increased or 'spastic' motor activity of the gastrointestinal tract.

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