Fat preload delays gastric emptying: reversal by cisapride

G. STACHER, H. BERGMANN, G. GAUPMANN, C. SCHNEIDER, A. KUGI, J. HÖBART, A. BINDER & G. MITTELBACH-STEINER

Psychophysiology Unit at the Departments of Psychiatry and Surgery I; Division of Nuclear Medicine at the Department of Medicine II; and Ludwig Boltzmann Institute of Nuclear Medicine; University of Vienna, Vienna, Austria

1 Meals empty more slowly when they contain fat.

2 This study investigated whether an intragastric fat preload in comparison with a water preload affected gastric emptying of a semisolid meal and antral motor activity, and whether cisapride reversed such effects.

3 Twelve healthy subjects were studied under three conditions each: (A), preload of 50 ml water orally; (B) and (C), preload of 50 ml cream (20 g fat). After preloads, subjects reclined right sided for 20 min. Thereafter, placebo in conditions (A) and (B) and 10 mg cisapride in (C) were administered i.v. in a random double-blind fashion and subjects ingested a semisolid radiolabelled 1150 kJ meal. Gastric emptying and antral motor activity were recorded scintigraphically for 50 min using a dual-headed gamma camera.

4 Gastric emptying was significantly slower ($P < 0.005$) after fat preload and placebo than after water preload and placebo. Cisapride administered after fat preload abolished the delaying effect of the fat preload ($P < 0.001$).

5 Antral contraction amplitudes after fat preload and placebo were higher ($P < 0.01$) than after water preload and placebo as well as fat preload and cisapride at the start of recording and decreased slightly thereafter, whereas slight increases occurred in the other conditions. Frequency and propagation velocity of contractions were not differently affected.

6 Gastric emptying is delayed after prior fat ingestion and this effect is abolished by cisapride.

Keywords fat-delayed gastric emptying semisolid meal antral motor activity cisapride

Introduction

In man, the effects of agents potentially accelerating gastric emptying ('prokinetic' drugs) have been evaluated in clinical conditions associated with compromised gastric motor function, such as longstanding diabetes mellitus (Horowitz *et al.*, 1985b), progressive systemic sclerosis (Horowitz *et al.*, 1987a), dystrophia myotonica

(Horowitz *et al.*, 1987b) and primary anorexia nervosa (Stacher *et al.*, 1987). However, patients suffering from these conditions are not seen in great numbers and are not always ready to give their consent to more than a single evaluation of their gastric emptying, which means that clinical trials often will extend over prolonged periods of

time. In healthy subjects, effects of prokinetic drugs cannot readily be evaluated, since the normal delivery of gastric contents into the duodenum is not accelerated systematically by doses effective in conditions of delayed emptying (Behar & Ramsby, 1978). Thus, attempts have been made to find models for studying the effects of potentially prokinetic agents in healthy subjects with gastric emptying delayed pharmacologically, i.e., by the dopamine precursor levodopa (Berkowitz & McCallum, 1980) or dopamine itself (Müller-Lissner *et al.*, 1986). However, dopamine administration affects only one mechanism in control of gastric emptying, is liable to induce nausea and the ensuing changes cannot directly be related to any normally occurring state. A state, in which gastric evacuation is slowed down physiologically, occurs after ingestion (Cunningham & Read, 1987; Kroop *et al.*, 1979) and intragastric (Ruskone *et al.*, 1987) or intraduodenal (Collins *et al.*, 1986; Valenzuela & Defilippi, 1981) administration of fat. This physiological state may be well suited for the evaluation of the effects of pharmacological agents promoting gastric emptying. However, no attempts to test this were undertaken so far. Therefore, the present investigation was carried out to evaluate, in healthy men, (i) the effects of the ingestion of 20 g of liquid fat in the form of 36% dairy cream in comparison with water on gastric emptying of a subsequently ingested semisolid standard meal, and (ii) to compare, under random double-blind conditions, the effects of intravenous (i.v.) cisapride with those of placebo on the emptying of the meal after both fat and water preloads.

Methods

Subjects

Studies were performed on 12 healthy male volunteers ranging in age from 23 to 35 years. Only subjects with no history of peptic ulcer and no abdominal operation except appendectomy and umbilical or inguinal herniorrhaphy were included. None of them took any drugs during the investigation. After the purpose of the research, the procedures to be followed and any possible risks or discomforts were explained, written consent was obtained from each subject. Before initiation, the study had been approved by the Institutional Committee on Studies Involving Human Beings.

Study design and procedure

Each subject took part in three recording sessions at 1 week intervals. The subjects were instructed to have their usual meal on the evening preceding the sessions but to refrain from eating after 22.00 h and to eat and drink nothing before coming to the laboratory on the study days. Recordings were carried out between 07.30 h and 10.30 h under three different conditions (A, B and C) according to a randomisation plan with four 3×3 Latin squares. In condition A, the subjects drank, 5 min after their arrival at the laboratory, 50 ml of water, whereas in conditions B and C, they drank 56 g of 36% dairy cream containing 20 g of fat. Thereafter, they lay on their right side for 20 min. Following this period of time, they received, in double-blind fashion, i.v. injections of differing content: placebo in conditions A and B, and 10 mg of cisapride in condition C. Twenty-five minutes after the ingestion of the water and fat preloads, respectively, the subjects started to eat a semisolid test meal.

Measurement of gastric emptying and antral contractile activity

Gastric emptying and antral motor activity were recorded by means of an isotope technique (Jacobs *et al.*, 1982; Stacher *et al.*, 1987). A semisolid test meal was labelled with a dose of 37 MBq (1 mCi) 99m-Technetium sulphur colloid diluted in isotonic saline (0.15 M). The adherence of the radiolabel to the test meal has been found to be reliable in previous *in vitro* experiments (Stacher *et al.*, 1987). The ingredients of the meal, which had a caloric content of 1150 kJ and an osmolality of 558 mmol kg^{-1} , were 250 ml 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. The subjects ate the test meal with a spoon. Throughout the recording period, they sat in an armchair tilted at an angle of 60 degrees backwards to avoid possible overprojection of the stomach and the small intestine. A dual-headed gamma scintillation camera (Rota-Camera, Siemens AG, Erlangen, West Germany) fitted with 140 keV parallel-hole collimators and interfaced to a computer system (System GAMMA-11, Digital Equipment Corporation, Marlboro, MA) was used, with one camera head in an anterior and the other in a posterior position. The patient was

positioned in such a way that the stomach appeared in the centres of the fields of view of the camera heads. Geometric means of anterior and posterior camera counts were calculated to correct for changing gamma ray attenuation by the subjects' tissues resulting from the movement of the labelled meal from the fundus to the antrum and from or towards the detectors (Christian *et al.*, 1980). Data were also corrected for radionuclide decay. For scatter and septal penetration, no corrections were necessary in view of the characteristics of the recording system and the fact that only one isotope, i.e., the low energy emitter 99m-Tc, was used (Loo *et al.*, 1984). Recording of the radioactivity began at the end of meal ingestion and continued for 50 min. In minutes 7 to 10 and 47 to 50 after the start of recording, data were acquired in frame mode with 80 serial images over 3 s each and in the remaining time with serial images of 1 min frame time. The 1 min frames were used to generate gastric emptying curves from a region of interest drawn visually around the stomach on the computer display. From these curves, background activity as counted in a region of interest drawn to the right of the gastric fundus and cranially of the antrum was subtracted, so that a falling count rate represented gastric emptying. The mean counts at each time were related to the counts at the start of recording, which were taken as 100%. 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 (Hunt & Spurrell, 1951). The 3 s frames were used to measure antral motility as quantitated by recording the variations of radioactivity in three small regions of interest selected at right angles to the axis of the antrum. The resulting more or less sinusoidal time-activity curves for each of these regions were high-pass filtered by transforming them into the Fourier space, applying a filter with a low frequency cutoff at $1.5 \text{ cycles min}^{-1}$, and back transformation. This procedure efficiently removed from the curves linear trends and other slowly varying components, which would have given rise to significant error in the subsequent computation of the mean modulation depth of the individual curves. This modulation depth, which corresponds to the amplitude of antral contractions, was derived from the standard deviation of the mean excursion of the individual points of the curves under the assumption that the variations followed a sinusoidal pattern (Jacobs *et al.*, 1982; Stacher *et al.*, 1987). After this procedure, the curve was low-pass filtered with a high frequency cutoff at $5.5 \text{ cycles min}^{-1}$ in order to remove components with higher

frequencies, such as respiration, cardiovascular pulsation, body movements and noise originating from the inherent statistical fluctuations generated by the radioactive decay. Then the autocorrelation function of the curve was computed and used to determine the frequency of antral contractions. The propagation velocity of contractions was determined by calculating the time it took a contraction wave to travel over the distances between adjacent regions of interest, i.e., the time lapse between the occurrence of an activity minimum at one region and its appearance at the next. The velocities measured between the first, most oral, and the second region of interest and between the second and the third region were averaged and expressed as mean propagation velocity. The total body radiation burden (0.1 milliSievert) resulting from one administered dose of the radionuclide as well as the dose absorbed by the stomach (1.2 milliSievert) were less than the radiation burden arising from a single abdominal X-ray and therefore could be regarded as acceptable for the three consecutive studies carried out in the present investigation (Horowitz *et al.*, 1985a; Siegel *et al.*, 1983). A lower radionuclide dose than the one used would not have permitted a reliable recording of antral motor activity: the scintillation counts in the 3 s frames underlying these evaluations would have been too small, which would have made the method susceptible to errors, mainly the one arising from a disproportionate increase of the inherent statistical fluctuations generated by the radioactive decay.

Assessment of side effects

Side effects as reported spontaneously by the subjects were recorded along with the investigators' observations.

Statistical analysis

The percentage of marker remaining in the stomach and the data on antral motor activity were subjected to analyses of variance for repeated measures (Games, 1975). The influences of the fixed factors 'condition' (conditions A, B and C), 'session' (recording sessions 1 to 3), 'time' (periods 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 min, and 7–10 and 47–50 min after the start of recording, respectively), and of the random factor 'subjects' (1 to 12) were studied. Differences between the mean effects of the three treatments were evaluated using a sequentially rejective multiple test procedure (Holm, 1979) based on the analysis of variance. In this

procedure, directional tests were carried out and an overall significance level of $\alpha = 0.05$ was adopted. Since half-emptying time values are not normally distributed, these data were analysed by a non-parametric test, i.e., the Sign Test for paired data (Conover, 1971).

Results

The analyses revealed that the sequence in which the subjects underwent the three experimental conditions in the three recording sessions had no significant influence on the variables measured.

Gastric emptying

Percentage of marker remaining in the stomach

The emptying curves over time followed closely a monoexponential pattern under all of the three experimental conditions. When subjects had ingested the standard meal after a water preload, the emptying rates were in the same range as in healthy subjects studied previously after the ingestion of an identical (Stacher *et al.*, 1984) or a very similar (Jacobs *et al.*, 1982) semisolid meal but without a water preload. The analysis showed that the values recorded under the three conditions differed significantly ($F(2,200) = 93.40$, $P < 0.001$). After fat preload and placebo administration, the subjects' stomachs emptied significantly slower than after water preload and placebo (Figure 1), and after fat preload and cisapride significantly faster than after fat preload and placebo administration. The rate of emptying after fat preload and cisapride did not differ from that after water preload and placebo.

Figure 1 Gastric emptying of the test meal. Percent of marker remaining in stomach $\pm$ s.e. mean emptied over the 50 min after water preload and administration of placebo (.....), fat preload and administration of placebo (-----) and fat preload and administration of cisapride (—).

Gastric half-emptying time In condition B, $t_{1/2}$ s ranged from 53.8 to 341.1 min (median: 99.2 min) and were longer than in condition A (range: 26.1 to 206.6 min; median: 51.0 min) in all subjects but one (Figure 2). The latter subject had a very long $t_{1/2}$ (206.6 min) already in condition A, and this was not changed in condition B ($t_{1/2}$: 204.1 min). In condition C, $t_{1/2}$ s were shorter than in condition B in all subjects and ranged from 23.9 to 80.8 min (median: 54.9 min). The differences in $t_{1/2}$ length between conditions A and B, and B and C were statistically significant (Sign Test, $P < 0.005$ and $P < 0.001$, respectively).

Antral motor activity

Amplitude of contractions In condition A (placebo after water preload), the amplitude of antral contractions increased from the 7–10 min to the 47–50 min recording period, and a similar increase was present also in condition C (cisapride after fat preload; Table 1). In condition B (placebo after fat preload), the amplitudes in the 7–10 min period were significantly higher ($P < 0.01$) than in the two other conditions, whereas they were about as high as in the other conditions in the 47–50 min period (Table 1).

Frequency of contractions After water preload and placebo as well as after fat preload and placebo, the frequency decreased slightly from

Figure 2 Gastric half-emptying time. Half-emptying times (in min) of the isotopically labelled test meal after water preload and administration of placebo, fat preload and administration of placebo and fat preload and administration of cisapride in the individual subjects.

Table 1 Antral contractile activity in the 12 subjects having received a water preload and placebo, a fat preload and placebo, and a fat preload and cisapride, respectively^a

	7–10 min	47–50 min
<i>Amplitude (modulation depth in %)</i>		
Water preload and placebo	24.58 ± 2.99	30.83 ± 4.37
Fat preload and placebo	34.33 ± 4.23 ^b	31.50 ± 1.94
Fat preload and cisapride	26.25 ± 3.76	31.33 ± 2.53
<i>Frequency (cycles min⁻¹)</i>		
Water preload and placebo	2.80 ± 0.10	2.74 ± 0.09
Fat preload and placebo	2.82 ± 0.08	2.60 ± 0.08
Fat preload and cisapride	2.55 ± 0.11	2.76 ± 0.07
<i>Propagation velocity (mm s⁻¹)</i>		
Water preload and placebo	1.66 ± 0.53	1.52 ± 0.47
Fat preload and placebo	1.75 ± 0.57	1.95 ± 0.61
Fat preload and cisapride	1.34 ± 0.41	1.57 ± 0.49

^aAmplitude (modulation depth), frequency and propagation velocity of contractions at 7–10 min and 47–50 min after the start of meal ingestion. Values are mean ± s.e. mean measured in the three regions of interest positioned across the antrum.

^bSignificantly different from water preload and placebo and fat preload and cisapride values ($P < 0.01$).

the 7–10 min to the 47–50 min recording period, whereas it increased slightly after fat preload and cisapride (Table 1). The analysis revealed no significant influence of any of the investigated factors.

Propagation velocity of contractions After water preload and placebo administration, the propagation velocity decreased slightly from the 7–10 min to the 47–50 min recording period, whereas there were slight increases in the other two conditions (Table 1). The analysis showed that none of the investigated factors had a systematic influence.

Side effects

No side effects were reported or observed after water preload and placebo administration. After fat preload, one subject reported a feeling of sickness starting 20 min after administration of placebo and lasting for 5 min and another, in minutes 3 and 4 after the administration of cisapride, a feeling of heat and the impression to hear everything from a distance. Both side effects were judged to be mild by the subjects and no action was taken.

Discussion

The results of the present study show that 20 g fat administered in form of dairy cream 25 min prior to a semisolid meal consistently delayed the emptying of that meal from the stomach. Consistent data have been reported earlier: Kroop *et al.* (1979) found that, in healthy men, 100 ml of cooked egg whites were emptied significantly slower when 45 ml of corn oil were added to this meal. Others (Ruskone *et al.*, 1987) comparing the effects of intragastrically or intraduodenally instilled with those of intravenously infused triglycerides, found gastric emptying of both liquids and solids to be delayed by intragastric and intraduodenal but not by intravenous triglycerides. It has also been described (Cunningham & Read, 1987) that a preload of fat in the form of 60 g margarine incorporated into soup slowed gastric emptying of a mashed potato meal ingested 20 min later. Interestingly, this slowing was due to an increase of the lag phase but not to an alteration of the slope of the emptying curve, whereas the incorporation of margarine into the mashed potatoes led to a flattening of the slope.

How the fat related delay in gastric emptying is brought about is not entirely clear. In dogs it

has been observed that oral administration of oleic acid was followed by a diminution of pyloric diameter together with a decrease in intragastric propulsive activity (Keinke & Ehrlein, 1983). In the present study, by contrast, antral contraction amplitudes in the period 7–10 min following meal ingestion were significantly higher after fat preload and placebo than after water preload and placebo as well as after fat preload and cisapride and these high amplitudes were associated with a significantly slower emptying of the meal. Thus, an increased force of phasic antral contractile activity might result, instead of an acceleration, in a deceleration of emptying. In other studies on healthy human beings it has been observed that the intragastric instillation of intralipid induced a sustained rise in pyloric basal pressure (White *et al.*, 1983) and, more recently, that intraduodenal lipid infusion was followed by a reduced flow of gastric contents through the pylorus and by the occurrence of isolated pyloric pressure waves (Touqas *et al.*, 1987). The latter type of contractions and a sustained increase in pyloric tone was also observed, together with a suppression of antral pressure waves, during intraduodenal infusion of triglycerides (Hedde *et al.*, 1988). Similarly, the ingestion of milk was found to be followed by a clear and abrupt change from co-ordinated antro-pyloro-duodenal pressure waves to isolated pyloric pressure waves (Houghton *et al.*, 1988). These changes in antro-pyloro-duodenal motor activity and the ensuing

slowing of gastric emptying could be brought about by an interaction of lipids with duodenal receptors but also via a release of cholecystokinin from the duodenal mucosa, which occurs after ingestion (Liddle *et al.*, 1985; Lilja *et al.*, 1982; Maton *et al.*, 1982) and intragastric (Kleibeuker *et al.*, 1986; Lee *et al.*, 1987) or intraduodenal (Guedon *et al.*, 1988; Kleibeuker *et al.*, 1986; Lamers *et al.*, 1979; Lilja *et al.*, 1982) instillation of fat. The latter possibility seems also to be suggested by the fact that gastric emptying is delayed at plasma levels of exogenous cholecystokinin which equate those prevailing physiologically after the ingestion of a mixed meal (Liddle *et al.*, 1985). The fact that cisapride reversed the delay in gastric emptying induced by a preload of fat is consonant with the finding that, in dogs, gastric emptying of a semisolid barium meal enriched with 20 ml of olive oil could be accelerated by intravenously administered cisapride (Janisch *et al.*, 1987). The mechanism, however, by which cisapride counteracts the delaying effect of fat on gastric emptying, remains to be explored. In conclusion, the results of the present investigation indicate that gastric emptying of a meal is delayed by the antecedent ingestion of relatively small amounts of fat and that this delay can be abolished by cisapride. Slowed gastric emptying after a fat preload thus seems to be a suitable model for the evaluation of potentially prokinetic agents in healthy man with normal gastric motor function.

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