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Slow Gastric Emptying Induced by High Fat Content of Meal Accelerated by Cisapride Administered Rectally

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The evaluation of agents potentially accelerating gastric emptying in gastric stasis syndromes is time-consuming. Since a previous study showed that emptying is slowed after antecedent fat ingestion and intravenous cisapride abolishes this effect, we investigated whether emptying delayed by fat incorporated into a meal is reversed by cisapride and thus could serve as a model for such evaluations. Twelve healthy males received, under double-blind conditions, 30 mg cisapride rectally or placebo, and 3 hr thereafter a semisolid meal of low (9.2 g) or high (37.9 g) fat content. The sequence of combinations placebo/low-fat meal, placebo/high-fat meal, and cisapride/high-fat meal was randomized. Gastric emptying and antral motility were recorded scintigraphically. After placebo/high-fat, emptying was significantly slower ($P < 0.05$) than after placebo/low-fat. After cisapride/high-fat, emptying was significantly faster ($P < 0.01$) than after placebo/high-fat and similar to that after placebo/low-fat. Antral motility was little affected. The slow emptying of a high-fat meal thus seems a suitable model for the evaluation of prokinetic drug effects.

KEY WORDS: gastric emptying; fatty meal; cisapride rectally; acceleration.

Pharmacological agents potentially accelerating gastric emptying have been evaluated in patients suffering from conditions associated with compromised gastric motor function (1–4). Since such patients are not seen in great numbers and are not always ready to consent to more than one study of their gastric emptying, clinical trials tend to be time-consuming. Thus, attempts have been made to find models for studying drug effects on the evacuation of ingesta from the stomach in healthy human subjects with gastric emptying delayed pharmacologically, ie, by the dopamine precursor levodopa (5) or dopamine itself (6). However, dopamine administration affects only one mechanism in control of gastric emptying, is liable to induce nausea, and the ensuing state cannot directly be related to any normally occurring state. Physiologically, gastric evacuation is slowed down after the ingestion of meals of high nutritive density (7), in particular after ingestion (7, 8) or intraduodenal instillation (9, 10) of fat. In a previous study in healthy men, the gastric emptying of a standard meal of low fat content was markedly slower after the ingestion of fat 25 min prior to mealtime than after a water preload, and this effect was abolished by intravenous administration of the prokinetic agent, cisapride (11). The present study was aimed at inves-

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tigating whether a similar slowing of emptying occurred also when fat was incorporated into a standard meal and whether this slowing occurred regularly enough to be suited for an evaluation of the effects of prokinetic drugs in a limited number of subjects. It further was aimed at investigating whether cisapride counteracted the delaying effect of fat when administered rectally. To this end, we compared (1) the gastric emptying of two semisolid standard meals of low and high fat content but otherwise identical composition, volume, and appearance under random single-blind conditions, and (2) the effects of cisapride, 30 mg administered rectally, with those of a placebo suppository on the emptying of the high-fat meal under random double-blind conditions. Cisapride acts via a facilitation of postganglionic acetylcholine release in the myenteric plexus (12) and has been shown to enhance gastric emptying in a variety of conditions associated with gastric stasis (2, 4, 13, 14).

MATERIALS AND METHODS

Subjects. Studies were performed on 12 healthy male volunteers. Their age ranged from 22 to 27 years (mean: 24.5 years ± 0.5 SEM) and their weight from 60 to 87 kg (mean: 74.7 ± 2.5 kg). Only subjects with no history of peptic ulcer and no abdominal operation except appendectomy and umbilical or inguinal herniorraphy were included. None of them took any drugs during the investigation. Written consent was obtained from each subject, after the purpose of the research, the procedures to be followed, and any possible risks or discomforts had been explained to them. Before its initiation, the study had been approved by the Institutional Committee on Studies Involving Human Beings.

Study Design and Procedure. Each subject participated, at one-week intervals, in three emptying studies taking place between 1200 and 1630 hr. The subjects were instructed to have their usual meal on the evening preceding the recording sessions but to refrain from eating after 2200 hr. On the study days, subjects were requested to eat, between 0700 and 0900 hr, a standard breakfast consisting of two slices of buttered bread and of mallow tea. Three and a half hours prior to the scheduled start of their study, subjects arrived at the laboratory. Three hours before the beginning of the gastric emptying study, a suppository containing either 30 mg of cisapride (Janssen Pharmaceutica, Beerse, Belgium) or placebo was administered under random double-blind conditions. Gastric emptying studies commenced after the subjects had ingested a semisolid standard meal. On one of the study days, this meal had a low and on two days a high fat content; although the appearance and the volume of the meals were identical. The sequence in which the three treatment combinations, ie, low-fat meal after placebo, high-fat meal after placebo, and high-fat meal after cisapride, were administered on the three study days was randomized according to a plan with four 3 × 3 Latin squares.

Measurement of Gastric Emptying and Antral Contractile Activity. Gastric emptying and antral motor activity were recorded by means of an isotope technique (4, 15). The test meals were labeled with a dose of 46 MBq ^{99m}technetium sulfur colloid diluted in isotonic saline (0.15 M). The ingredients of the low-fat meal were 250 ml milk (9.2 g fat, 8.5 g protein, 12.3 g carbohydrates), 15 g sugar, 14 g maize starch (Maizena, Knorr, Wels, Austria; 11.9 g carbohydrates), and, for flavoring, cinnamon. Its caloric content amounted to 1168 kilo-Joule (kJ) and its osmolality to 558 mmol/kg. The high-fat meal had about fourfold the fat and about twofold the caloric content of the low-fat meal, ie, 37.9 g fat and 2239 kJ, respectively, and an osmolality of 585 mmol/kg. Its ingredients were 90 ml cream (32.0 g fat, 2.0 g protein, 2.7 g carbohydrates), 160 ml milk (5.9 g fat, 5.4 g protein, 7.9 g carbohydrates), 15 g sugar, 14 g maize starch, and cinnamon. These ingredients were cooked slowly under continuous stirring until a semisolid consistency of the meal was reached. After cooling to a temperature at which they could be ingested, they were mixed thoroughly with the radioisotope.

Throughout the recording period, the subjects 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 Equipments Corporation, Marlboro, Massachusetts) was used, with one camera head in an anterior and the other in a posterior position.

Recording of the radioactivity over the stomach and the remaining abdomen began at the end of meal ingestion and continued for 50 min. From 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 sec each and in the remaining time with serial images of 1 min frame time. To correct for changing gamma-ray attenuation by the subjects' tissues resulting from the movement of the labeled meal from and towards the detectors, geometric means of anterior and posterior camera counts were calculated for each of the serial images. Data also were corrected for radionuclide decay. 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. The mean counts at each time were related to the counts at the start of recording, which were taken as 100%. Background activity was calculated and subtracted from the total, so that a falling count rate represented gastric emptying. In addition, the half-emptying time ($T1/2$) was calculated from the regression line of the count rate plotted on a logarithmic scale against time on a linear scale (16). The emptying pattern of the semisolid meals equals that of a solid meal except for the absence of a lag phase (15), which has to be attributed to the fact that semisolid meals need little or no grinding.

Antral motility was quantitated by recording the variations of radioactivity in three small regions of interest selected at right angles to the axis of the antrum, using the

serial images of 3-sec frame time. 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 cycles per minute (cpm), and back transformation. This procedure efficiently removed from the curves linear trends and other slowly varying components. Subsequently, the modulation depth of the individual curves, which corresponds to the amplitude of antral contractions, was derived from the standard deviation of the mean excursion of the individual points on the curves under the assumption that the variations followed a sinusoidal pattern (4, 15). After this procedure, the curve was low-pass filtered with a high-frequency cutoff at 5.5 cpm 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. Based on this frequency, a "gated" study (17) was generated by adding all images of the 3-sec frames representing the same state of contraction of the antral wall. An amplitude and a phase image were obtained by applying a Fourier analysis of the first component, ie, by fitting only the first sinusoid of the Fourier expansion to the time–activity curve for each pixel of the gated study. Since, in the phase image, regions of equal phase appear in the same color, 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, ie, the time lapse between the occurrence of a certain contraction state at one region and its appearance at the next. The velocities measured between these regions were averaged and expressed as mean propagation velocity.

Assessment of Blood Pressure, Pulse Rate, Subjective Feelings, and Side Effects. Before the administration of the suppositories, before meal ingestion, and after the termination of recording in each session, systolic and diastolic blood pressure as well as radial pulse rate were recorded and the volunteers asked to complete self-rating visual analog scales, which were recorded along with the investigators' observations.

Statistical Analysis. The percentages of marker remaining in the stomach and the data on antral motor activity were subjected to analyses of variance for repeated measures (18). The influences of the fixed factors treatment combination (combinations 1–3), study day (study days 1–3), 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 (1–12) were studied. Since half-emptying time values are not normally distributed, these data were analyzed using a nonparametric test, ie, the sign test for paired data (19).

RESULTS

The analyses revealed that the sequence in which the three treatment combinations were administered on the three study days had no significant influence on the variables measured.

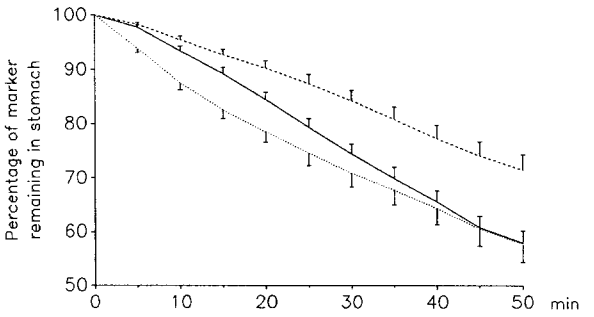

Fig 1. Gastric emptying of the test meal. Percentage of marker remaining in stomach ± SEM over the 50 min after rectal administration of placebo and ingestion of the low-fat meal (· · · ·), rectal administration of placebo and ingestion of the high-fat meal (– – –), and rectal administration of cisapride and ingestion of the high-fat meal (——).

Gastric Emptying. The emptying curves over time, ie, the percentage of marker remaining in the stomach at the various time points, followed closely a monoexponential pattern after all of the three treatment combinations. After placebo administration and ingestion of the high-fat meal, gastric emptying was markedly slower than after placebo and ingestion of the low-fat meal. When cisapride had been administered rectally before the ingestion of the high-fat meal, emptying was somewhat slower in the first 30 min of recording than after placebo and the low-fat meal, but at the end of the 50 min recording period, the percentages of marker remaining in the stomach in these two treatment conditions did not differ (Figure 1).

The analysis showed that the three treatment combinations had significantly differing effects [F (2,22) = 14.72, $P < 0.001$]. Emptying was significantly slower after placebo administration and the high-fat meal than after placebo and the low-fat meal [F (1,22) = 28.06, $P < 0.001$]. After cisapride and ingestion of the high-fat meal, the emptying was significantly faster than after placebo and the high-fat meal [F (1,22) = 13.52, $P < 0.002$], but slightly slower than after placebo and the low-fat meal [F (1,22) = 2.63, NS]. The $T1/2$s after ingestion of the high-fat meal and rectal administration of placebo (range, 52.3–190.6 min; median, 105.5 min) were longer in ten and shorter in two subjects (sign test, $P < 0.05$) than after ingestion of the low-fat meal and placebo administration (range, 32.2–114.4 min; median, 63.6 min; Figure 2). After ingestion of the high-fat meal and cisapride administration, $T1/2$s (range, 38.3–91.1 min; median 60.9 min) were

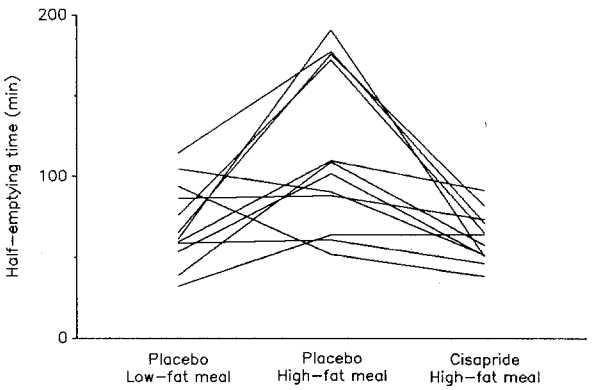

Fig 2. Gastric half-emptying time. Half-emptying times (in minutes) of the isotopically labeled test meal after rectal administration of placebo and ingestion of the low-fat meal, administration of placebo and ingestion of the high-fat meal, and administration of cisapride and ingestion of the high-fat meal in each of the 12 subjects.

TABLE 1. AMPLITUDE, FREQUENCY, AND PROPAGATION VELOCITY OF ANTRAL CONTRACTIONS OF THE 12 SUBJECTS AFTER PLACEBO AND LOW-FAT MEAL, PLACEBO AND HIGH-FAT MEAL, AND CISAPRIDE AND HIGH-FAT MEAL RESPECTIVELY*

	7–10 min	*47–50 min*
Amplitude (modulation depth in %)		
Placebo/low-fat meal	23.31(1.75)	23.14(2.92)
Placebo/high-fat meal	19.65(1.55)	20.59(1.95)
Cisapride/high-fat meal	20.47(1.61)	24.31(1.99)
Frequency (cycles/min)		
Placebo/low-fat meal	2.96(0.08)	2.80(0.09)
Placebo/high-fat meal	2.85(0.11)	2.81(0.06)
Cisapride/high-fat meal	2.95(0.07)	2.76(0.09)
Propagation velocity (mm/sec)		
Placebo/low-fat meal	2.38(0.11)	2.28(0.15)
Placebo/high-fat meal	2.88(0.29)	2.54(0.20)
Cisapride/high-fat meal	2.28(0.12)	2.21(0.09)

*Values (mean and SEM) measured in the periods 7–10 min and 47–50 min after the start of meal ingestion.

shorter than after the high-fat meal and placebo in 11 subjects and equally long in one (sign test, $P < 0.01$). In eight subjects, *T*1/2s were even shorter following the high-fat meal and cisapride than following the low-fat meal and placebo.

Antral Motor Activity

In all of the three treatment conditions, a phasic contractile activity of the gastric antrum was present throughout the 7–10 min and 47–50 min recording periods and no acontractile phases were observed in any subject.

Amplitude of Contractions. In the period 7–10 min after ingestion of the high-fat meal, contraction amplitudes were slightly lower following both placebo and cisapride administration than after ingestion of the low-fat meal and placebo (Table 1). In the 47- to 50-min period, amplitudes after placebo and both the low-fat and the high-fat meal hardly differed from those measured in the 7- to 10-min period. When the high-fat meal had been ingested after cisapride administration, the amplitudes were somewhat higher in the 47- to 50-min than in the 7- to 10-min period (Table 1). The analysis of variance, however, yielded no indication for differing treatment effects [F (2,22) = 1.98, NS]. The height of the contraction amplitude correlated negatively with the *T*1/2s, ie, higher contraction amplitudes tended to be associated with shorter *T*1/2s. For the amplitudes measured in the 47- to 50-min period, this correlation was significant [r (34) = −0.374, $P < 0.05$].

Frequency of Contractions. The contraction frequency generally decreased from the 7- to 10-min to the 47- to 50-min recording period (Table 1). In the analysis of variance, this was reflected by a significant F ratio for the influence of the time factor [F (1,11) = 16.83, $P < 0.002$]. After placebo and the low-fat meal, as well as after placebo and the high-fat meal, these decreases were only slight, whereas there was a more pronounced decrease in frequency after cisapride and the high-fat meal, which corresponded to the increase in contraction amplitude.

Propagation Velocity. Under all of the three treatment conditions, propagation velocities were slightly higher in the 7- to 10-min than in the 47- to 50-min period (Table 1). The treatment effects differed significantly [F (2,22) = 4.32, $P < 0.05$]. After placebo and the high-fat meal, propagation was faster than after both placebo and the low-fat meal, and cisapride and the high-fat meal.

Blood Pressure, Pulse Rate, Subjective Feelings, and Side Effects. Neither at the time point immediately before the ingestion of the test meals nor after the emptying study did blood pressure, pulse rate, and self-rated subjective feelings show any significant changes from the values recorded before drug administration. The number, the nature, and the intensity of sensations reported or observed as side effects did not differ under the influences of the three treatment combinations. No severe side effects of any sort were reported or observed, and no subject complained of nausea.

DISCUSSION

The present data show that a mixed meal containing a high amount of fat is emptied significantly slower from the stomach than a meal of low fat content but otherwise identical composition. This slowing of gastric emptying can be counteracted by prior rectal administration of cisapride. The results confirm earlier observations, which showed that meals of a high nutritive density, in particular meals containing large amounts of fat, are emptied slower than meals of low nutritive density (7) and low fat content (7, 8) and that meals empty slower when fat is instilled into the duodenum (9, 10).

There is good evidence suggesting that this slowing of emptying results from fat-induced release of cholecystokinin from the duodenal mucosa (20–25). Exogenous cholecystokinin has been found to inhibit gastric emptying at plasma concentrations that equal those prevailing physiologically in the postprandial state (24, 25). Such a mechanism also is suggested by the finding that, in healthy men, the cholecystokinin receptor antagonist, loxiglumide, not only abolished the delaying effects of exogenous cholecystokinin, but also reduced the effect of fat on gastric emptying of a peptone meal (26). In another study in healthy men, loxiglumide significantly accelerated the emptying of a liquid meal (30.1% fat, 16.7% protein, 53.2% carbohydrate) and also abolished gallbladder contraction stimulated by that meal (27). In dogs, the specific cholecystokinin A-receptor antagonist, L 364,718, increased gastric emptying of a nutrient containing liquid meal, but had only minimal effects on the emptying of a solid meal (28). In mice, the selective antagonists at peripheral cholecystokinin receptor sites, BIM-18216, MK-329, and loxiglumide, blocked the inhibitory effects of both cholecystokinin octapeptide and fat on gastric emptying of liquid test meals (29). Thus, fatty meals decelerate gastric evacuation possibly via a stimulation of cholecystokinin release. This means that the model of fat-delayed emptying may not account for the mechanisms by which other nutrients modify gastric motor function.

The effect of cisapride, however, cannot be ascribed to an interaction with a mechanism involving cholecystokinin, since there is no published evidence to assume that cisapride directly interfered with the effects of that peptide or interacted with its release. The slow emptying of the fat-rich meal was accelerated by cisapride to such an extent that its evacuation was nearly as fast as that of the low-fat meal following placebo administration. Thus, cisapride stimulates emptying not only in clinical conditions such as progressive systemic sclerosis (2), primary anorexia nervosa (4), gastroparesis diabeticorum (13), and chronic idiopathic dyspepsia (14), but also in the physiological state prevailing after the ingestion of a fatty meal. A consonant effect of cisapride has been demonstrated in dogs, in which the slowing of gastric emptying of a barium meal induced by the addition of olive oil was partly counteracted by an intravenous dose of 0.25 mg/kg cisapride (30). The results of the present study, which demonstrate that rectally administered cisapride abolishes the deceleratory effects of fat incorporated into a standard meal, are in accordance also with the results of an earlier study. In that study, intravenous cisapride reversed the delay in emptying of a standard meal of low fat content, which had occurred when 20 g fat in the form of dairy cream had been ingested 25 min before meal time and drug administration (11).

The association of low antral contraction amplitudes with long $T1/2$s as observed in the present study suggests that the delayed emptying of fat-rich meals results, at least in part, from a reduced force of antral pressure waves. Consonant effects of fat ingestion on antral contractile activity have been reported in a number of papers. In dogs, it has been observed that a fat-containing meal decreased antral motor activity (31) and diminished the incidence of antral slow waves with superimposed action potentials (32). In healthy man, the intragastric instillation of 10% Intralipid resulted in a cessation of the contractile activity characteristic for the antrum in the fasting state and in a sustained rise in pyloric pressure (33, 34). Other investigators have found that, in healthy subjects, the drinking of chocolate milk was followed by a cessation of antral contractions and an increase in the number of isolated pyloric pressure waves (35). Similar changes in antral and pyloric contractile activity occurred also during intraduodenal lipid perfusion (36).

Recent findings demonstrating that the rate of gastric emptying is correlated with the presence and the propagation of antral contractions into the duodenum, and inversely related with the number of isolated pyloric pressure waves (37), point in the same direction. The fact that, in the present study, antral contraction amplitudes after the high-fat meal and placebo administration were only slightly smaller than after the low-fat meal and placebo,

whereas fat had much more accentuated effects in previous studies (33–36), might be explained by the differing techniques employed to record antral motor activity. Using perfused catheters (33–36), contractions of low amplitude may escape detection, since they may not be sufficiently strong to occlude the antral lumen so that no pressure increase is sensed as the contraction wave passes the recording orifice. The scintigraphic technique, by contrast, which revealed a continuous phasic contractile activity even after the high-fat meal, does not depend on the building up of pressure at a distinct point: this means that all contraction waves indenting the antrum are recorded, irrespective of the degree of occlusion they produce and the effect they have on intraluminal pressure. Hence, manometric studies may overestimate the attenuating effects of fat on antral contractile activity. This is also suggested by the results of studies in which recording devices other than manometric catheters were employed. In dogs, extraluminal force transducers revealed a reduction, but not complete inhibition, of antral contractile activity to prevail after the administration of a fat-containing liquid meal (31). Using a balloon positioned into the antrum of healthy volunteers under fluoroscopic control, Smith and Code (38) recorded an increase of type I waves (amplitude less than 5 cm of water) occurring at the three-per-minute rhythm after the ingestion of an "excessively" fatty breakfast, although the incidence of type II contractions (amplitude more than 5 cm of water) decreased.

It is concluded that a mixed meal of high fat content is evacuated significantly slower from the stomach than a mixed meal of low fat content and that this deceleration of emptying can be counteracted by prior rectal administration of cisapride. Fat-delayed gastric emptying thus seems a suitable model for the evaluation of pharmacological agents potentially enhancing the emptying function of the stomach.

REFERENCES

1. Horowitz M, Harding PE, Chatterton BE, Collins PJ, Shearman DJC: Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. Dig Dis Sci 30:1–9, 1985
2. Horowitz M, Maddern GJ, Maddox A, Wishart J, Chatterton BE, Shearman DJC: Effect of cisapride on gastric and esophageal emptying in progressive systemic sclerosis. Gastroenterology 93:311–315, 1987
3. Horowitz M, Maddox A, Maddern GJ, Wishart J, Collins PJ, Shearman DJC: Gastric and esophageal emptying in dystrophia myotonica. Effect of metoclopramide. Gastroenterology 92:570–577, 1987
4. Stacher G, Bergmann H, Wiesnagrotzki S, Kiss A, Schneider C, Mittelbach G, Gaupmann G, Höbart J: Intravenous cisapride accelerates delayed gastric emptying and increases antral contraction amplitude in patients with primary anorexia nervosa. Gastroenterology 92:1000–1006, 1987
5. Berkowitz DM, McCallum RW: Interaction of levodopa and metoclopramide on gastric emptying. Clin Pharmacol Ther 27:414–420, 1980
6. Müller-Lissner SA, Fraas C, Härtl A: Cisapride offsets dopamine-induced slowing of fasting gastric emptying. Dig Dis Sci 31:807–810, 1986
7. Hunt JN, Stubbs DF: The volume and energy content of meals as determinants of gastric emptying. J Physiol (London) 245:209–225, 1975
8. Kroop HS, Long WB, Alavi A, Hansell JR: Effects of water and fat on gastric emptying of solid meals. Gastroenterology 77:997–1000, 1979
9. Valenzuela JE, Defilippi C: Inhibition of gastric emptying in humans by secretin, the octapeptide of cholecystokinin, and intraduodenal fat. Gastroenterology 81:898–902, 1981
10. Collins PJ, Heddle R, Horowitz M, Read NW, Dent J, Chatterton BE: The effect of intraduodenal lipid on gastric emptying and intragastric distribution of a solid meal. Gastroenterology 90:1377, 1986 (abstract)
11. Stacher G, Bergmann H, Gaupmann G, Schneider C, Kugi A, Höbart J, Binder A, Steiner-Mittelbach G: Fat preload delays gastric emptying: Reversal by cisapride. Br J Clin Pharmacol 30:839–845, 1990
12. Schuurkes JAJ, van Nueten JM, van Daele PGH, Reyntjens AJ, Janssen PAJ: Motor stimulating properties of cisapride on isolated gastrointestinal preparations of the guinea pig. J Pharmacol Exp Ther 234:775–783, 1985
13. Feldman M, Smith HJ: Effect of cisapride on gastric emptying of indigestible solids in patients with gastroparesis diabeticorum: A comparison with metoclopramide and placebo. Gastroenterology 92:171–174, 1987
14. Jian R, Ducrot F, Ruskone A, Chaussade S, Rambaud JC, Modigliani R, Rain JD, Bernier JJ: Symptomatic, radionuclide and therapeutic assessment of chronic idiopathic dyspepsia. A double-blind placebo-controlled evaluation of cisapride. Dig Dis Sci 34:657–664, 1989
15. Jacobs F, Akkermans LMA, Oei Hong Yoe, Hoekstra A, Wittebol P: A radioisotope method to quantify the function of fundus, antrum, and their contractile activity in gastric emptying of a semisolid meal. *In* Motility of the Digestive Tract. M. Wienbeck (ed). New York, Raven Press, 1982, pp 233–240
16. Hunt JN, Spurrell WR: The pattern of emptying of the human stomach. J Physiol (London) 113:157–168, 1951
17. Geffers H, Meyer G, Bitter F, Adam WE: Analysis of heart function by gated blood pool investigation (camera cinematography). *In* Information Processing in Scintigraphy. Proceedings of the IVth International Conference, Orsay, 15–19 July 1975. C Raynaud, A Todd-Pokropek, (eds). Saclay, Service de Documentation du CEN, 1976, pp 462–465
18. Games PA: Computer programs for robust analyses in multifactor analysis of variance designs. Educ Psychol Measur 35:147–152, 1975
19. Conover WJ: Practical Nonparametric Statistics. New York, John Wiley & Sons, 1971

20. Lilja P, Fried GM, Wiener I, Inoue K, Thompson JC: Comparison of concentrations of plasma cholecystokinin in pig, dog and man after food or intraduodenal fat. Gastroenterology 82:1118, 1982 (abstract)
21. Walsh JH, Lamers CB, Valenzuela JE: Cholecystokinin-octapeptidelike immunoreactivity in human plasma. Gastroenterology 82:438–444, 1982
22. Lee PC, Elitsur Y, Chaichanwanakul K, Leung YK, Lebenthal E: Cholecystokinin (CCK) release following high carbohydrate (C) and high fat (F) meal in humans. Lack of correlation to plasma insulin (I) and glucose (G). Gastroenterology 92:1498, 1987 (abstract)
23. Guedon C, Ducrotte P, Chayvialle JA, Lerebours E, Denis P, Colin R: Effects of intravenous and intraduodenal fat on jejunal motility and on plasma cholecystokinin in man. Dig Dis Sci 33:558–564, 1988
24. Liddle RA, Morita ET, Conrad CK, Williams JA: Regulation of gastric emptying in humans by cholecystokinin. J Clin Invest 77:992–996, 1986
25. Kleibeuker JH, Beekhuis H, Jansen JBMJ, Lamers CBHW, Piers DA: Infusion of physiologic doses of cholecystokinin inhibits gastric emptying of food in man. Gastroenterology 90:1495, 1986 (abstract)
26. Konturek SJ, Kwiecien N, Obtulowicz W, Kopp B, Oleksy J, Rovati L: Cholecystokinin (CCK) in the inhibition of gastric secretion and gastric emptying in humans. Gastroenterology 98:A368, 1990 (abstract)
27. Meyer BM, Beglinger C, Jansen JBMJ, Rovati LC, Werth BA, Hildebrand P, Zach D, Stalder GA: Role of cholecystokinin in regulation of gastrointestinal motor functions. Lancet 2:12–15, 1989
28. Cheng S, Novich K, Sankaran H, Deveney CW: Role of CCK in gastric emptying of liquids and solids in dogs. Gastroenterology 98:A336, 1990 (abstract)
29. Liberge M, Droy-Lefaix MT, Jutteau J, Bueno L: BIM-18216 elicits CCK antagonist properties in CCK8 and fat induced inhibition of gastric emptying in mice. *In* Abstracts I, The World Congress of Gastroenterology, August, 26–31, 1990, Sydney, Australia (abstract)
30. Janisch HD, Thies P, Wolf KU, Hampel KE: Gastric emptying and plasma VIP in response to oil in the stomach and the influence of cisapride. *In* Abstracts Submitted for the XI International Symposium on Gastrointestinal Motility, September 7–11, 1987, Oxford, England. Oxford, 1987, p 205 (abstract)
31. Weisbrodt NW, Wiley JN, Overholt BF, Bass P: A relation between gastroduodenal muscle contractions and gastric emptying. Gut 10:543–548, 1969
32. Kelly KA, Code CF: Effect of transthoracic vagotomy on canine gastric electrical activity. Gastroenterology 57:51–58, 1969
33. White CM, Poxon V, Alexander-Williams J: Effects of nutrient liquids on human gastroduodenal motor activity. Gut 24:1109–1116, 1983
34. Hasler W, Bowling B, Owyang C: Intraduodenal lipids induce pyloric contractions: role of cholecystokinin and the cholinergic and opiate pathways. Gastroenterology 96:A200, 1989 (abstract)
35. Houghton LA, Read NW, Heddle R, Maddern GJ, Downton J, Toouli J, Dent J: Motor activity of the gastric antrum, pylorus, and duodenum under fasted conditions and after a liquid meal. Gastroenterology 94:1276–1284, 1988
36. Heddle R, Dent J, Read NW, Houghton LA, Toouli J, Horowitz M, Maddern GJ, Downton J: Antropyloroduodenal motor responses to intraduodenal lipid infusion in healthy volunteers. Am J Physiol 254:G671–G679, 1988
37. Fone DR, Horowitz M, Read NW, Dent J, Maddox A: The effect of terminal ileal triglyceride infusion on gastroduodenal motility and the intragastric distribution of a solid meal. Gastroenterology 98:568–575, 1990
38. Smith AWM, Code CF: The effect of an ordinary and of an excessively fatty breakfast on human gastric antral motility. Gastroenterology 35:398–405, 1958