Small Bowel Motility Affects Glucose Absorption in a Healthy Man

MATTHIJS P. SCHWARTZ, MD, PHD
MELVIN SAMSOM, MD, PHD
WILLEM RENOOIJ, PHD
LEO W. VAN STEENDEREN,
MARC A. BENNINGA, MD, PHD
ERWIN-JAN M. VAN GEENEN,
MARGOT A. VAN HERWAARDEN, MD, PHD
MARTIN B.M. DE SMET,
ANDRÉ J.P.M. SMOUT, MD, PHD

OBJECTIVE — To investigate the relationship between duodenojejunal motor activity and glucose absorption and to evaluate the effect of modification of duodenojejunal motility on glucose absorption by using the prokinetic drug cisapride.

RESEARCH DESIGN AND METHODS — We examined seven healthy males, mean age 22 years, who were treated with cisapride 10 mg t.i.d. and placebo during 3 days in a randomized order, with a 2-week time interval. Duodenojejunal manometry was performed after each treatment on the morning of day 3, using an 18-lumen catheter. A liquid nutrient (3 kcal/min) was administered intraduodenally for 30 min, followed by a bolus of the glucose analog 3-*O*-methylglucose (3-OMG). Plasma 3-OMG concentrations were measured to assess absorption kinetics.

RESULTS — The area under the 3-OMG concentration curve in the first 30 min after infusion was related to the number of antegrade propagated pressure waves ($r = 0.49$, $P < 0.05$), but not to the peak concentration, time to peak, and absorption fraction. The mean amplitude of pressure waves was higher during cisapride than placebo ($P < 0.05$), but the reoccurrence of interdigestive motility, numbers of pressure waves, and propagated pressure waves, as well as 3-OMG absorption characteristics, were not significantly different between the two treatments. During both treatments >60% of antegrade propagated pressure waves were propagated over a very short distance (1.5 cm).

CONCLUSIONS — Glucose absorption in the human small intestine is related to short-traveling propagated intestinal contractile activity. Cisapride increases the amplitude of pressure waves, but does not affect the organization of pressure waves or the absorption of 3-OMG.

Diabetes Care 25:1857–1861, 2002

Digestion and absorption of nutrients are the primary functions of the small bowel. Small intestinal motor activity serves to facilitate exposure of luminal contents to the mucosal surface. Studies demonstrating the interactions between intestinal motility and nutrient absorption are few and have yielded conflicting results (1–5). This may be due to the fact that the interaction is complex and dependent on the organization of motor activity (i.e., propagated or nonpropagated) and is also affected by neuroendocrine factors.

Recent studies have provided insights into the relationships between gastrointestinal motor function and glucose absorption, showing that variation in the rate of gastric emptying accounts for ~35% of the variance in peak blood glucose concentrations after ingestion of glucose, and that increased small intestinal–propagated activity results in the blunting of the postprandial glycemic peak (6).

In the present study we used the prokinetic drug cisapride as a tool to modify small intestinal transit. Transit studies have shown the propulsive properties of cisapride in the small intestine (7,8) and its effects on fasting and postprandial gastrointestinal motility have been well established (9–13).

Several reports have shown that the spatiotemporal organization of pressure waves (i.e., propagation of waves) is a more important determinant of luminal flow than the number or amplitude of pressure waves (14,15). We therefore used an 18-channel manometry catheter with closely spaced duodenojejunal sideholes to record motility.

The objectives of this study were to investigate in healthy volunteers during the fed state *1*) the interactions between small intestinal motility and glucose absorption and *2*) the influence of cisapride on duodenojejunal motility and glucose absorption.

RESEARCH DESIGN AND METHODS

Subjects

Studies were performed in seven healthy males (mean age 22 years, range 20–25; BMI 22.3 kg/m^2, range 20.1–24.6) who had no history of gastrointestinal disease and were not taking any medication. The study was approved by the Ethics Committee of the University Medical Center Utrecht, and informed written consent was obtained from each subject.

Study protocol

A randomized, double-blind, placebo-controlled, crossover study design was used. Subjects were treated with cisapride 10 mg t.i.d. or matching placebo (both manufactured by Janssen-Cilag, Beerse, Belgium) for 3 days before and on the morning of the experiments during which gastrointestinal motility and absorption were studied. There was a time interval of

From the Gastrointestinal Research Unit, Departments of Gastroenterology and Surgery, University Medical Center, Utrecht, The Netherlands.

Address correspondence and reprint requests to M.P. Schwartz, Department of Gastroenterology, University Medical Center, P.O. Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: m.p.schwartz@azu.nl.

Received for publication 17 January 2002 and accepted in revised form 11 July 2002.

Abbreviations: 3-OMG, 3-*O*-methylglucose; APPW, antegrade propagated pressure wave; AUC, area under the curve; TMPD, transmucosal potential difference.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

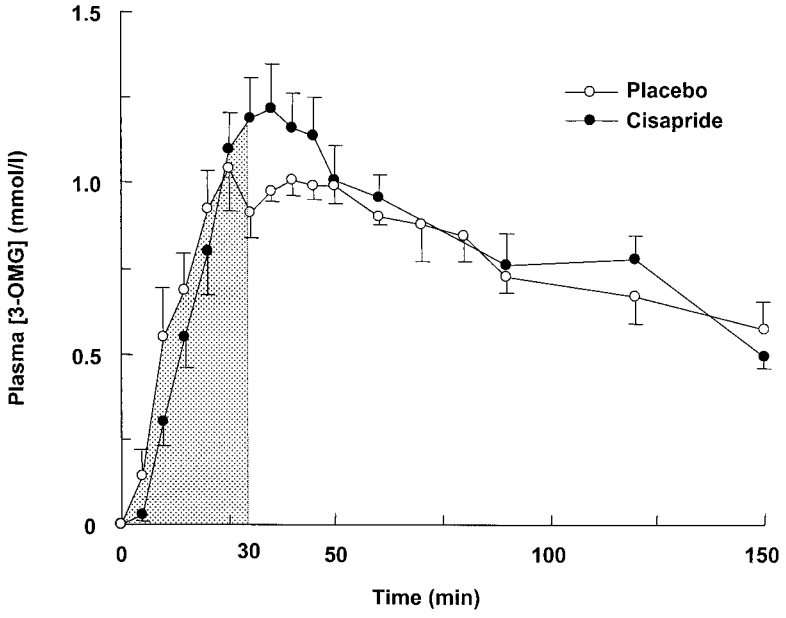

Figure 1—*Plasma 3-OMG concentrations. The shaded area represents the AUC in the 30 min following 3-OMG infusion* (t = *0–30*).

2 weeks between the two experiments in each subject.

After an overnight fast, the manometric catheter was introduced transnasally and positioned across the pylorus. When an interdigestive phase II was present in the small intestine, a mixed nutrient liquid of 13% protein, 48% carbohydrate, 39% fat, and 1.5 kcal/ml energy content (Nutridrink; Nutricia, Zoetermeer, The Netherlands) was infused intraduodenally for 30 min at a rate of 2 ml/min (3 kcal/min; 90 kcal in total) via the duodenal infusion port of the catheter. At the end of this infusion (at $t = 0$ min) 7 g of 3-*O*-methylglucose (OMG) dissolved in 30 ml distilled water was administered intraduodenally over 3 min to assess glucose absorption kinetics. Blood samples were taken at $t = 0$, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 90, 120, and 150 min for measurement of the plasma 3-OMG concentrations.

Manometric technique

A 21-channel water-perfused silicone rubber catheter (outside diameter 4 mm, length 160 cm, channel diameter 0.4 mm, perfusion rate 0.2 ml/min) was used (Dentsleeve, Adelaide, Australia). The assembly incorporated 18 manometric sideholes (S1–S18, spaced at 1.5-cm intervals). S1 was located 14.5 cm distally to the midpylorus. A duodenal infusion port was located at 5 cm from the midpylorus.

Continuous measurement of the antroduodenal transmucosal potential difference (TMPD) was carried out via two sideholes spaced at a 7-cm interval, using established criteria (16), which enabled us to monitor and maintain correct catheter position. Pressures from the perfused sideholes were recorded via external transducers (Abbott, Chicago, IL). Digital data were stored in two 12-channel dataloggers (Medical Measurement Systems, Enschede, The Netherlands) with a memory capacity of 4 Mb each, using a sample frequency of 8 Hz for pressure and 1 Hz for TMPD signals.

Manometric analysis

Interdigestive phases were recognized visually according to established criteria (17). The manometric recordings obtained after completion of the intraduodenal nutrient infusion were analyzed in 10-min blocks. A locally developed computer program was used for calculation of numbers, amplitude, and spatiotemporal characteristics of duodenal pressure waves. Only pressure waves with amplitude of >1.4 kPa were detected. The algorithms used have been described in detail before (18). In short, for each sidehole the number of antegrade propagated pressure waves (APPWs), starting at this recording site and propagating over at least two sites, was calculated. Pressure waves were considered propagated when the propagation velocity was between 0.9 and 16 cm/s (18). APPWs were divided into seven categories according to distance of propagation: over 2 sites (1.5 cm), over 3 sites (3.0 cm), over 4 sites (4.5 cm), over 5 sites (6.0 cm), over 6 sites (7.5 cm), over 7 sites (9.0 cm), or over 8–18 sites (10.5–25.5 cm).

Absorption of 3-OMG

3-OMG is a glucose analog, which is absorbed by the same active intestinal transport mechanism as glucose, but is not metabolized by the liver and is renally cleared. Plasma concentrations of 3-OMG may therefore be used as an index of glucose absorption (19). Plasma glucose was measured according to standard clinical chemical procedures, and plasma 3-OMG was measured according to trimethylsilyl derivative by gas-liquid chromatography, as described by Jansen et al. (20). 3-OMG concentrations were calculated from the areas under the curve (AUCs) of glucose and 3-OMG on the chromatograms in relation to the known plasma glucose concentrations. The absorption fraction (in percent per minute) was calculated from the 3-OMG concentration curve using Wagner-Nelson kinetics (21); maximal absorption was taken as 100% and individual data were calculated accordingly.

Statistical analysis

Repeated-measures ANOVA was used to test the effect of cisapride on the number and amplitude of pressure waves over the various time periods. The paired two-tailed *t* test was used to analyze the effect of cisapride on the 3-OMG absorption characteristics. The unpaired *t* test was used to analyze the effect of cisapride on the duration of the postprandial period, because the reoccurrence of phase III was not necessarily matched in each subject. Data of the two treatments were combined to evaluate relationships between motility (number and amplitude of pressure waves) and 3-OMG absorption (AUC, absorption fraction, and time to the peak concentration, $t = \max$), using the partial correlation coefficient, which controlled for the treatment variable. Relationships were calculated for the time period directly after 3-OMG infusion ($t = 0$ to $t = \max$), because the increment of the plasma 3-OMG concentration most appropriately reflects the absorptive phase of the curve (which is a net reflection of intestinal absorption and renal clearance). $P < 0.05$ was considered sta-

Table 1—*3-OMG concentration characteristics*

	Cisapride	Placebo
Peak concentration (mmol/l)	1.3 ± 0.1	1.2 ± 0.1
Time to peak (min)	32 ± 2	30 ± 5
AUC (t = 0–30) (arbitrary units)	17 ± 2	19 ± 2
Absorption fraction (% per min)	4.9 ± 0.2	5.7 ± 0.7

Data are means ± SEM.

tistically significant. Data are presented as means ± SEM.

RESULTS

3-OMG concentration

Immediately following intraduodenal 3-OMG administration, the plasma concentration rose sharply, reaching a peak at around 30 min during both treatments (Fig. 1 and Table 1).

Duodenojejunal motility

Phase III occurred in five of seven subjects during both cisapride and placebo treatment during the recording period of maximally 150 min, with a mean onset after the end of nutrient infusion of 65 min (range 46–84) vs. 79 min (range 58–130) (cisapride versus placebo, NS) (Fig. 2).

The mean amplitude of pressure waves during the postprandial period was higher during cisapride treatment than during placebo (3.8 ± 0.1 vs. 3.1 ± 0.1 kPa, $P < 0.05$). There were no significant effects of cisapride treatment on the number of pressure waves and APPWs (data not shown) or on the distance of propagation of APPWs (Fig. 3). Most APPWs were propagated over short distances during both treatments; 62 vs. 66% (cisapride versus placebo) traveled over two sites (1.5 cm), 23 vs. 21% over three sites (3 cm).

3-OMG absorption and motility

In the 30-min period following 3-OMG administration, the AUC positively correlated with both the total number of pressure waves (partial correlation coefficient 0.50 for t = 0–10, $P = 0.08$; 0.53 for t = 0–20 and t = 0–30, both $P = 0.06$) and APPWs (partial correlation coefficient 0.55 for t = 0–10, $P = 0.05$; 0.58 for t = 0–20, $P < 0.04$ [Fig. 4]; 0.49 for t = 0–30, $P < 0.05$). There was a trend for an inverse relation between t = max, and the number of pressure waves recorded during t = 0–30 ($r = -0.38$, $P = 0.15$). Similar correlations were present, although not significant, on data of cisapride or placebo treatment alone. The number of pressure waves or APPWs did not correlate with either the absorption fraction or the peak plasma concentration. The amplitude of pressure waves did not correlate to any of the absorption parameters.

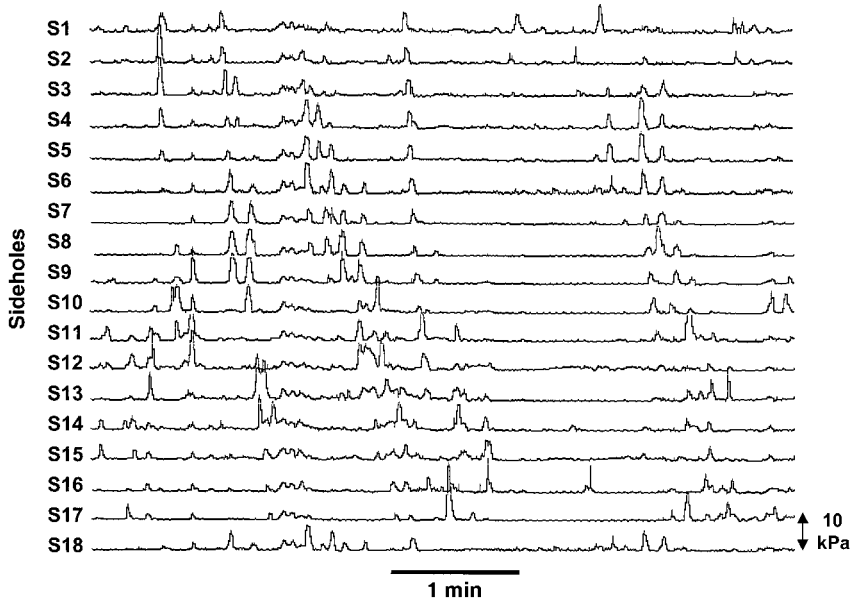

Figure 2—*Example of an 18-channel manometric recording, showing duodenojejunal antegrade propagating pressure waves traveling over various propagation distances.*

3-OMG absorption and cisapride

Cisapride did not significantly affect the peak of the plasma 3-OMG concentration, the t = max, the AUC during the period t = 0–30, or the 3-OMG absorption fraction (Table 1).

CONCLUSIONS— The main findings of this study were that, in healthy subjects, an increase in number of duodenojejunal pressure waves and APPWs was related to an increase in small intestinal glucose absorption; treatment with cisapride increased the mean amplitude of duodenojejunal pressure waves, but did not affect the number of pressure waves and spatiotemporal organization of APPWs; and cisapride treatment did not affect glucose absorption.

Studies on the interaction between intestinal motility and glucose absorption have yielded conflicting results, one demonstrating increased absorption during more intense contractility (1) and others showing the opposite (2–5). This is probably caused by differences in study designs (e.g. in vivo experiments or use of segmental bowel loops, nature and amounts of infusions, and the way absorption was assessed). In some reports plasma glucose concentrations were used as parameters of absorption (1,4), which could be greatly influenced by hepatic glucose production or metabolization. For this reason, we chose to use the glucose analog 3-OMG, which is not metabolized in the liver (19). In addition, absorption studies in the fed state differ greatly from fasting studies, probably caused by hormonal rather than motility factors (2). Most importantly, small intestinal transit studies cannot be compared with manometric studies as such, because transit appears to be determined by the length of propagated pressure waves, rather than by the number of pressure waves per se (22).

Our study provided further evidence that glucose absorption is positively related to motor activity, but our data do

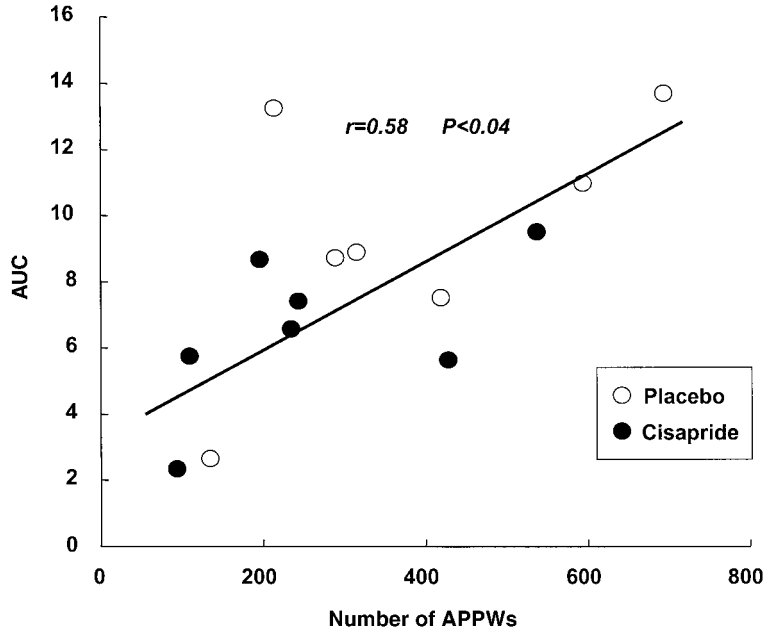

Figure 3—*Total number of APPWs propagated over 2, 3, 4, 5, 6, 7, and 8–18 sites in the 60 min following intraduodenal nutrient infusion.*

not support the view that glucose absorption is related to small intestinal contractions propagated over long distances. There were no important differences between the correlation coefficients of AUC with pressure waves or APPWs, and the majority (>60%) of propagated sequences traveled over a distance of only 1.5 cm. Thus, short-distance propagated sequences appear to be responsible for the observed relationship between motility and absorption. In other, less-detailed, manometric studies, these sequences would probably have been classified as isolated phasic contractions or would not have been picked up at all. We suggest that the short-distance propagated sequences serve to mix the luminal contents, spreading glucose locally, hence enhancing contact with the mucosal surface and facilitating absorption.

Knowledge of small intestinal glucose absorption in diabetic patients is very limited. Disordered gastric emptying in diabetes has been shown to affect glucose absorption and vice versa, possibly resulting in poor postprandial glycemic control (23). In the present study, the effects of gastric emptying on glucose absorption were overcome by administering both nutrients and 3-OMG intraduodenally. Glucose absorption has been reported to be normal in type 1 diabetes, whereas it may be slightly reduced in type 2 diabetes (6). The magnitude of the contribution of disordered small intestinal motility to postprandial hyperglycemia in type 1 diabetes requires further research.

Several limitations of the present study should also be acknowledged. Firstly, although two experiments were performed in each subject, the total number of subjects was relatively small. Secondly, the carbohydrates in the administered nutrient could have theoretically inhibited intestinal absorption of 3-OMG (19), although presumably to an equal extent in each experiment. A single bolus of 3-OMG was given because this facilitates the kinetic measurements, and a previous study has demonstrated that the chosen amount of 3-OMG produced a dose-response curve with an acceptable analytical accuracy (24).

Our findings regarding the effect of cisapride on duodenojejunal motility appear to be in agreement with most previous reports on the effects of cisapride in healthy subjects (9–11,25). Studies that have measured amplitudes of pressure waves have also shown an increase in amplitude as a result of cisapride treatment (9,11), or an increase in motility index (10), also likely to be a reflection of a higher amplitude of pressure waves. Two postprandial duodenal motility studies found no increase in number of pressure waves (11,13), as in the present study. One study in humans (12) found an increased incidence of jejunal contractions after a single dose of cisapride. It is likely that pharmacokinetic differences were responsible for these discordant findings.

In conclusion, short-traveling pres-

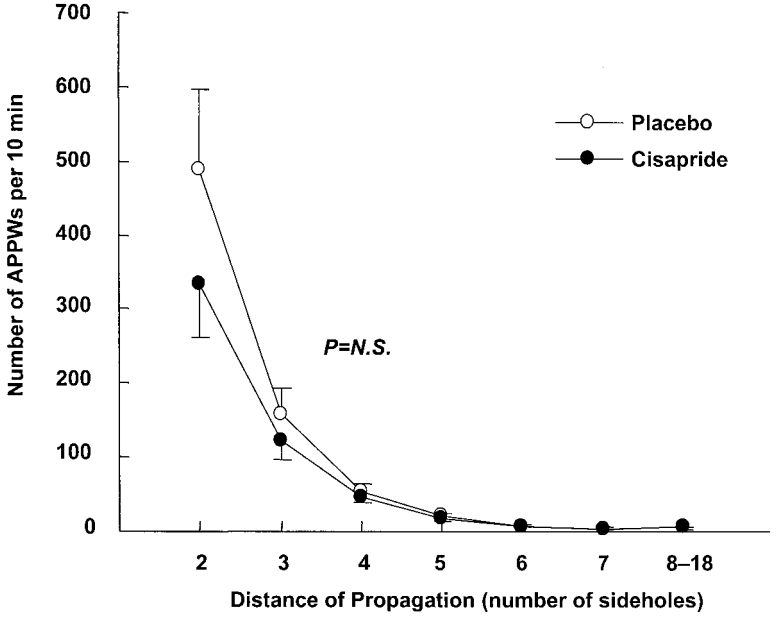

Figure 4—*Relationship between 3-OMG absorption (AUC) and number of APPWs during the first 20 min following 3-OMG infusion* (t = *0–20).*

sure waves are related to the rate at which glucose is absorbed in the proximal small intestine, possibly via optimizing mucosal contact of glucose. The prokinetic cisapride enhances the amplitude of duodenojejunal pressure waves, but does not influence the number of pressure waves and intestinal absorption of glucose.

Acknowledgments— Dr. M. Samsom is a fellow of the Royal Netherlands Academy of Arts and Sciences. The authors thank Dr. J.A.J. Faber of the Center for Biostatistics for his help with the statistical analyses.

References

1. Fioramonti J, Bueno L, Ruckebusch M: Blood sugar oscillations and duodenal migrating myoelectric complexes. *Am J Physiol* 242:G15–G20, 1982
2. Sarr MG, Kelly KA, Phillips SF: Canine jejunal absorption and transit during interdigestive and digestive motor states. *Am J Physiol* 239:G167–G172, 1980
3. Sjovall H, Hagman I, Abrahamsson H: Relationship between interdigestive duodenal motility and fluid transport in humans. *Am J Physiol* 259:G348–G354, 1990
4. Cherbut C, Bruley des Varannes S, Schnee M, Rival M, Galmiche JP, Delort-Laval J: Involvement of small intestinal motility in blood glucose response to dietary fibre in man. *Br J Nutr* 71:675–685, 1994
5. Defilippi C, Gomez E: Effect of casein and casein hydrolysate on small bowel motility and D-xylose absorption in dogs. *Neurogastroenterol Motil* 7:229–234, 1995
6. Rayner CK, Samsom M, Jones KL, Horowitz M: Relationships of upper gastrointestinal motor and sensory function with glycemic control. *Diabetes Care* 24:371–381, 2001
7. Schemann M, Ehrlein HJ: 5-Hydroxytryptophan and cisapride stimulate propulsive jejunal motility and transit of chyme in dogs. *Digestion* 34:229–235, 1986
8. Edwards CA, Holden S, Brown C, Read NW: Effect of cisapride on the gastrointestinal transit of a solid meal in normal human subjects. *Gut* 28:13–16, 1987
9. Stacher G, Gaupmann G, Mittelbach G, Schneider C, Steinringer H, Langer B: Effects of oral cisapride on interdigestive jejunal motor activity, psychomotor function, and side-effect profile in healthy man. *Dig Dis Sci* 32:1223–1230, 1987
10. Lux G, Katschinski M, Ludwig S, Lederer P, Ellermann A, Domschke W: The effect of cisapride and metoclopramide on human digestive and interdigestive antroduodenal motility. *Scand J Gastroenterol* 29:1105–1110, 1994
11. Benson MJ, Castillo FD, Deeks JJ, Wingate DL: Assessment by prolonged ambulatory manometry of the effect of oral cisapride on proximal small bowel interdigestive motility. *Dig Dis Sci* 37:1569–1575, 1992
12. Stacher G, Gaupmann G, Steinringer H, Schneider C, Stacher-Janotta G, Steiner-Mittelbach G, Abatzi TA: Effects of cisapride on postcibal jejunal motor activity. *Dig Dis Sci* 34:1405–1410, 1989
13. Fraser RJ, Horowitz M, Maddox AF, Dent J: Postprandial antropyloroduodenal motility and gastric emptying in gastroparesis-effects of cisapride. *Gut* 35:172–178, 1994
14. Kerlin P, Zinsmeister A, Phillips S: Relationship of motility to flow of contents in the human small intestine. *Gastroenterology* 82:701–706, 1982
15. Samsom M, Fraser R, Russo A, Berry M, Smout AJPM, Horowitz M: Propagated pressure wave sequences determine postprandial luminal flow in the proximal small intestine in man (Abstract). *Gastroenterology* 116 (Suppl. 2):A1073, 1999
16. Samsom M, Akkermans LMA, Jebbink HJA, van Isselt H, van Berge Henegouwen GP, Smout AJPM: Gastrointestinal motor mechanisms in hyperglycaemia-induced delayed gastric emptying in type I diabetes mellitus. *Gut* 40:641–646, 1997
17. Edelbroek M, Sun WM, Horowitz M, Dent J, Smout A, Akkermans L: Stereospecific effects of intraduodenal tryptophan on pyloric and duodenal motility in humans. *Scand J Gastroenterol* 29:1088–1095, 1994
18. Samsom M, Smout AJPM, Hebbard G, Fraser R, Omari T, Horowitz M, Dent J: A novel portable perfused manometric system for recording of small intestinal motility. *Neurogastroenterol Motil* 10:139–148, 1998
19. Fordtran JS, Clodi PH, Soergel KH, Ingelfinger FJ: Sugar absorption tests, with special reference to 3-O-methyl-d-glucose and d-xylose. *Ann Intern Med* 6:883–890, 1962
20. Jansen G, Muskiet FA, Schierbeek H, Berger R, van der SW: Capillary gas chromatographic profiling of urinary, plasma and erythrocyte sugars and polyols as their trimethylsilyl derivatives, preceded by a simple and rapid prepurification method. *Clin Chim Acta* 157:277–293, 1986
21. Rowland M, Tozer TN: *Clinical Pharmacokinetics: Concepts and Applications*. Philadelphia, PA, London, Lea & Febiger, 1989, p. 479–483
22. Schemann M, Ehrlein HJ: Postprandial patterns of canine jejunal motility and transit of luminal content. *Gastroenterology* 90:991–1000, 1986
23. Horowitz M, Wishart JM, Jones KL, Hebbard GS: Gastric emptying in diabetes: an overview. *Diabet Med* 13:S16–S22, 1996
24. Samsom M, Benninga M, van Steenderen L, Renooij W, de Smet M, Akkermans LMA, Smout AJPM: Inhibition of small intestinal motility decreases glucose absorption in humans (Abstract). *Gastroenterology* 116 (Suppl. 2):A1073, 1999
25. Fraser R, Horowitz M, Maddox A, Dent J: Dual effects of cisapride on gastric emptying and antropyloroduodenal motility. *Am J Physiol* 264:G195–G201, 1993