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Effects of Iberogast® on Proximal Gastric Volume, Antropyloroduodenal Motility and Gastric Emptying in Healthy Men

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OBJECTIVE: The herbal preparation Iberogast® has been reported to improve upper abdominal symptoms in functional dyspepsia (FD) and to decrease fundic tone, increase antral contractility, and decrease afferent nerve sensitivity in experimental animals. The effects of Iberogast on the human gastrointestinal tract have not been evaluated.

METHODS: We investigated the effects of oral control and Iberogast, each administered as a single dose (1.1 mL), in a double-blind randomized fashion, on proximal gastric volume (part A), antropyloroduodenal motility (part B), and gastric emptying and intragastric distribution of a solid/liquid meal (part C) for 120 minutes, in nine (part A), 12 (part B), and eight (part C) healthy men.

RESULTS: Iberogast increased proximal gastric volume (max volume; control 104 ± 12 mL, Iberogast 174 ± 23 mL, $P < 0.05$) (part A), increased the motility index of antral pressure waves in the first 60 minutes ($P < 0.05$) without affecting pyloric or duodenal pressures (part B), and slightly increased the retention of liquid in the total stomach between 10 and 50 minutes ($P < 0.01$), but had no effect on gastric emptying of solids or intragastric distribution (part C).

CONCLUSIONS: Iberogast affects gastric motility in humans, probably in a region-dependent manner. The stimulation of gastric relaxation and antral motility may contribute to the reported therapeutic efficacy of Iberogast in FD.

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INTRODUCTION

Abnormalities in gastric motor and sensory function have been investigated widely as a potential cause of symptoms in functional dyspepsia (FD) (1–11). The documented disturbances include delayed gastric emptying (1), impaired proximal gastric relaxation (2–4), lower contractile activity of the antrum (5), and abnormal duodenal motility (6), as well as greater sensitivity to mechanical (7–9) and chemical (10, 11) stimuli. Treatment for symptom relief is, accordingly, frequently directed at the normalization of gastroduodenal motility using prokinetic drugs (12–14). However, the beneficial effect of these drugs is relatively small and variable (12–14), and their adverse effects can be substantial (15).

Herbal drug preparations have recently received considerable interest as an alternative treatment option in FD (16–18). Clinical trials of herbal medicines, administered either alone (16, 17) or as combination preparations (18), have established their capacity to improve symptoms. A commercially available herbal preparation, Iberogast® (Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany), which contains nine plant extracts, has been evaluated in a number of trials and demonstrated to be superior to placebo (19, 20), and of comparable efficacy with pharmacological agents, including metoclopramide (21) and cisapride (22), in improving symptoms in FD and irritable bowel syndrome. In these studies, Iberogast was administered at a dose of 20 drops (1.1 mL) three times per day over periods of 2 (21) or 4 (19, 20, 22) wk. Iberogast has not been associated with any adverse effects.

To date, the limited number of studies that has investigated the potential mechanisms of action underlying the beneficial effects of Iberogast has been performed primarily in animal models (23–25), with some preliminary evidence

from human gastric tissue (26). These studies suggest that Iberogast has a dual action on the gastrointestinal tract. For example, Iberogast decreases fundic tone, while increasing antral motility, in muscle strips from guinea pig stomach in a concentration-dependent manner (25). Preliminary experiments on human gastric muscle preparations demonstrated that Iberogast relaxes the proximal stomach, comparable in magnitude with the effect in the guinea pig stomach (26). Additional actions of Iberogast in rats include lower sensitivity of vagal and spinal afferents to low- and high-pressure distension in response to chemical (5-HT and bradykinin) and mechanical (distension) stimuli (23), indicating that Iberogast also affects sensory gut function.

The aims of this study were to determine the effects of Iberogast on proximal gastric volume, pressures in the antrum, pylorus, and duodenum, and gastric emptying (including intragastric meal distribution) in healthy men.

MATERIALS AND METHODS

Subjects

Healthy male subjects were studied. None had a history of gastrointestinal disease or symptoms, was taking medication known to affect gastrointestinal motility, smoked, or habitually consumed >20 g alcohol per day. The Royal Adelaide Hospital Investigational Drug Sub-Committee and Research Ethics Committee approved the study protocol (approval date April 15, 2004), and all subjects provided written, informed consent prior to their inclusion.

Study Design

The study consisted of three parts that evaluated the effects of Iberogast (Donated by Mr. N. Pollard, Flordis Herbal Medicines Pty Ltd., Epping, NSW, Australia) on (a) proximal gastric volume ("relaxation") (part A), (b) antropyloroduodenal (APD) motility (part B), and (c) gastric emptying and intragastric distribution (part C). Subjects attended, at 0900 h after an overnight fast (14 h for solids and 12 h for liquids), either at the Discipline of Medicine (parts A and B) or the Department of Nuclear Medicine, PET, and Bone Densitometry (part C). In each part, subjects were studied on two occasions, separated by 3–10 days, on which they received, in a double-blind, randomized fashion, an oral dose (1.1 mL) of either control or Iberogast, each with 50 mL water. Part A was performed first, followed by part B, then part C. Ten of the 14 subjects recruited participated in more than one part.

Based on previous studies (27–29), it was calculated that sample sizes of nine, 12, and eight subjects would enable a detection of 20% difference in proximal gastric volume, APD motility, gastric emptying, and intragastric distribution, respectively, between Iberogast and control with 80% power assuming a 2-sided significance level of 5%.

Iberogast and Preparation of Control Solution

Iberogast is a complex herbal preparation, containing nine constituents, including fresh plant extract of *Iberis amara* (bitter candy tuft) and the extracts of eight dried herbs (*Angelicae radix* [angelica roots], *Matricariae flos* [camomile flowers], *Carvi fructus* [caraway fruit], *Cardui mariae fructus* [St. Mary's thistle fruit], *Melissae folium* [balm leaves], *Menthae peperitae folium* [peppermint leaves], *Chelidonii herba* [greater celandine], and *Liquiritiae radix* [liquorice root]) in 30.9% ethanol.

The control solution was prepared by diluting 100% ethanol with water to achieve an alcohol content of 30.9%, thus 1.1 mL of solution contained 0.34 mL ethanol. Iberogast was administered in the recommended dose of 1.1 mL (20 drops). The solutions were drawn into a syringe, which had been covered with aluminum foil by one of the investigators who was not directly involved in the performance of the study or data analysis, and injected into the subject's mouth.

PROTOCOL

Part A: Effect of Iberogast on Proximal Gastric Volumes

Nine healthy men (age 29 ± 4 yr, body mass index [BMI] 23 ± 1 kg/m^2) were included. Subjects swallowed a single-lumen polyvinyl orogastric catheter (OD 4 mm, ID 2 mm; Tygon® Tubing, Saint Gobain Performance Plastics, Akron, OH), which had an ultrathin, flaccid polyethylene bag (capacity 1,200 mL) tightly wrapped around its distal end (30). The proximal end of the catheter was connected via a three-way tap to a gastric barostat (Distender Series II™, G & J Electronics Inc, Toronto, Ontario, Canada). The intragastric bag was positioned in the fundus of the stomach, as described previously (30). Subjects were then seated in a 75° recumbent position. The minimal distending pressure (MDP), defined as the intrabag pressure that first resulted in a bag volume over 30 mL (31), was determined. Intrabag pressure was then set at MDP. After 10 minutes ("baseline"), each subject was given either control or Iberogast with 50 mL water. Volume changes in the bag were recorded for 120 minutes. The catheter was then removed, and the subject allowed to leave the laboratory.

Intrabag pressures and volumes were digitized and recorded on a computer-based system running commercially available software (Protocol Plus™, G & J Electronics, Toronto, Ontario, Canada). Absolute volumes were expressed as means of 10 minute-segments for baseline (*i.e.*, t = –10 to 0 minutes) and during the following 120 minutes. The average maximum volume was calculated by determining the highest volume, and time point at which this occurred, in each subject. The area under the curve (AUC) for gastric volume between t = 0 and t = 120 minutes was determined using the trapezoidal rule.

Part B: Effect of Iberogast on APD Pressures

Twelve healthy men (age 28 ± 4 yr, BMI 24 ± 2 kg/m^2) were included. A 16-channel manometric catheter (OD 3.5 cm; Dentsleeve International Ltd, Mui Scientific, Mississauga, Ontario, Canada) was inserted into the stomach through an anesthetized nostril and allowed to pass into the duodenum by peristalsis. The catheter consisted of 16 side-holes, spaced at 1.5 cm intervals. Six side-holes (channels 1–6) were positioned in the antrum, a 4.5-cm sleeve sensor (channel 7),

with two side-holes on the back of the sleeve (channels 8 and 9), across the pylorus, and seven side-holes (channels 10–16) in the duodenum. The correct positioning of the catheter was maintained by measurement of the transmucosal potential difference (TMPD) (32). Once the catheter was positioned correctly, fasting motility was monitored until the occurrence of a phase III of the interdigestive migrating motor complex (MMC) (32). At t = 0 minutes, *i.e.*, during phase I of the MMC, the subject was given either control or Iberogast with 50 mL water, and APD pressures were monitored for 120 minutes. The manometric assembly was then removed and the subject allowed to leave the laboratory.

Manometric pressures were digitized and recorded on a computer-based system running commercially available software (Flexisoft®, Version 3, Assoc Prof GS Hebbard, Royal Melbourne Hospital, Melbourne, Australia, written in Labview 3.1.1 [National Instruments]). APD pressures were analyzed for (a) number and amplitude of antral pressure waves (PWs), (b) basal pyloric pressure and number and amplitude of isolated pyloric pressure waves (IPPWs), and (c) number and amplitude of duodenal PWs, as described in detail previously (33).

Baseline values were calculated as the means of values obtained between t = –10 and t = 0 minutes for the number and amplitude of antral and duodenal PWs, IPPWs, and basal pyloric pressure. Basal pyloric pressures and the number and amplitude of IPPWs and antral and duodenal PWs were expressed as the mean of the 10-minute segments. Antral and duodenal motility indices (MI) were also calculated (34). The AUC for the number, amplitude, and MI of antral and duodenal PWs, basal pyloric pressure, and number and amplitude of IPPWs from t = 0–120 minutes was determined using the trapezoidal rule. Episodes of phase III of the MMC were excluded if they occurred more than 60 minutes after the treatment was given (*i.e.*, t = 60–120 minutes), *i.e.*, when they were more likely to be the result of fasting rather than of the treatment.

Part C: Effect of Iberogast on Gastric Emptying and Intragastric Distribution

Eight healthy men (age 31 ± 4 yr, BMI 25 ± 1 kg/m^2) were included. Subjects were seated with their back upright against a gamma camera. Each subject was given either control or Iberogast with 50 mL of water, immediately before a mixed solid/liquid meal, which was consumed within 5 minutes. The meal consisted of 100 g ground beef patty labeled with 20 MBq ^{99m}Tc-sulfur colloid chicken liver, followed immediately by 150 mL 10% dextrose solution labeled with 6 MBq ^{67}Ga-EDTA (35). The time of completion of the meal was defined as t = 0 minutes. Gastric emptying was measured for 120 minutes.

Radioisotopic data were acquired in 1-minute frames for the first 60 minutes and in 3-minute frames between t = 60 and t = 120 minutes. Data were corrected for subject movement, radionuclide decay, and gamma-ray attenuation (36). Regions-of-interest were drawn for total, proximal, and distal gastric regions. For both the solid and the liquid meal components, the amount remaining in the total, proximal, and distal stomach between t = 0 and t = 120 minutes was derived at 10-minute intervals, as well as the AUC. The lag phase for solid and liquid was determined as the time period between meal completion and the appearance of radioactivity in the proximal small intestine (36). The amount of solid remaining in the stomach at t = 100 minutes and the time for 50% of the liquid to empty (T50) were calculated (36). Gastric emptying was classified as delayed when the percent solid retention at t = 100 minutes was >61% and/or liquid T50 was >31 minutes, based on an established normal range (37).

Statistical Analysis

Gastric volume (part A), number, amplitude, and MI of antral and duodenal PWs, basal pyloric pressure, number and amplitude of IPPWs (part B), and amount of solid and liquid remaining in the total, proximal, and distal stomach (part C), between 0–60 minutes and 0–120 minutes, were analyzed by repeated-measures analysis of variance (ANOVA), with time and treatment as factors. AUCs for gastric volume, APD motility and the amount of solid and liquid remaining in the total, proximal, and distal stomach, the maximal effect of treatment (and the time at which this occurred) on gastric volume, the lag phase of solid and liquid, retention of solid at t = 100 minutes, and the T50 of liquids were analyzed by Student's *t* test. Statistical significance was accepted at $P < 0.05$, and data are presented as mean ± SEM.

RESULTS

The studies were tolerated well. Only one subject was able to distinguish between control and Iberogast; four subjects reported a mildly unpleasant taste after both treatments that lasted for a few seconds. None of the subjects experienced any adverse effects (including nausea).

Part A: Effect of Iberogast on Intrabag Volume Changes ("Gastric Relaxation")

Mean MDP was 8 ± 0 mmHg for control and 8 ± 1 mmHg for the study with Iberogast. The balloon volumes at MDP, before administration of the treatments, did not differ on the 2 days (control 49 ± 4 mL, Iberogast 53 ± 5 mL). There was an effect of treatment and time on intrabag volume between 0 and 120 minutes (Fig. 1)—while intrabag volume increased gradually on both days, the magnitude of this increase was greater with Iberogast than control ($P < 0.05$). The increase in intrabag volume from baseline was marginal for control, and evident only between 100 and 120 minutes ($P < 0.05$), whereas the rise after Iberogast was substantial and occurred between 40 and 120 minutes ($P < 0.05$). Maximum intrabag volume (control 104 ± 12 mL at 64 ± 15 minutes, Iberogast 174 ± 23 mL at 69 ± 12 minutes, $P < 0.05$ for volume) and the AUC (control 7,130 ± 765 mL min, Iberogast 12,400 ± 1,850 mL min, $P < 0.05$) were also greater with Iberogast.

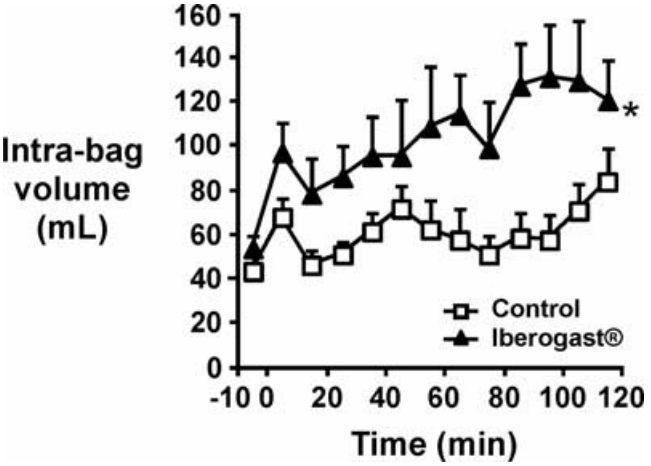

Figure 1. Intrabag volume, as mean of 10-minute segments, after oral administration of 1.1 mL control solution or Iberogast, with 50 mL water. Iberogast increased intrabag volume when compared with control ($^*P < 0.05$ *vs* control). Data are mean ± SEM (N = 9).

Part B: Effect of Iberogast on APD Motility

Phase III episodes were observed in five subjects (in two subjects they occurred during both control and Iberogast, in two subjects during Iberogast only, and in one subject during control only), and on three occasions, this was in the first 60 minutes (twice during control and once during Iberogast treatment).

Antral Pressures. There was no effect of treatment on the number (Fig. 2A) or amplitude (Fig. 2B) of antral PWs, although mean values were slightly greater following Iberogast when compared with control. However, there was an effect of treatment on the MI (Fig. 2C) of antral PWs. The MI was greater following Iberogast compared with control in the first 60 minutes ($P < 0.01$). There was no effect of treatment on the AUCs for the number, amplitude, or MI (Table 1), although mean values were greater following Iberogast when compared with control.

Pyloric Pressures. There was no effect of treatment on basal pyloric pressure, or the number or amplitude of IPPWs (data not shown). There was an effect of time on both the number and amplitude of IPPWs; after an initial rise during the first 20 minutes following administration of both control (non-significant) and Iberogast ($P < 0.05$), values returned to near baseline. There was no effect of treatment on the AUCs for basal pyloric pressure, or the number or amplitude of IPPWs (Table 1).

Duodenal Pressures. There was an effect of time, but not of treatment, on the number, amplitude, and MI of duodenal PWs (data not shown). During both treatments there was an initial rise ($P < 0.05$) in all three parameters, and while the effect of Iberogast appeared to be slightly greater than that of control, this was not significant. There was no effect of treatment on the AUCs for the number, amplitude, or MI (Table 1).

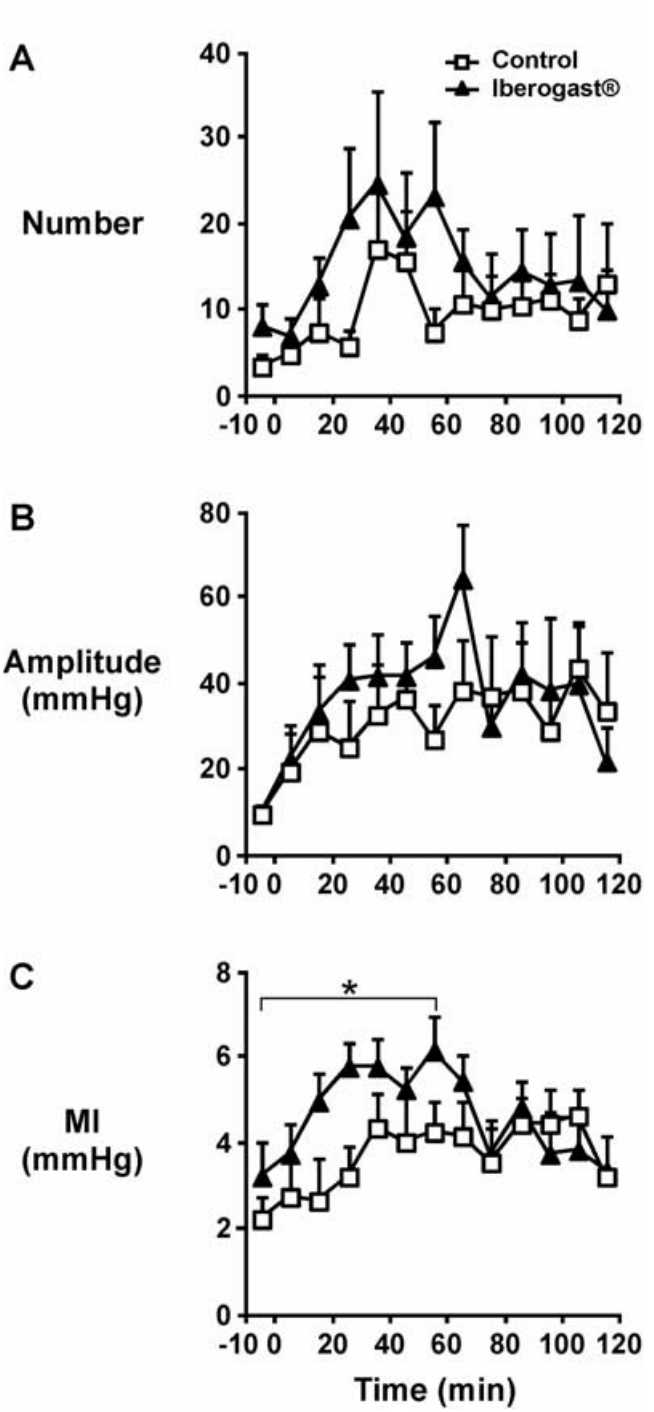

Figure 2. (*A*) Number, (*B*) amplitude, and (*C*) motility index (MI) of antral pressure waves, as a mean of 10-minute segments, after oral administration of 1.1 mL control solution or Iberogast, with 50 mL water. Iberogast increased the MI between 0 and 60 minutes when compared with control ($^*P < 0.01$ *vs* control). Data are mean ± SEM (N = 12).

Table 1. Area Under the Curves for the Number, Amplitude, and MI of Antral and Duodenal PWs, Basal Pyloric Pressure, and Number and Amplitude of IPPWs after Control or Iberogast Between t = 0 and t = 120 min

	Control	Iberogast
Antral pressure waves		
Number (min)	1,150 ± 279	1,810 ± 598
Amplitude (mmHg min)	3,730 ± 480	4,490 ± 612
MI (mmHg min)	447 ± 49	559 ± 48
Pyloric pressures		
Basal pyloric pressure (mmHg min)*	–94 ± 89	–102 ± 76
Number IPPWs (min)	267 ± 79	264 ± 57
Amplitude IPPWs (mmHg min)	2,510 ± 484	2,500 ± 493
Duodenal pressure waves		
Number (min)	8,040 ± 1150	10,390 ± 1940
Amplitude (mmHg min)	3,230 ± 192	3,450 ± 226
MI (mmHg min)	799 ± 38	880 ± 42

Data are mean ± SEM; N = 12.
MI = motility index; IPPWs = isolated pyloric pressure waves.
*The negative values indicate that both treatments decreased tone compared with baseline.

Part C: Effect of Iberogast on Gastric Emptying and Intragastric Distribution

Solid Meal. There was no difference in the lag phase (control 16 ± 4 minutes, Iberogast 19 ± 5 minutes), the amount of solid remaining in the total (Fig. 3A), proximal (Fig. 3B), or distal (Fig. 3C) stomach, or the AUCs (Table 2) between treatments. There was no difference in the percent retention of solids at t = 100 minutes between the two treatments (control 40 ± 4%, Iberogast 43 ± 5%). Gastric emptying was delayed in one subject during Iberogast treatment (retention at 100 minutes = 63%).

Liquid Meal. There was no difference in the lag phase between treatments (control 1 ± 0 minutes, Iberogast 1 ± 0 minutes); however, there was a treatment × time interaction for the amount of liquid remaining in the total stomach ($P < 0.01$) (Fig. 3D). Intragastric retention of liquid was slightly greater during Iberogast when compared with control between 10 and 50 minutes ($P < 0.05$). There was no difference between treatments in the amount of liquid remaining in the proximal (Fig. 3E) or distal (Fig. 3F) stomach. There was no effect of treatment on AUCs for liquid emptying in the total, proximal, or distal stomach (Table 2). There was no difference in the T50 of liquid between the two treatments (control 20 ± 3 minutes, Iberogast 23 ± 2 minutes). Gastric emptying was delayed in one subject during Iberogast treatment (T50 = 32 minutes).

DISCUSSION

This study establishes for the first time that Iberogast affects gastric motility in humans and suggests that these effects may be region-dependent. Specifically, Iberogast increased proximal gastric relaxation substantially, increased the MI of antral PWs, and slowed gastric emptying of liquid slightly, but had no significant effect on fasting duodenal or pyloric motility, solid gastric emptying, or intragastric meal distribution, in healthy men.

The pathophysiology of FD remains poorly defined and heterogenous. Treatment options, including prokinetics (12–14) and proton pump inhibitors (38), have resulted in variable and less than optimal responses. The therapeutic benefits of relatively inexpensive herbal drugs in patients with functional gastrointestinal disorders appear to be significant and their use is devoid of adverse effects. For example, Iberogast is superior to placebo (19, 20) and comparable with metoclopramide (21) and cisapride (22) in the management of FD. We demonstrated that Iberogast increases proximal gastric relaxation, as reflected by an increase in intrabag volume at constant pressure, which was sustained for the duration of the study (120 minutes), and also increases the MI of antral PWs during the first 60 minutes after administration. These results are consistent with observations in animals (25) and suggest that the effects of Iberogast on gut motility are also region-dependent in healthy humans. Moreover, these effects may potentially account for improvement in dyspeptic symptoms, as impaired proximal gastric relaxation and antral hypomotility affect some 40–70% of FD patients (2–4, 39). In contrast, Iberogast had no apparent effect on duodenal pressures, phasic, and tonic pyloric motility, or solid gastric emptying, and had a minimal, albeit significant, effect to slow liquid emptying. The latter is not surprising, given that Iberogast relaxes the fundus and increases contractile activity in the antrum; one would, therefore, not expect any major change in gastric emptying. The absence of any effect of Iberogast on intragastric meal distribution is perhaps surprising, given the enhancement of proximal gastric relaxation, but this may be because the test meal was relatively small and low in energy (330 kcal). It would be of interest to evaluate the effects of Iberogast on the intragastric distribution of meals of higher caloric content and volume. In a rat model, Iberogast decreased afferent nerve sensitivity in response to mechanical ramp distension of an intestinal loop at increasing pressures (0–60 cm H_2O) (23); accordingly, evaluation of the effects of Iberogast on gastric sensitivity in humans is also warranted. Studies to evaluate the effects of Iberogast on proximal gastric accommodation, antral, pyloric, and small intestinal motility, and gastric emptying, as well as gastric sensitivity, in FD patients are indicated, particularly given that our study has now demonstrated that Iberogast modulates gastric motility in humans.

While our data do not provide any insight regarding the site of action of Iberogast, our recent study on isolated guinea pig stomach preparations clearly indicates a direct muscle effect of the drug (25). In contrast, the site of action of Iberogast in regard to its effect on gastric sensitivity has not been established, and the concept that the effect of Iberogast may be mediated from the small intestine, as is the case with nutrient regulation of gastric emptying (40), warrants exploration.

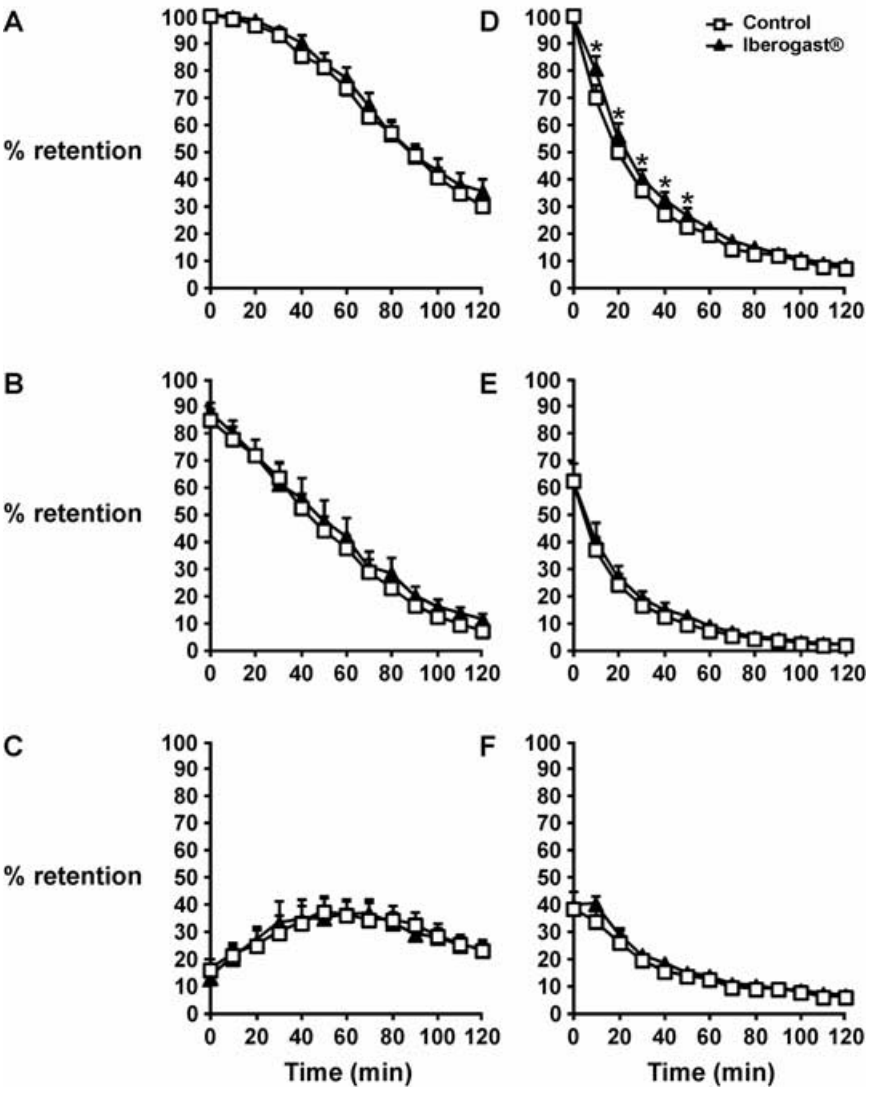

Figure 3. Gastric emptying and intragastric distribution of solid (*A–C*) and liquid (*D–F*) meal components, after oral administration of 1.1 mL control solution or Iberogast, with 50 mL water. Iberogast had no effect on solid or liquid emptying when compared with control, but increased retention of liquid in the total stomach between 10 and 50 minutes ($^*P < 0.05$ *vs* control). Data are mean ± SEM (N = 8).

It is important to recognize the potential limitations of our study. Iberogast contains a number of components, and it is, therefore, unknown, which extract(s) is (are) responsible for the demonstrated effects on proximal gastric relaxation, antral motility, and liquid gastric emptying in humans. However, the mode of action of Iberogast has recently been investigated in guinea pig stomach preparations, and the data provide evidence that the region-dependent effects of Iberogast are not because of the differential actions of the individual components of Iberogast on the fundus or antrum, but rather the specific properties of fundus *versus* antrum muscle (26). The effects of Iberogast on gastric motility are not attributable to the ethanol in this preparation, as the control solution contained an identical amount, and concentration, of alcohol. We evaluated the effects of a single dose of Iberogast, and the effects of different doses, as well as chronic administration, are unknown. In addition, our study was an investigation in a relatively small number of healthy subjects, therefore, future

Table 2. Area Under the Curves for the Gastric Emptying Profiles of Solid and Liquid Meal Components from the Total, Proximal, and Distal Stomach After Control or Iberogast from t = 0–120 minutes

	Control	Iberogast
Solid gastric emptying		
Total (%.min)	8,330 ± 286	8,580 ± 348
Proximal (%.min)	4,810 ± 439	5,120 ± 600
Distal (%.min)	3,530 ± 593	3,490 ± 539
Liquid gastric emptying		
Total (%.min)	3,310 ± 247	3,720 ± 237
Proximal (%.min)	1,520 ± 200	1,720 ± 242
Distal (%.min)	1,780 ± 243	2,000 ± 175

Data are mean ± SEM; N = 8.

studies in male and female patients with FD are required. Furthermore, while our study evaluated the effects of Iberogast in the fasting gastrointestinal tract, the evaluation of the effects of Iberogast on postprandial gastrointestinal motor function is of high clinical relevance. Iberogast and control solutions were consumed immediately before 50 mL of water, and only one subject was able to distinguish between control and Iberogast and only four reported a transient (*i.e.*, immediately after the treatment was taken) unpleasant taste following both treatments. Accordingly, the observed effects on motility are most unlikely to be attributable to an aversive effect.

In summary, we have demonstrated that Iberogast has region-dependent effects on gastric motility in humans—Iberogast increased proximal gastric relaxation, increased antral motility, and slowed gastric emptying of liquid slightly, but had no effect on pyloric and duodenal motility or solid gastric emptying in healthy male subjects. The effects on gastric motility may contribute to the beneficial effect of Iberogast in FD.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Iberogast improves symptoms in patients with functional dyspepsia.
- Iberogast decreases fundic tone in muscle strips from the guinea pig.
- Iberogast increases antral motility in muscle strips from the guinea pig.

What Is New Here

In humans, Iberogast:

- increases proximal gastric relaxation.
- increases the motility index of antral pressure waves.
- slows gastric emptying of liquids slightly.

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CONFLICT OF INTEREST

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