Acid infusion enhances duodenal mechanosensitivity in healthy subjects

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Acid infusion enhances duodenal mechanosensitivity in healthy subjects. Am J Physiol Gastrointest Liver Physiol 285: G309–G315, 2003. First published April 9, 2003; 10.1152/ajpgi.00242.2002.—Duodenal acid has been suggested to be of importance for dyspeptic symptoms. We investigated the effects of acid on duodenal mechanosensitivity and antroduodenal motility in 10 healthy subjects before and during duodenal infusion of acid (0.1 N HCl) or water by using a combined barostat-manometry assembly. During acid infusion, increased sensitivity to balloon distension was seen, with reduced perception (P = 0.04) and discomfort thresholds (P = 0.06) and higher intensity of discomfort (P = 0.02) compared with water. Higher balloon volumes were seen during acid infusion, indicating decreased tone (P = 0.05). Large volume waves were more prevalent during acid than water infusion (P = 0.009). The acid infusion suppressed antral contractions (P = 0.04) and increased the number of contractions in the proximal duodenum (P = 0.02) compared with before the infusion. In conclusion, duodenal acid enhances mechanical sensitivity in the duodenum, affects gastroduodenal motor function, and might be of importance for dyspeptic symptoms.

antroduodenal motility; duodenal tone; compliance; perception

dyspeptic symptoms are very common in Western society and constitute a great burden for the health care system (14). However, despite extensive diagnostic workup, the vast majority of those who seek medical attention with recurrent upper abdominal symptoms have no identifiable cause of their symptoms. Today these patients are referred to as suffering from functional dyspepsia (30). Several pathophysiological mechanisms have been proposed to be of importance in this syndrome, such as delayed gastric emptying, impaired gastric accommodation to a meal, gastric and duodenal hypersensitivity, abnormal small bowel motility, *Helicobacter pylori* infection, and psychological disturbance (2, 9, 11, 25, 26, 28, 31).

The role of acid in the pathophysiology of functional dyspepsia is unclear. The gastric acid secretion is normal in the majority of these patients (5), and the gastric mucosa does not seem to be abnormally sensitive to acid or duodenal contents (7). However, in a small subset of patients, acid-suppressive therapy seems to provide symptom relief (29). Recently, an abnormal clearance of exogenous acid from the duodenum and a decreased duodenal motor response to duodenal acid were demonstrated in patients with functional dyspepsia (22). Moreover, the duodenal bulb seemed to be hypersensitive to acid infusion, which induced nausea. In a 24-h study of duodenal pH (15), our group has shown an exaggerated and prolonged acid exposure after a meal in this patient group, but no direct relationship between acid exposure and symptoms could be demonstrated. However, duodenal acid exposure could still contribute to symptoms if it enhanced other pathophysiological mechanisms. In barostat studies, intraesophageal acid perfusion was shown to sensitize the esophagus to mechanical distension (13), and gastric acid infusion was shown to increase the sensitivity to gastric distensions (4). Therefore, instead of the duodenal acid itself having a direct effect on symptoms, the prolonged acid exposure might induce altered duodenal mechanosensory function. Another possibility is that the duodenal acid exposure may enhance chemosensitivity not specifically related to acid and that an altered responsiveness to duodenal nutrients is a feature of functional dyspepsia (6). Although several studies have investigated the motor effects of duodenal acid (12, 16–18, 20, 21, 34), the influence of acid on duodenal mechanosensitivity has not been evaluated.

Therefore, to evaluate the role of acid in the generation of dyspeptic symptoms, the primary aim of the present study was to examine the effect of duodenal acid infusion on mechanosensitivity in the duodenum in healthy volunteers. Furthermore, we also wanted to investigate alterations in duodenal tone and non-lumen-occlusive phasic contractions during duodenal acid infusion measured by an electronic barostat compared with the effects on lumen-occlusive contractions measured with antroduodenjejunal manometry.
Study Subjects

Ten healthy volunteers (5 men, 5 women; mean age 26 yr, age range 22–35 yr; body mass index 23 ± 3.6 kg/m²) were included in the study. All subjects were free of gastrointestinal symptoms and had no evidence of acute or chronic illness. Apart from oral contraceptives, none of the subjects were taking any medication. Written informed consent was obtained from each participant before the study. The ethics committee of the University Hospital had previously approved the protocol.

Recording Technique

In the present study, we used a multilumen combined barostat-manometric tube assembly with an outer diameter of 6.0 mm that incorporated seven pressure-recording side ports (Zinetics SVS barostat catheter; Medtronics Functional Diagnostics, Skoveland, Denmark). The barostat balloon was made of polyethylene, and the attachment sites of the barostat balloon were situated 17 and 27 cm from the distal end of the catheter. Distension to a maximal volume of 200 ml resulted in a cylindrical balloon. The barostat balloon was connected to a computer-driven, programmable, volume-displacement barostat device (Synectics Visceral Stimulator; Synectics, Stockholm, Sweden). The pressure-recording side ports of the tube assembly were situated 2, 7, 12, 32, 37, 42, and 47 cm from the tip of the catheter. The side port situated 32 cm from the end of the catheter, i.e., 5 cm orad to the proximal end of the balloon, was used for infusion of acid or water, but the other six were used for manometry recording. These were connected to capillaries and perfused with water at 0.4 ml/min under low-compliance conditions by using a pneumohydraulic infusion pump (Arndorfer Medical Specialties, Greendale, WI). The catheter was connected to pressure transducers, and recordings were made with a polygraph (PC Polygraf 16 HR; Synectics), which converted the pressure data to digital information at 16 Hz. The information obtained from the barostat and the polygraph was transferred to a computer, displayed on the screen, and stored for later analysis by using specially designed software (Synectics). A pH antimony electrode (Synectics) was attached to the assembly with its tip 33 cm from the distal end, i.e., 1 cm orad to the side port used for acid and water infusion. The pH data were stored on a portable digital recorder (Digitrapper Mk III; Synectics).

Study Design

The studies took place on two separate days 9 ± 5 days apart. Subjects were randomized to receive either 0.1 N HCl (5 ml/min) or water (5 ml/min) in a single-blind fashion through the tube assembly into the descending part of the duodenum. Otherwise the procedures were the same on both study days.

After patients fasted overnight, the barostat-manometric tube assembly was introduced through the mouth. The assembly was then advanced under fluoroscopic guidance until the barostat balloon was situated in the horizontal part of the duodenum. The catheter was then secured to the subject’s chin with adhesive tape, and the tube assembly was connected to the barostat and to the infusion pump. With the balloon in the horizontal part of the duodenum, the infusion port and the pH electrode were situated in the distal part of the descending part of duodenum. Normally, one manometric recording point was in the antrum, two were in the proximal duodenum, two were in the distal duodenum, and one was in the proximal jejunum. Manometry and pH were continuously recorded during the whole experiment.

To unfold the barostat balloon, it was inflated with a fixed volume of 60 ml for 1 min with the subject in a recumbent position and was again deflated completely. The subjects were then positioned in a comfortable sitting position with the knees bent (45°) and the trunk upright (45°) in a specially designed bed. Thereafter, the minimal distending pressure (MDP) was determined by increasing the intraballoon pressure by 1 mmHg every minute until respiratory variations in the balloon volume appeared. Again the balloon was deflated, and after a short adaptation period the first distension sequence was started as long as no manometric evidence of an ongoing phase III was present. We used isobaric phasic distensions of 2-min duration starting at MDP with stepwise increments of 2 mmHg. The corresponding volume was continuously recorded. The subjects were instructed to score their perception of the abdominal sensation at the end of every distension step by using a graphic rating scale that combined verbal descriptors on a scale graded 0–6, where 0 represented the absence of any sensation, and 5 represented the maximum discomfort, and 6 pain (19). The distension sequence ended when the subject reported discomfort or pain, at which time the barostat balloon was immediately deflated and a resting period of 20 min was allowed. At the end of every distension step, the subjects were also instructed to rate the intensity of nine different upper abdominal symptoms (discomfort, bloating, fullness, belching, nausea, burning in the chest, epigastric burning, satiety, and pain) on a 100-mm visual analog scale (VAS) with verbal descriptors at the beginning (“none”) and at the end (“worst possible”) of the scale. After the first distension sequence and the short resting period, balloon volumes as an indicator of duodenal tone were recorded with the pressure set to 1 mmHg above the MDP for 15 min without duodenal infusion and for 15 min during infusion with 0.1 N HCl (5 ml/min) or water (5 ml/min). The subjects were blinded to what solution they received. During these periods, the subjects were asked every 5 min to rate the intensity of the nine upper abdominal symptoms used in the distension sequence. The balloon was then deflated, and the distension sequence was repeated during continuous duodenal infusion of acid or water. After the end of the study, the position of the tube assembly was once again checked fluoroscopically.

Data Analysis

During the distension sequences, the perception threshold was defined as the first level of pressure and the corresponding volume (averaged over the 2-min distension period) that evoked a perception score of 1 or more. Discomfort threshold was defined as the first level of pressure and the corresponding volume that provoked a score of 5 or more. Pressure thresholds are expressed as pressures relative to MDP. Also, pressure-perception curves were obtained from the stepwise distensions by using data from the pressure steps, where 75% of the subjects still had not reached the level of perceived discomfort or pain. By using the averaged intragastric volumes during each 2-min distending period, pressure-volume curves were created, and the compliance was calculated as the slope of the curve. We also obtained pressure-intensity curves by plotting the VAS scores for the different sensations during the distensions against the distending pressure. Duodenal balloon volumes, reflecting tone, were assessed with the pressure set at 1 mmHg above MDP. The balloon volumes were averaged over 5-min periods, and mean vol-
umes were obtained for 15 min before and 15 min during the infusion of acid or water, respectively. We also used the data obtained from the barostat recording to evaluate the effect of the infusions on phasic contractility, which corresponds to slow changes in baseline volumes. After filtering out respiratory artefacts, we performed a baseline reconstruction by using a computerized algorithm. A motility index (MI) (ml/s) was then calculated as the area between the signal from the barostat and the baseline normalized over time (27). The MI was also averaged over 5-min periods, and mean MI were obtained for 15 min before and 15 min during the infusion of acid or water, respectively. As a barostat measure of susceptibility, we assessed the number of volume waves obtained from the barostat recording to evaluate the effect of the infusions on phasic contractility, which corresponds to slow changes in baseline volumes. After turning to 75% of the baseline volume within 60 s (not to be confused with changes in tone). The duration had to be 15–60 s. These features distinguished large volume waves from normal phasic events (data not shown). The number of large volume waves was determined for 15 min before and during the infusions. The manometry recordings were used to assess the effects of the infusions on the lumen-occlusive contractions. For analysis, the antral recording point was used together with the recording points 5 cm oral to the infusion port (proximal duodenum) and 5 cm aboral to the distal margin of the balloon (distal duodenum). The number of contractions and the cumulative MI (MI = ln[(area/min) + 1]) was determined by using specially designed software (1) for 15 min before and during the infusions. Moreover, we also assessed the number of phase III-like activities in the proximal duodenum during 15 min before and during the infusions. The mean pH was assessed during 15 min before and during the infusions.

Statistics

A paired t-test was used for comparison of pressure and volume thresholds, mean balloon volumes, compliance, large volume waves, the barostat MI, mean pH, and the manometry variables before vs. during the infusions and also for the changes in these parameters pre- vs. postinfusion between the water and acid experiments. We applied a general linear model with repeated measures to compare the pressure-perception/volume/intensity curves before vs. during the infusions and also to compare the shift of these curves between the acid and water experiments. The proportion of patients with reduced sensory thresholds post- vs. preinfusion were compared between the acid and water experiments with Fischer’s exact test. One-way ANOVA for repeated measures with post hoc analysis with the Bonferroni correction was utilized for VAS scores before vs. during the infusions, and a general linear model with repeated measures was used to compare these scores between the acid and water infusions. Statistical significance was generally accepted at the P < 0.05 level. All data are given as means ± SD unless otherwise stated.

RESULTS

All volunteers fulfilled both study days, and a good position of the balloon was obtained in all subjects. The infusions were generally well tolerated, and the volunteers were unable to tell which infusion they received. The mean pH during the water infusion was 6.4 ± 0.5 compared with 1.8 ± 1.2 during acid infusion (P < 0.0001). In four of the volunteers (3 during acid experiment, 1 during water), there was a modest distal displacement (<10 cm) of the tube assembly, as shown by fluoroscopy after the study. In these subjects, no antral manometry recording was obtained.

Distensions

Perception. During the acid infusion, compared with before the infusion, reduced pressure perception (3.0 ± 2.5 vs. 5.0 ± 4.7 mmHg above MDP; P = 0.03) and discomfort thresholds (11 ± 3.7 vs. 15 ± 4.0 mmHg above MDP; P < 0.0001) were seen (Fig. 1A). Also, the corresponding volume at the discomfort threshold was reduced during the acid infusion (73 ± 11 vs. 83 ± 17 ml; P = 0.01), whereas the volume at the perception threshold remained unaltered [40 ± 17 vs. 35 ± 18 ml; not significant (NS)]. During the water infusion, no effect on the pressure perception (4.8 ± 2.5 vs. 5.0 ± 3.3 mmHg; NS) or discomfort thresholds (15 ± 5.2 vs. 15 ± 4.6 mmHg; NS) were observed compared with before the infusion (Fig. 1B). Likewise, the corresponding volumes at the perception (44 ± 13 vs. 41 ± 10 ml; NS) and discomfort thresholds (87 ± 19 vs. 86 ± 22 ml; NS) were unaffected by the water infusion. The change in pressure pre- vs. postinfusion was bigger during the acid compared with the water experiment, both for perception (2.0 ± 2.5 vs. 0.2 ± 1.5 mmHg; P = 0.04) and discomfort thresholds (4.6 ± 1.9 vs. 0.8 ± 4.4 mmHg; P = 0.06). Moreover, all 10 subjects reduced their discomfort threshold during acid infusion compared with before the infusion, whereas only 3 subjects did so during the water infusion (P = 0.003). The pressure-perception curve was significantly shifted toward higher perception scores for the same distending pressures during acid infusion compared with before
infusion \((P = 0.001)\) (Fig. 2A), whereas the pressure-perception curve was not altered by the water infusion \((P = 0.04)\). This shift of the pressure-perception curve differed significantly between the acid and water experiments \((P = 0.04)\).

Intensity of symptoms. The pressure-intensity curves obtained during the distension sequences were significantly shifted toward higher VAS scores for the same distending pressures during acid infusion compared with before infusion \((P = 0.01)\) (Fig. 3A), fullness \((P = 0.01)\), bloating \((P = 0.01)\), and pain \((P = 0.02)\). The pressure-intensity curves were not significantly affected by the water infusion, as exemplified with discomfort in Fig. 3B. When comparing the acid and the water experiments, we found the shift of the pressure-intensity curve to be significantly more pronounced during the acid infusion for discomfort \((P = 0.02)\), and there was a trend in the same direction for fullness \((P = 0.09)\) and bloating \((P = 0.09)\).

Compliance. During the acid infusion, the pressure-volume curve was significantly shifted toward higher volumes for the same distending pressures compared with before the infusion \((P = 0.003)\). However, the slope of the pressure-volume curve was not altered during acid infusion compared with before infusion \((4.5 \pm 1.9 \text{ vs. } 4.3 \pm 1.3 \text{ ml/mmHg; NS})\). During water infusion, the position of the pressure-volume curve was unaltered compared with before infusion, as was the slope \((4.1 \pm 1.4 \text{ vs. } 4.1 \pm 1.3 \text{ ml/mmHg; NS})\). A direct comparison between the shift of the pressure-volume curves or the slopes during the acid infusion compared with the water infusion did not detect any significant differences.

Results During the Infusions

Intensity of symptoms. With the balloon pressure set at \(1 \text{ mmHg} \) for \(15\) min before and during the infusions, there was a small, gradual increment for the VAS scores for several of the symptoms assessed with time. However, no significant differences in the VAS scores between the acid and the water experiments could be detected \((P > 0.15\) for all comparisons). When we compared the VAS scores for each 5-min period during the infusion with the score just before the infusion alone, significant increments in the intensity of satiety \((P = 0.04)\) and nausea \((P = 0.01)\) occurred (Fig. 4), as did a tendency toward increased intensity of fullness \((P = 0.06)\), bloating \((P = 0.10)\), and epigastric burning \((P = 0.07)\) during acid infusion. The VAS scores increased successively during the infusions, except for nausea, for which the maximum intensity was reported \(5\) min after the start of the acid infusion \((P < 0.05\) vs. before the infusion and \(10\) min after the start of infusion). No increments in the intensity of symptoms were observed during the water infusion. Despite the above-mentioned significant increments in symptom intensities during acid infusion, the VAS scores were low in general, indicating very mild symptoms.

Duodenal tonic and phasic activity: barostat measurement. The MDP was similar on both study days \((13 \pm 3.0 \text{ vs. } 13 \pm 3.7 \text{ mmHg; NS})\) (Table 1). During the acid infusion, the mean balloon volumes increased sig-
significantly compared with before the infusion \((P = 0.03)\), indicating reduced tone, whereas no changes in balloon volumes were observed during the water infusion (Fig. 5). The change in balloon volume was more pronounced during the acid infusion compared with the water infusion \((9.4 \pm 11.7 \text{ ml vs. } 1.5 \pm 4.8 \text{ ml; } P = 0.05)\). The barostat MI, as a measure of total phasic contractile activity, was reduced during the 15 min of acid infusion compared with before infusion \((P = 0.03)\). No effect on the MI was seen during the water infusion compared with before infusion. The change in MI before vs. during the infusion did not differ significantly between the water and acid infusions.
the acid infusion. In a follow-up study (23), the same group reported a modest effect of treatment with a proton pump inhibitor on the duodenal acid hypersensitivity in functional dyspepsia. Our group (15) was not able to confirm a direct relationship between acid infusion and the occurrence of symptoms in this patient group. However, the patients demonstrated an exaggerated and prolonged acid exposure in the duodenum following meal ingestion compared with controls. Therefore, instead of a direct relation with symptoms, acid might induce long-term alterations in duodenal sensorimotor function in functional dyspepsia. Indeed, in our study of healthy volunteers, acid infusion in the duodenum was able to induce enhanced duodenal sensitivity. Our suggestion is that this may be one mechanism through which the prolonged postprandial duodenal acid exposure in patients with functional dyspepsia can affect the symptom pattern. Although the existing results regarding duodenal sensitivity in functional dyspepsia are far from clear, there appears to be a group of patients with functional dyspepsia with increased duodenal mechanosensitivity in terms of reduced sensory thresholds (10, 11) or induction of symptoms by duodenal distension (3). Of course, it remains to be proven that acid infusion affects the duodenal mechanosensitivity in a similar way in patients as in controls. Moreover, the effects of an infusion of acid into the duodenum for <0.5 h, yielding in the majority of the subjects a pH of 1–3, cannot directly be translated into the effects of prolonged acidity after a meal to a pH level of 3–4, day after day, in some patients with functional dyspepsia. The possibility of studying the effect of long-term, low-grade acid exposure in an experimental human setting is of course for ethical reasons limited, especially if it is believed to induce long-lasting hypersensitivity.

Altered antroduodenjejunal motility demonstrated by manometry recordings is present in a number of patients with functional dyspepsia. Several authors (8, 24) have reported antral hypomotility, and, at the level of the small bowel, increased, more irregular motor patterns resembling a neuropathic abnormality have been observed (2, 33). Moreover, delayed gastric emptying is present in a significant minority of these patients (25). In our study, as well as in previous studies (12, 16), the effect of acid exposure in the duodenum was to stimulate duodenal contractions, induce phase III-like activities, and inhibit antral contractility, in agreement with the described alterations in functional dyspepsia. Therefore, one might speculate that exaggerated and prolonged acid exposure might similarly affect motility patterns in these patients. However, the link between motor events and symptoms is still far from clear.

A surprising finding in our study was the net relaxation of the duodenum during acid infusion, especially with the findings of Rao et al. (21) in mind, who reported tonic occlusion of the duodenum following acid infusion. However, in that study another technique was used to study tone, i.e., simultaneous videofluoroscopy and manometry, which may explain some of the differences. More importantly, they only used the simultaneous recordings for ~1 min following the acid infusion, which also only lasted for 1 min, compared with 20- to 25-min acid infusion in our study (depending on the length of the second distension sequence) and continuous tone recording for 15 min. Early after the start of the acid infusion in our study, several of the subjects exhibited so-called large volume waves as well as phase III-like activities as indicators of increased phasic activity initially, which then slowly faded away. The net effect might be a temporal duodenal occlusion. The increased balloon volumes, indicating decreased tone, appeared slowly and gradually during the acid infusion, and the maximal balloon volume was always demonstrated toward the end of
In conclusion, we have demonstrated that duodenal acid infusion enhances duodenal mechanosensitivity in healthy subjects and affects gastroduodenal motor function. These findings might be of importance in the indirect generation of dyspeptic symptoms and deserve to be further studied.

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