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An alginate-antacid formulation (Gaviscon Double Action Liquid®) can eliminate the postprandial “acid pocket” in symptomatic GERD patients

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SUMMARY

BACKGROUND—Recently, an “acid pocket” has been described in the proximal stomach, particularly evident postprandially in GERD patients, when heartburn is common. By creating a low density gel “raft” that floats on top of gastric contents, alginate-antacid formulations may neutralize the “acid pocket”.

AIM—We hypothesized that the postprandial “acid pocket” can be displaced distal to the esophagogastric junction (EGJ) by an alginate-antacid formulation.

METHODS—The “acid pocket” was studied in ten symptomatic GERD patients. Measurements were made using concurrent stepwise pH pull-throughs, high resolution manometry, and fluoroscopy in a semi-recumbent posture. Each subject was studied in three conditions: fasted, 20 min after consuming a high-fat meal and 20 min later after a 20 ml oral dose of an alginate-antacid formulation (Gaviscon Double Action Liquid®). The relative position of pH transition points (pH > 4) to the EGJ high-pressure zone was analyzed.

RESULTS—Most patients (8/10) exhibited an acidified segment extending from the proximal stomach into the EGJ when fasted that persisted postprandially. Gaviscon neutralized the acidified segment in 6 of the 8 subjects shifting the pH transition point significantly away from the EGJ. The length and pressure of the EGJ high-pressure zone were minimally affected.

CONCLUSIONS—Gaviscon can eliminate the “acid pocket” in GERD patients. Considering that EGJ length was unchanged throughout, this effect was likely attributable to the alginate “raft” displacing gastric contents away from the EGJ. These findings suggest the alginate-antacid formulation to be a well-targeted postprandial GERD therapy.

Keywords

acid pocket; alginate; antacid; gastroesophageal reflux; Gaviscon

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INTRODUCTION

The concept of the “acid pocket” emerged from the observation that postprandial reflux episodes achieved nadir pH values lower than the corresponding values in the gastric body where acidity was buffered by the meal. The observation that newly secreted acid layered on top of the ingested meal emerged as the explanation for this paradox, based on studies in dyspeptic patients and healthy volunteers.¹ Furthermore, the proximal extent of this acidity extended close to or even proximal to the squamocolumnar junction (SCJ) in the postprandial period. Subsequent observations suggested this effect was more pronounced in patients with gastroesophageal reflux disease (GERD) and in those with large hiatal hernias.^{2,3} In these patients, the extension of acidity proximal to the SCJ occurred despite the EGJ being contracted suggesting it to be only a thin “acid film” of liquid tracking into the sphincter.^{2,3} The EGJ of GERD patients, particularly those with hiatal hernia, is known to be more compliant than that of controls⁴ and modeling experiments suggest that the barrier function of the EGJ is compromised when the liquid film coating the mucosa exceeds 0.4 mm in thickness,⁵ making it very attractive to relate these observations as the mechanism by which acidity tracks into the distal esophagus. In some cases the “acid film” can extend up to 6 cm above the SCJ,³ but in GERD patients without a hiatal hernia, the proximal extent was typically confined to within 3 cm above the SCJ.²

Apart from representing an alternative mechanism of distal esophageal acid exposure in GERD, the “acid pocket” also represents a unique therapeutic target. Specifically, alginates, based on the concept of forming a gel-like barrier on top of gastric content, may displace or eliminate the “acid pocket”. Alginates are natural polysaccharide polymers isolated from brown seaweed (*Phacophyceae*). On contact with gastric acid, alginate precipitates into a low density viscous gel of near neutral pH in a matter of seconds *in vitro* or a few minutes *in vivo*.⁶ With the pH change, the sodium bicarbonate contained in the alginate-antacid formulation releases carbon dioxide, which is then trapped in the alginate gel causing it to float to the top of the gastric contents like a “raft”.^{6,7} Hence, alginate-based formulations with sodium bicarbonate may effect direct and immediate neutralization of the acid pocket/film. The duration of *in vivo* action likely varies, but the raft of the original alginate-based formulation (Gaviscon), developed as an offshoot of a radiologic contrast agent, remained in the stomach for up to 4 hours⁸ and is retained on top of the meal for the duration of its emptying.⁹ The quantities of alginate and sodium bicarbonate, as well as other antacid components, vary widely among the commercial products marketed internationally, with a notable absence of relevant labeling information for preparations sold in the U.S.^{6,10} However, *in vitro* testing suggests a lesser amount of raft formation by the U.S. formulations compared to those sold in the U.K.,¹⁰ indicating that the U.K preparations have greater potential to target the acid pocket. Consequently, the aim of this study was to assess the ability of a commercial high-concentration alginate-antacid formulation (Gaviscon® Double Action Liquid) to neutralize and/or displace the acid pocket in GERD patients.

MATERIALS AND METHODS

Subjects

Ten symptomatic GERD patients (5M, ages 26–46, GERDQ score 9–14) were studied after remaining off acid-suppressive medications for at least one week prior. Acid neutralizing medications were allowed as needed except for the day of the study. None of the patients had a history of upper gastrointestinal surgery. The patients were enrolled from the Gastrointestinal Diagnostic Laboratory at Northwestern Memorial Hospital. The study protocol was approved by the Northwestern University Institutional Review Board and informed consent was obtained from all participants.

Study Medication

Sodium alginate-bicarbonate (Gaviscon Double Action Liquid[®], Reckitt Benckiser Healthcare, Hull, U.K.) is an oral liquid suspension that belongs in the pharmacotherapeutic group A02BX (other drugs for peptic ulcer and gastroesophageal reflux disease). Its mode of action does not depend on absorption into the systemic circulation. The medication is a combination of two antacids (calcium carbonate and sodium bicarbonate) and alginate. Each 20 ml dose contains 1000 mg sodium alginate, 426 mg sodium bicarbonate, and 650 mg calcium carbonate with a neutralizing capacity of approximately 18.1 mEq H⁺.

pH Measurement

A single-sensor antimony pH catheter (VersaFlex[®] Z, Alpine Biomed, Corp., Fountain Valley, CA, U.S.A.) was connected to an ambulatory pH recorder set at a sampling rate of 1 Hz (Ohmega, Medical Measurement Systems B.V., Enschede, The Netherlands) and connected to a PC for real-time display using proprietary software (version 8.11 B1835, Medical Measurement Systems B.V.). The pH electrode was first calibrated at room temperature in pH 7.01 and pH 4.01 buffer solutions (Medtronic Inc., Shoreview, MN, U.S.A.). After calibration, the pH catheter was passed transnasally into the stomach with videofluoroscopic confirmation.

High Resolution Manometry

High resolution esophageal pressure topography data were obtained using a solid-state manometric assembly (4.2 mm outer diameter) with 36 circumferential sensors spaced at 1-cm intervals (Given Imaging, Los Angeles, CA), the recording characteristics of which have been described previously.¹¹ Studies were done after at least a 6-hour fast. Pressure transducers were calibrated at 0 and 300 mmHg using externally applied pressure prior to the study. Pressure topography data were analyzed using ManoView[™] analysis software (Given Imaging, Los Angeles, CA, USA).

Study Protocol

Patients were studied after a 6-hr fast. Each patient was intubated with the HRM assembly for continuous monitoring of the EGJ high-pressure zone for the duration of the study. The HRM assembly was affixed to the nose to maintain its position throughout. The pH catheter was passed transnasally alongside the HRM assembly into the proximal stomach. During the recording, the patients were supine on a fluoroscopic table tilted head-up to ~30° (easy DIAGNOST 15/30, Philips Medical Systems DMC GmbH, Germany/ Phillips Medical Systems, Shelton, CT, U.S.A.) and shielded below the umbilicus with a lead apron, along with a lead collar for thyroid protection. Concurrent with fluoroscopy, a station pull-through was performed at 0.5-cm intervals until the pH electrode was 3 cm above the proximal margin of the EGJ as denoted on HRM. Fluoroscopic images were recorded using a DVD recorder (Magnavox ZV457MG9, Funai Electric Co. Ltd., Lockbourne, OH, U.S.A.) and synchronized with manometric and pH data using an event marker each time fluoroscopy was initiated. Each pull-through station was maintained for at least 15 seconds or until a stable pH reading was obtained. After completing the fasting protocol, the pH electrode was repositioned in the stomach and the patients consumed a meal consisting of a McDonald's[®] Double Quarter Pounder with Cheese and small serving of fries (970 kcal, 49 % fat) with 250 ml of water. The pull-through protocol was repeated after 20 min. After completing the postprandial protocol, the pH electrode was repositioned into the stomach and the patients swallowed a 20-ml dose of the Gaviscon Double Action Liquid[®]. The pull-through protocol was repeated after 20 min. The presence of reflux related symptoms was assessed using visual analogue scales (VAS) in the fasted state, 20 minutes into the postprandial stage and 20 minutes after ingestion of the Gaviscon, immediately prior to the pH pull-throughs.

Patients were asked to rate the severity of “burning feeling behind the breastbone”, “pain behind the breastbone”, “acid taste in the mouth” and “unpleasant movement of material upwards from the stomach” along the 100-mm long line (100 point scale, 0 = no symptom, 100 = severe symptom). A total VAS score (max. 400) was calculated by summing the scores reported for the four symptoms at each pull-through.

Ex-Vivo Study

An ex-vivo study was performed to determine the ability of Gaviscon Double Action Liquid® to form a barrier, i.e. “raft”, above an unbuffered layer of acid on top of a homogenized meal. Firstly, the ability of acid to partition on top of the homogenized meal was assessed as per Fletcher *et al.*¹ The study test meal was blended to form a consistency of porridge and transferred to a transparent container. 0.1N hydrochloric acid was distributed over the surface of the homogenized meal with a syringe to form a 2-cm layer of acid. The pH electrode was positioned in the surface layer of acid and then advanced downward. The meal was then gently agitated for 1 minute until it had a homogenous appearance. The pH electrode was once again advanced through the mixture. A 20-ml dose of the sodium alginate was dispersed over the surface of the homogenized meal-acid mixture and the pH electrode was again advanced through the mixture.

Data Analysis

The “acidified segment” was defined as the region in which the pH was less than 4.^{1–3} The position of the proximal pH transition point was related to the EGJ high-pressure zone by correlation with the fluoroscopic images. Baseline non-deglutitive EGJ pressure at the time of the pH transition was quantified using ManoView™ software during expiration relative to gastric pressure.

Statistical Analysis

All measures were expressed as median (5th – 95th percentile) unless otherwise stated. Comparison between fasted, postprandial and after dosing with Gaviscon conditions were performed with the nonparametric Friedman test. The statistical significance was set according to Dunn-Bonferroni correction for multiple comparisons at $p < 0.0167$ for three groups.

RESULTS

The effect of Gaviscon Double Action Liquid® on the acid pocket in-vivo

All patients had a fasting gastric pH less than 4. The resting length of the EGJ HPZ was 2.9 (2.6 – 3.6) cm and none of the subjects had spatial separation between the LES and crural diaphragm. The proximal pH transition point was located 2.4 cm (0.4 – 3.4) cm above the distal margin of the EGJ high-pressure zone in nine of the ten patients (Figure 1). The transition point was at 6.9 cm below the distal margin in one patient. After the test meal, the proximal pH transition point remained above the distal EGJ margin in 8/10 patients, while in two cases the transition point was located 0.9 and 1.9 cm below the distal margin (Figure 1). The EGJ length was unaffected by the meal at 2.8 (2.4 – 3.4) cm ($p > 0.05$ vs. fasted state) and the acidity extended into the EGJ in six and into the esophagus in two patients. As expected, the pH profile increased to greater than 4 defining the distal margin of the acid layering over the meal in all patients. This “acid pocket” was 2.5 (0.5 – 3.9) cm deep. Postprandial decrease of the EGJ pressure to 2 (0 – 10) mmHg from 7 (0.5 – 21) mmHg in the fasted state was negligible ($p > 0.05$).

Gaviscon ingestion profoundly shifted the proximal pH transition point away from the EGJ into the stomach compared to the fasted and postprandial state ($p = 0.02$, Figure 1). This was

remarkably evident in 6/10 patients. In fact, no region with $\text{pH} < 4$ was detected in the proximal stomach in two patients such as the example in Figure 2. In these cases, the location of the transition point was taken as a default value of 10 cm below the distal EGJ margin. The length of the EGJ remained constant at 2.9 (2.1 – 3.3) cm ($p > 0.05$ vs. postprandial state) and EGJ pressure remained comparable to the postprandial state at 4 (0 – 15) mmHg ($p > 0.05$). Of the four cases without profound shift of the proximal pH transition, the transition point remained within the EGJ in three cases and 0.9 cm distal in one. In effect, the proximal pH transition point shifted aborally in 7/10 patients.

The severity of burning, pain behind the breastbone, acid taste or unpleasant movement of material upwards from the stomach reported by the patients at the fasted state was not significantly altered (multiple comparisons at $p < 0.0167$) after ingestion of the meal and with subsequent dosing with sodium alginate (Table 1). Likewise, there was no significant difference in the total score for the reported symptoms at each pH pull-through testing stage. However, it is worth noting the tendency of the severity of acid taste which increased postprandially to be diminished by the Gaviscon ($p = 0.04$, Table 1).

Ex-vivo study

The 0.1N hydrochloric acid poured onto the homogenized meal formed a separate layer floating on the surface of the meal. The pH electrode recorded a pH of 1.1 in the layer of surface acid and as it was pushed down into the homogenized meal the pH increased to 5.6 (Figure 3A). After gentle agitation, the acid and the meal formed a mix that looked homogenous, but the layering of the acid persisted. The second test revealed a pH of 2.5 on the surface, increasing to 6.7 deeper in the mix (Figure 3B). Hence, the layer of the acid remained unbuffered on top of the homogenized meal. After addition of the 20-ml dose of Gaviscon, the pH profile was altered showing uppermost layer with a pH of 8.1, a layer underneath of pH 1.8 and a pH of 6.7 deeper in the mix (Figure 3C) indicating the formation of a buffering layer (raft) on top of an “acid pocket”.

DISCUSSION

Recent investigations have clearly established that stomach content is not of uniform acidity in the postprandial period. Rather, meal-stimulated acid secretion surrounds and layers on top of the more solid chyme, particularly in the proximal stomach.¹² This phenomenon is a natural consequence of the digestive process wherein gastric secretions emanate from the glandular stomach lining and little mixing occurs in the proximal stomach. The result has been described as an “acid pocket” and occurs in healthy volunteers as well as GERD patients with or without hiatal hernia.^{1–3} Because of its proximity to the EGJ, the acid pocket has pathophysiological relevance in GERD: 1) it is the likely origin of postprandial acidic reflux, 2) it can track across the SCJ forming an acidic film on the distal esophageal mucosa even in the absence of a discrete reflux event, and 3) it can form a reservoir for acid reflux in the setting of hiatus hernia, particularly when in a supine posture.^{2, 3, 13} Given this potential mechanistic significance, the acid pocket also becomes an attractive therapeutic target. One particularly appealing concept is the possibility to cap the acid pocket with a viscous antacid gel matrix that floats on top, physically isolating the EGJ. It was in this context that these experiments were done using an alginate-antacid formulation (Gaviscon Double Action Liquid®). The major finding of this study was that Gaviscon Double Action Liquid® effectively eliminated the acid pocket in the majority test subjects with symptomatic GERD. Both in vivo and in vitro, the formulation localized on top of the acid pocket and replaced it with a region of more neutral pH. In vitro, this was visually attributable to the formation of a gel-like “raft” that floated on top of the more liquid acid layer.

Alginates are natural polysaccharides that polymerize when exposed to acid forming gel matrices that are further stabilized by Ca^{++} ions. In Gaviscon Double Action Liquid® the rafting property is further enhanced by NaHCO_3 because the later generates CO_2 when combined with acid adding buoyancy to the raft. Depending on the specifics of the alginate formulation, the gel matrix formed can have up to 1400 times the viscosity of water.¹⁴ Raft strength, measured in grams can be quantified with an instrument that determines the force necessary to pull an L-shaped test probe across the surface.¹⁰ Relevant variables of the formulation include the species of alginate, the presence of stabilizing (Ca^{++}) or destabilizing (Al^{++}) ions, and the pH of the solution.^{10, 15} Ideally, the raft would spread over the entire surface of the acid pocket completely separating it from the esophageal mucosa, so that in the event of reflux the raft would be either the first intragastric layer to come in contact with the esophageal mucosa or the sole refluxate constituent. Studies in adult and pediatric populations in which reflux was monitored postprandially with a pH electrode 5 cm above the EGJ with or without impedance monitoring consistently report a reduction in esophageal acid exposure and in the number acidic and non-acidic reflux events when alginate-antacid formulations were given after the meal.^{16–21} Concomitant with this, patients reported greater than 70% symptom relief.²² One caveat of this is that the observed protection was better when patients were in an upright position¹⁷ suggesting that the location as well as the physical properties of the raft to be important variables.

In conclusion, it is an attractive hypothesis that a strong alginate-antacid raft capping the acid pocket may reduce or even prevent postprandial acid reflux. Results of the current trial suggest that the alginate-antacid raft does, indeed, form in an appropriate position and does eliminate postprandial acidity in the proximal stomach. However, many relevant variables remain to be explored including the persistence of the raft effect and the degree to which it results in the suppression of acid reflux. Further experimentation aimed at defining or even improving the alginate-antacid preventative effect on reflux will require ambulatory studies of the postprandial period, likely using an antacid comparator to differentiate between alginate effect and antacid effect. Nonetheless, our results and existing reports on postprandial reflux monitoring, suggest that alginate-antacid formulations with robust rafting properties may provide a welcome alternative to systemically absorbed medications in the treatment of postprandial heartburn.

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Figure 1. Proximal pH transition point location relative to the distal margin of the EGJ fasting, postprandially, and after dosing with Gaviscon. The position of the proximal pH transition point demarcated an acidified segment that extended from the proximal stomach into the EGJ and the esophagus. The unbuffered segment persisted postprandially. Gaviscon neutralized the acidified segment, eliminating the “acid pocket” in majority of the GERD patients indicated by the significant relocation of the pH transition point away from the EGJ. Data shown as medians and interquartile ranges.

Figure 2.

Example of a pH pull-throughs in a single GERD patient. Position data are relative to the nares (x-axis) with the corresponding location of the EGJ high-pressure zone (shaded band) and the proximal pH transition point (black dot). In the fasted state (top panel), an acidified segment was detected extending proximally beyond the distal EGJ margin as film of acidity within the EGJ. Postprandially (middle panel) the proximal transition pH point remained within the EGJ and an equivalent distal transition pH point (white dot) was detected with the stomach. Both pH transition points demarcated the “acid pocket” layered on top of the ingested meal in the proximal stomach with an “acid film” within the EGJ. After ingestion

of the Gaviscon, the acidified segment was no longer detected either in the proximal stomach or the EGJ (bottom panel).

Figure 3.

The effect of Gaviscon on acid layered on top of a homogenized meal ex-vivo. The pH recording profile (A) showed a distinctive change in pH as the pH electrode was advanced through the layer of the acid poured on top of a homogenized meal, (B) after gentle 1-minute agitation of the acid and the homogenized meal showed persisting layering of the acid indicative of an “acid pocket”, and (C) after pouring of a 20-ml dose of Gaviscon on top of the agitated mixture showed formation of a “raft” floating on top and buffering the acid pocket.

Table 1

Symptom severity reported by the patients prior to each pH pull-through using visual analogue scales (VAS) with a score range of 0 – 100 for each symptom. The score range for the total VAS score was 0 – 400. Data shown as median (5th – 95th percentile).

Symptom	Fasted	Postprandial	Post-sodium alginate	p-value‡
burning feeling behind the breastbone	3 (0 – 14)	12 (1 – 20)	6 (0 – 43)	0.2
pain behind the breastbone	5 (0 – 17)	9 (1 – 36)	4 (1 – 61)	0.6
acid taste in the mouth	1 (0 – 16)	12 (2 – 47)	6 (0 – 25)	0.04
unpleasant movement of material upwards from the stomach	13 (1 – 39)	19 (2 – 42)	14 (1 – 40)	0.2
Total VAS score [†]	32 (5 – 72)	69 (11 – 101)	41 (6 – 145)	0.3

[†]Total VAS score represents the sum of the four symptoms VAS scores; [‡]Based on nonparametric Friedman test with statistically significant at $p < 0.0167$