Reflux disease and achalasia: Failure of the gatekeeper
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Chapter 8

An alginate-antacid formulation (Gaviscon Double Action) targets the acid pocket to reduce acid reflux in symptomatic GERD patients

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ABSTRACT

Background & Aims:
Alginate rafts may directly target the acid pocket, an important source of postprandial acid reflux, but this has never been visualized in vivo. This study determined the location of an alginate formulation in relation to the acid pocket and the corresponding effects on reflux parameters and acid pocket positioning in symptomatic patients with gastroesophageal reflux disease (GERD).

Methods:
In this randomized controlled study, 16 GERD patients with a large hiatal hernia received either 111In-labeled alginate-antacid (Gaviscon Double Action Liquid) or antacid (Antagel) after a standard meal. The relative positions of labeled alginate and acid pocket were analyzed for two hours using scintigraphy and reflux episodes were detected using concurrent high-resolution manometry and pH-impedance monitoring.

Results:
The alginate-antacid labeling co-localized with the acid pocket. The number of acid reflux episodes (antacid 15 [5-50] vs. alginate-antacid 3.5 [0-6.5], \( p=0.03 \) was significantly reduced, whereas the time to acid reflux was significantly increased (antacid 14 minutes [9-23] vs. alginate-antacid 63 minutes [23-92], \( p=0.01 \)). The acid pocket was more frequently located below the diaphragm after alginate-antacid treatment than with antacid (below diaphragm 71% [27-78] vs. 21% [10-51] respectively; \( p=0.08 \)). Sub-diaphragmatic positioning of the acid pocket negatively correlated with acid reflux (\( r=-0.76, p<0.001 \)).

Conclusions:
The alginate-antacid raft co-localized with the postprandial acid pocket and displaced it below the diaphragm resulting in significant suppression of postprandial acid reflux. This demonstrates the importance of the acid pocket in GERD pathogenesis and establishes alginate-antacid as an appropriately targeted treatment for postprandial acid reflux.
INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common condition where backflow of gastric contents into the esophagus causes symptoms and/or esophageal damage.\(^1\) The majority of acidic gastroesophageal reflux and symptoms, such as heartburn, occur after eating, which is somewhat paradoxical given that the buffering effect of food causes a reduction in intra-gastric acidity.

An explanation for this paradox was provided by Fletcher et al. who were the first to detect an unbuffered pool of acid that floats on top of ingested food, referred to as the gastric acid pocket.\(^4\) The acid pocket develops as a result of poor mixing of newly secreted acid and food in the proximal stomach, which remains relatively quiescent after a meal compared to the distal stomach.\(^5\) We recently reported that the position of the acid pocket relative to the crural diaphragm is an important determinant of the acidity of the refluxate.\(^6\) In GERD, proximal extension of the acid pocket above the diaphragm increases the risk for acid reflux.\(^6,7\) The acid pocket is therefore an important source of postprandial acid in GERD and, as such, represents a unique therapeutic target.\(^8\)

Emerging evidence suggests that alginates may act through direct targeting of the acid pocket. Alginates are natural polysaccharide polymers which, on contact with gastric acid, precipitate into a low-density viscous gel of near-neutral pH within minutes.\(^9,10\) The change in pH triggers the sodium bicarbonate in the formulation to release carbon dioxide, which becomes trapped in the alginate gel, causing it to float to the top of the gastric contents like a "raft".\(^9,10\) MRI shows that alginate rafts form in the proximal stomach close to the esophagogastric junction (EGJ), precisely where the acid pocket develops.\(^11\) Furthermore, a commercial alginate-antacid formulation, Gaviscon Double Action Liquid (Reckitt Benckiser Healthcare, Hull, UK) has been shown to shift the postprandial acidified segment in the proximal stomach away from the EGJ in the majority of GERD patients tested.\(^12\) The raft of Gaviscon Double Action is reported to remain in the stomach, on top of the meal, for more than four hours,\(^11\) while the acid pocket is reported to remain for up to 120 minutes.\(^6,14\) It is attractive to hypothesize that the mode of action of alginates allows direct capping and displacement of the acid pocket, isolating it from the EGJ and reducing postprandial acid reflux events.\(^12\) However, the position of the alginate raft in relation to the acid pocket has never been visualized in vivo.

The aim of this study is to visualize the position of the alginate raft after administration of Gaviscon Double Action in GERD patients and to concurrently assess the effect on reflux parameters and position of the acid pocket compared with a commonly used antacid control.
MATERIALS AND METHODS

Subjects
The study was performed in 16 patients with proven GERD, defined by the presence of esophagitis observed during upper endoscopy and/or pH-metry with an acid exposure of >4.5%, in combination with typical GERD symptoms. None of the subjects had previous gastrointestinal surgery or was taking medication known to influence esophageal motor function. Hiatal hernia size was measured by high-resolution manometry (HRM), and patients with small or no hiatal hernia (<3 cm) were excluded. Patients with confirmed long segment Barrett’s epithelium, or who were unable to stop the use of proton pump inhibitors for one week, or who had participated in another study using radioactivity within the last year were also excluded. The study was approved by the medical ethics committee of the Academic Medical Center. Written informed consent was obtained from all subjects before enrolment in the study.

Study medication
Sodium alginate-bicarbonate (Gaviscon Double Action Liquid) is an oral liquid suspension, directly acting without absorption into the systemic circulation. The medication is a combination of two antacids (calcium carbonate and sodium bicarbonate) and sodium alginate. Each half-maximal 10 mL dose contains 500 mg sodium alginate, 213 mg sodium bicarbonate and 325 mg calcium carbonate with a neutralizing capacity of approximately 10mEq H+. Gaviscon was labeled with 1 MBq indium-111 (\(^{111}\text{In}\))-chloride according to the established labeling procedure.\(^{16,17}\) Antagel is a common antacid drug with a neutralizing capacity of 30mEq H+. Each 10 mL dose contains 200 mg magnesium hydroxide and 400mg aluminum oxide.

Study design
In this parallel designed study, 16 GERD patients were randomized to \(^{111}\text{In}\)-labeled alginate-antacid (n=8) or antacid (n=8). Reflux episodes were detected using concurrent HRM and pH impedance monitoring, and scintigraphy was performed to localize the alginate-antacid raft and the acid pocket relative to the crural diaphragm (Figure 1). Acid-suppressive medication was stopped at least 7 days before the study day. Patients were allowed to use antacids except for on the study day. Subjects fasted overnight for at least 12 hours. On the day of study 350 MBq technetium-99m (\(^{99m}\text{Tc}\))-pertechnetate was injected intravenously. \(^{99m}\text{Tc}\)-pertechnetate behaves as a chloride ion, and is secreted by the parietal cells of the stomach.\(^{20}\) When this technique is used, acid distribution in the stomach can be visualized scintigraphically, as validated previously.\(^{4}\)

Before introduction of the HRM catheter, two sealed markers impregnated with \(^{99m}\text{Tc}\)-pertechnetate were attached to the catheter to visualize the exact location of the catheter during scintigraphy. This makes it possible to integrate the distances from the manometry and the scintigraphy,
to relate the acid pocket to the crural diaphragm. The HRM catheter and the pH-impedance catheter were inserted trans-nasally, through the pharynx and esophagus, into the stomach. The pH sensor of the pH-impedance catheter was placed 5 cm above the upper border of the lower esophageal sphincter (LES). Subsequently, the patients were positioned in an upright position in front of the scintigraphy camera. After positioning of the catheters, 5 min of baseline fastings measurements were obtained. Subjects then consumed a standardized meal within 10 min, consisting of 200 ml orange juice and two pancakes with jam (510 kcal). Thirty minutes after starting the measurement patients drank 10 ml of Gaviscon Double Action or 10 ml of Antagel. After 2 h of measurement catheters were removed (Figure 1).

**Figure 1** | Study design
HPM: high-resolution manometry

**Recording methods**
HRM was performed using a 21 lumen water-perfused HRM catheter (MMS, Enschede, the Netherlands). Eleven distal side holes were positioned at 1 cm intervals, and the 10 proximal side holes were spaced at 3 cm intervals. The side holes were perfused with distilled water at 0.15 mL/min, using a pneumohydraulic capillary perfusion pump (MMS, Enschede, the Netherlands) and hydraulic flow restrictors. For pH-impedance measurement a Unisensor pH-impedance catheter (Unisensor, Attikon, Switzerland) containing one ISFET pH sensor and eight impedance electrodes was used, allowing impedance recordings at 3, 5, 7, 9, 15 and 17 cm above the upper border of the LES. The sample rate was 50 Hz, and data were collected and analyzed with the MMS Solar system (MMS, Enschede, the Netherlands). Before each study the pH electrode was calibrated with pH 4.0 and pH 7.0 solutions (Medtronic A/S, Skovlunde, Denmark). Dynamic scintigraphic images were acquired on a gamma camera system (Diacam; Siemens Medical Solutions, Illinois, USA), equipped with a medium-energy collimator. Dynamic recordings were made in posterior view for 2 h (720 views, 10 s/view, 120 min total acquisition time). Gamma radiation of $^{99m}$Tc-pertechnetate and $^{111}$In have different energy levels, and can therefore be detected separately. Every acquisition...
was processed on a Hermes processing station (Hermes Medical Solutions, Stockholm, Sweden) for further analysis.

**Data analysis**
An acid pocket was considered as present when a clear pool of radiolabelled activity was distinguishable in the proximal stomach. The radiolabelled markers on the catheter were scintigraphically visualized as clear dots. Reflux episodes were detected by pH impedance and each liquid or mixed reflux event was defined as acidic reflux when pH<4, as weakly acidic when pH≥4 and pH<7.

HRM recordings were used to determine the exact distance from the crural diaphragm to the markers on the catheter for the position of the acid pocket. The lower and upper border of the crural diaphragm and the middle of the LES zone were determined. Subsequently, calibrated Hermes software was used to measure the distance from the proximal end of the gastric acid pocket to the markers on the catheters on one image to calculate the distance between the acid pocket and the crural diaphragm: below the diaphragm, at the level of the diaphragm or above the diaphragm. Measurements of the distances between the acid pocket and the diaphragm were made through a straight line in a planar posterior view of the stomach.

**Statistical analysis**
Based on the mean numbers of acid reflux episodes reported previously, a sample size of 7 per group in a parallel design will have 80% power to detect a difference in means of 5.8 (e.g. a first condition mean of 8.4 and a second condition mean of 2.6), assuming a standard deviation of differences of 3.5, using a Student t-test with a 0.05 two-sided significance level. To compensate for potential drop-outs, 16 patients with GERD were included. Statistical analysis was performed using SPSS 19.0 software for Windows (IBM, New York, USA). Results are presented as mean ± SEM in the case of a normal distribution or as median [interquartile range] for variables with a skewed distribution. For statistical analysis, the Mann-Whitney test was used. Correlations were determined using Spearman’s correlation coefficient.

**Figure 2** | Scintigraphic images of \[^{99m}Tc\]-pertechnetate-labeled acid pocket (A) and \[^{113m}In\]-indium-labeled alginate-antacid (B) and the two scintigraphic recordings superimposed (C).
RESULTS

Relative localization of the alginate-antacid raft and the acid pocket in vivo

Scintigraphy allowed independent visualization of the $^{99m}$Tc-pertechnetate acid pocket and $^{111}$In-dium-labeled alginate raft (Figure 2; panels A and B). The radiolabeled acid pocket was scintigraphically visible in all patients within 15 min of meal ingestion. The indium labeled alginate-antacid was directly visible after administration. When the two simultaneous scintigraphic recordings were superimposed, the alginate raft co-localized precisely with the acid pocket (Figure 2; panel c). The acid pocket and raft were visible for the entire length of the study.

Reflux episodes and esophageal acid exposure

The 16 GERD patients included in the study had a large hiatus hernia (≥3cm as seen on endoscopy or HRM) resulting in a high rate of acid reflux episodes. A total of 266 reflux episodes were detected, of which 138 (52%) episodes were acidic. Compared with the antacid, the total number of reflux episodes was reduced with alginate-antacid ingestion (median 21 [15-27] vs 14 [8.5-17], respectively; $p=0.05$) (Figure 3).

Figure 3 | The mean number of reflux events (A), acid reflux episodes (B) and esophageal acid exposure (C) were reduced by alginate-antacid compared with antacid but the mean number of weakly acid reflux episodes was higher with alginate-antacid (D).
The number of acid reflux episodes and the rate of acid reflux were also significantly lower after treatment with alginate-antacid, compared with antacid (15 [5.5-20] vs 3.5 [0-6.5], p=0.03 and 68% [40-79] vs 21% [0-44], p=0.02) and there was a trend towards reduced esophageal acid exposure (7.4 [2.1-22] vs 0.2 [0-4.1]; p=0.08) (Figure 3). Conversely, the number of weakly acid reflux episodes were not significantly different between alginate-antacid and antacid-treated patients (antacid 6 [6.0-7.5] vs. alginate-antacid 8 [6.0-13.0]; P=0.38) (Figure 3).

**Buffering time and time to acid reflux**

A pH sensor was continuously positioned in the acid pocket to allow comparison of buffering time after administration of alginate-antacid and antacid. The buffer time (amount of time that the acid pocket pH>4) was not significantly different after antacid and alginate-antacid ingestion (3.5 min [0.3-4.5] vs. 6 min [3-12], respectively; p=0.13) and the mean pH of the acid pockets were similar (2.1 [2.0-2.4] vs. 2.5 [1.7-2.8], respectively; p=0.71). However, compared with antacid, the time to acid reflux (antacid 14 min [9-23] vs. alginate-antacid 63 min [23-92]; p=0.01) and the mean pH of reflux episodes were significantly increased with alginate-antacid (antacid 3.5 [2.0-5.0] vs. alginate-antacid 5.0 [4.1-6.2]; p<0.05) (Figure 4).

**Acid pocket position and acid reflux events**

Acid reflux occurred mainly when the acid pocket was located above (78/95 reflux episodes; 82%), or at the level of (47/78 [60%]) of the diaphragm, but seldom when the pocket was located below the diaphragm (13/88; 15%). There was a trend towards a higher rate of sub-diaphragmatic positioning of the acid pocket with alginate-antacid, compared with antacid (71% [27-78] vs. 21% [10-51] respectively p=0.08) (Figure 5; panel A). The rate of sub-diaphragmatic positioning of the acid pocket had a significant negative correlation with the rate of acid reflux (r=-0.76, p<0.001), that is, acid pocket positioning below the diaphragm corresponds to a lower rate of acid reflux (Figure 5; panel B).
Increased acid reflux after meals is a hallmark of GERD, with the amount of acid exposure determining the severity of symptoms and complications. The acid pocket, being the most immediate source of postprandial refluxate in GERD, represents an important therapeutic target.

Among current therapies, alginates, with their raft-forming mode of action in the proximal stomach, are the most interesting candidates for direct targeting of the acid pocket. Gaviscon Double Action has been shown previously to neutralize the acid pocket in GERD patients, significantly shifting the pH transition point away from the EGJ. It was hypothesized that the alginate raft may cap and displace the acid pocket to a more distal position; but the localization of alginate in relation to the acid pocket had never been visualized in vivo.

Here we demonstrate for the first time that the alginate raft targets the acid pocket. The scintigraphic recordings clearly showed the alginate raft forming within minutes of ingestion and co-localizing with the acid pocket. The alginate-antacid labeling persisted in the proximal stomach for the entire two-hour study. Acid reflux episodes were reduced by more than 75% compared with antacid and reflux was delayed for more than an hour after the meal, compared to just 15 minutes with antacid. The buffering capacity of the two agents was similar; confirming the difference in acid reflux rates was not a pH effect. Rather, these findings suggest that the alginate acts to suppress reflux in the proximal stomach by effectively ‘capping’ the acid pocket. Given the properties of the buoyant alginate raft, it is likely that the raft is able to adapt to the acid pocket as it develops, continuously floating above newly-secreted acid close to the EGJ.
Consistent with previous findings, non-acid reflux events were not reduced. Despite a similar buffering capacity, the acidity of the refluxate was significantly reduced with alginate-antacid compared with antacid. This discrepancy between acid pocket pH and refluxate pH is most likely due to additional effects by the alginate on the position of the acid pocket. In healthy volunteers the pocket is highly acidic but gastroesophageal refluxate is usually weakly acidic. In GERD patients there is proximal migration of the acid pocket and increased rates of acid reflux. Therefore, displacement of the acid pocket distally in GERD patients would be expected to create a situation similar to healthy volunteers; a shift from acidic to weakly acidic events, owing to the fact that the acid pocket is no longer the most immediate source of refluxate. Our previous observations in GERD patients with large hiatus hernia show that the acid pocket frequently extends into the hiatal sac above the diaphragm and that this significantly increases the risk for acid reflux. This may explain why hiatal hernia size correlates closely with esophageal acid exposure and esophageal damage.

In a previous study we found that the prokinetic agent azithromycin is able to alter the acid pocket position from supra-diaphragmatic to sub-diaphragmatic in patients with a small hiatus hernia, but that this effect was eliminated by a large hiatus hernia. The data presented here confirms that the raft-forming mode of action of alginate is not compromised by a large hiatus hernia (≥3 cm). Furthermore, the rate at which the acid pocket was located below the diaphragm was more than three times greater with alginate-antacid compared with antacid (although not reaching statistically significance, p=0.08). This confirms that the alginate-antacid raft can displace the acid pocket distally, out of the hiatal sac, and builds on the previous data of Kwiatek et al. who showed significant distal shifting of the pH transition point. Sub-diaphragmatic positioning of the acid pocket had a significant negative correlation with acid reflux confirming that the effect of alginate-antacid on acid pocket position contributes to the observed reduction in acid reflux.

Further experimentation using a larger population of patients and/or a maximal dose of Gaviscon are needed to establish the outcomes that were approaching significance, such as esophageal acid exposure and acid pocket positioning below the diaphragm (p=0.08 for both). It would also be interesting to determine if distal displacement of the acid pocket plays a role in the reduction of acid reflux seen in patients with no hiatus hernia, and to confirm whether the observed reduction in acid reflux suppression translates to a reduction in GERD symptoms. This seems likely considering a previous systematic review of randomized, placebo-controlled trials that demonstrated a benefit in symptomatic improvement over placebo of 60% with alginate-antacid compared with an 11% improvement for antacid.

In summary, Gaviscon Double Action forms a robust and persistent alginate raft that caps the acid pocket, displacing it distally and reducing acid reflux events. These findings demonstrate the
value of directly targeting the acid pocket with a non-systemic, alginate-antacid formulation for the treatment of postprandial acid reflux in GERD. This may have clinical implications for patients who suffer primarily from postprandial reflux, who may be able to adequately control their symptoms with optimized use of alginate-antacid. Alginate may also benefit patients with insufficient response to PPIs. We have observed that the acid pocket persists after PPI treatment in GERD patients, and thus, may play a role in the residual symptoms that can occur despite PPI therapy. If this is the case, direct capping of the acid pocket would be expected to benefit these patients. In support of this, a recent study in patients with non-erosive reflux disease (NERD) demonstrated that supplementing PPI therapy with alginate more than doubled the number of patients who experienced complete reflux symptom relief.
REFERENCES


