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Gaviscon Double Action Liquid (antacid & alginate) is more effective than antacid in controlling post-prandial oesophageal acid exposure in GERD patients: a double-blind crossover study

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SUMMARY

Background
Recent studies have shown that Gaviscon Double Action Liquid (a combination alginate-antacid) administered post-prandially co-localises with the acid pocket, the 'reservoir' for post-prandial acid reflux.

Aim
To compare the effectiveness of Gaviscon Double Action Liquid to an equivalent strength antacid without alginate in controlling post-prandial acid reflux in GERD patients.

Methods
Fourteen GERD patients undertook two 3.5-h high-resolution manometry/pH-impedance studies during which they ate a standardised meal. In a double-blinded randomised crossover design they then took Gaviscon or CVS brand antacid, each with ~18 mmol/L acid neutralising capacity. The primary outcome was distal oesophageal acid exposure; secondary outcomes were number of reflux events, proximal extent of reflux, nadir pH of the refluxate, mechanism of reflux and reflux symptoms scored with a validated instrument.

Results
Ten patients completed the study. Gaviscon studies had significantly less distal oesophageal acid exposure and greater nadir refluxate pH in the 30–150 min post-prandial period than antacid studies. There were no differences in the number of reflux events (acid or weakly acidic) or the number of proximal reflux events (15–17 cm above the LES) with either study medication.

Conclusions
Gaviscon Double Action Liquid is more effective than an antacid without alginate in controlling post-prandial oesophageal acid exposure. However, the number and spatial distribution of reflux events within the oesophagus are similar. This suggests that Gaviscon main effectiveness relates to its co-localisation with and displacement/neutralisation of the post-prandial acid pocket, rather than preventing reflux.

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INTRODUCTION

Heartburn is a cardinal symptom of gastro-oesophageal reflux disease (GERD) and is among the most common patient complaints encountered by Internists and Gastroenterologists. A nationwide telephone survey of 21 000 representative US adults found that 6.3% of respondents experienced heartburn on at least a twice-weekly basis.[1] In most instances, heartburn is experienced post-prandially. A seeming paradox of post-prandial heartburn is that it occurs during the period that one might expect gastric acid to be buffered by the meal. That paradox was partially resolved with the description of the 'acid pocket', the phenomenon by which newly secreted gastric acid layers on top of, rather than mixing with, the ingested meal.[2, 3] This puts acid in close proximity to the gastro-oesophageal junction as soon as 17 min after eating.[4] Investigations using either technetium labelled acid and scintigraphic monitoring[5] or high-resolution post-prandial pH recordings[4] have confirmed that the acid pocket is the source of post-prandial acid reflux. Furthermore, the acid pocket tends to localise within a hiatal hernia, when present,[5] and to facilitate the migration of acid across the squamocolumnar junction in patients with hernias or GERD.[5, 6] Hence, selectively targeting the acid pocket becomes an attractive therapeutic approach for the management of post-prandial heartburn.

Consistent with the central role of gastric acid in the genesis of reflux symptoms and mucosal pathology, the inhibition of gastric acid secretion has been the mainstay of the medical management of GERD.[7] Proton pump inhibitors (PPIs) are particularly potent and have proven to be extremely effective treatment for esophagitis. Not surprisingly, PPIs have also been shown to both decrease the size of and the acidity within the acid pocket.[8, 9] However, PPI therapy has limitations. Many patients have an incomplete symptom response and others, either because of general unease with open-ended pharmacotherapy or because of the intermittent nature of reflux symptoms, prefer to address reflux symptoms with prn medication. The problem has been the limited efficacy of this approach; antacids neutralise gastric acid in a short timeframe after ingestion but the effect is soon overcome by meal-stimulated acid secretion. Alternatively, an alginate-antacid combination creates a 'raft' floating on top of the ingested chyme that co-localises in the region of the acid pocket, potentially offering more effective targeted therapy.[10] This study compared the effect of Gaviscon Double Action Liquid (Reckitt Benckiser Healthcare, Hull, UK) to a store-brand antacid in controlling post-prandial acid reflux in GERD patients.

METHODS

Study subjects

Typical GERD patients with past or present LA A or B esophagitis and/or abnormal pH monitoring study (>5% distal oesophageal acid exposure on Bravo pH monitoring) along with a significant frequency-severity of typical gastro-oesophageal reflux symptoms gauged by the GerdQ instrument (score ≥8) were recruited from a pool of patients referred to the Northwestern Medical Faculty Foundation (NMFF) Gastroenterology out-patient practice or the gastrointestinal diagnostic laboratory at Northwestern Memorial Hospital from August 2011 to March 2013. Those with prior gastrointestinal surgery, or significant cardiopulmonary, renal, neurological or psychiatric disorders were excluded. Study participants were asked to refrain from taking any proton pump inhibitors or H_2-receptor antagonists for 7 days prior to their study sessions. Acid neutralising medications were allowed as needed except for the day of the study. All subjects gave written informed consent and the Northwestern University Institutional Review Board (IRB) approved the study protocol.

Study medications

Gaviscon Double Action Liquid (sodium alginate-bicarbonate) is an oral liquid suspension that belongs in the pharmacotherapeutic group A02BX (other drugs for peptic ulcer and gastro-oesophageal reflux disease). Its mode of action is local, not depending on absorption into the circulation. The medication is a combination of two antacids (calcium carbonate and sodium bicarbonate) and sodium alginate. Each 20 mL dose contains 1000 mg sodium alginate, 426 mg sodium bicarbonate and 650 mg calcium carbonate with an acid neutralising capacity of approximately 18.1 mmol/L. Antacid Supreme (CVS brand Antacid Liquid Supreme) is an oral liquid suspension that contains calcium carbonate 400 mg and magnesium hydroxide 135 mg in each 5 mL dose. Each 10 mL dose has acid neutralising capacity of approximately 25.2 mmol/L. The volumes used were 20 mL of Gaviscon Double Action Liquid and 7.5 mL of CVS antacid, each with ~18 mmol/L acid neutralising capacity.

High-resolution manometry

High-resolution manometry data were obtained using a solid-state assembly (4.2 mm outer diameter) with 36 circumferential sensors spaced at 1-cm intervals (Given Imaging, Duluth, GA, USA), the recording characteristics of which have been described previously.[11] Studies were

performed after at least a 6-h fast in a sitting position. Pressure transducers were calibrated at 0 and 300 mmHg using externally applied pressure prior to the study. Pressure topography data were analysed using Manoview analysis software (Given Imaging).

pH-impedance measurement

After manometric localisation of the lower oesophageal sphincter (LES), an intraluminal pH-impedance catheter [Sandhill Scientific, Highlands Ranch, CO, USA or Medical Measurement Systems (MMS), Enshede, the Netherlands] was positioned trans-nasally into the oesophagus such that the oesophageal pH sensor was 5 cm above the proximal margin of the LES. Intraluminal impedance was continuously measured from six impedance-recording segments; the middle of each impedance segment was located at 3, 5, 7, 9, 15 and 17 cm above the proximal border of the OGJ as previously determined by HRM. Impedance signals were recorded on a portable digital data logger (Sandhill Scientific or MMS).

Study protocol

The protocol consisted of two 3.5-h study sessions, at least 4 days apart. The GerdQ instrument was administered to assess symptom severity for the 7 days prior to each session during which time they were taking no acid-suppressive medications. The HRM and pH-impedance catheters were placed and recording begun. Participants then consumed a standardised meal consisting of a McDonald's double quarter pounder with cheese and small fries (970 kcal) within about 15 min. Five minutes after completion of the meal, one of the two medications was administered by syringe into the subject's mouth, the identity of which was blinded to the patient. The sequence of medication was allocated according to an on-line computerised randomisation site (www.randomizer.org). Post-prandial pH-impedance and HRM recordings continued for 180 min, during which the patients were asked to complete a modified GerdQ each 30 min. At the completion of the recording period, both catheters were removed and the subjects were discharged.

Data analysis

The primary outcome of the study was the time that the distal oesophageal pH was <4 in the 3-h post-prandial period. Secondary outcomes were number of reflux events, acid reflux events, proximal reflux events (15–17 cm proximal to the LES), nadir pH of the refluxate and post-prandial symptoms experienced. Manometric tracings were also analysed for the mechanism of reflux associated with each reflux event. Criteria used to define transient lower oesophageal sphincter relaxations (TLESRs) were adapted from those proposed by Roman *et al.* for pressure topography studies[12] consistent with the evolving recommendations of a multicenter expert panel focused on this topic. All studies were reviewed by two investigators (SR and AdR); discrepancies in interpretation were resolved by discussion inclusive of PJK. The investigators were unaware of the medication given.

Statistical analysis

Data were expressed as median and interquartile range (IQR) if nonparametric or mean ± S.E.M. if parametric. The Wilcoxon Rank Sum test and the Kruskal–Wallis test were used to compare differences in nonparametric metrics between groups. A paired *t*-test was used to compare parametric results. All *P*-values were two-tailed with the level of significance defined at 0.05. The study was IRB approved to enrol a maximum of 20 subjects based on the objective of detecting a 50% difference in acid exposure time between study conditions and experiencing a high number of anticipated dropouts owing to the rigours of the study.

RESULTS

Ten patients successfully completed both test sessions with good quality recordings. Two subjects completed only one session, declining to participate further, one subject's recording in one arm of the study was lost after 2 h of recording, and one subject's recordings were corrupted and unusable. Table 1 details the demographics and entry characteristics of the completed patients.

All patients had typical GERD symptoms, evident by all abnormal GerdQ scores prior to the first study day. Most of them (80%) were enrolled on the basis of having had the recent demonstration of low-grade (LA A or B) esophagitis on a recent endoscopy and the remaining 20% had pathological acid exposure on pH monitoring performed while not taking a PPI.

Post-prandial oesophageal acid exposure

Evident in Table 2, the primary outcome of the study, distal oesophageal acid exposure, was significantly less following Gaviscon compared to antacid.

Figure 1 illustrates the median, IQR, range and paired oesophageal acid exposure data for each study participant, showing reasonable consistency in the effect among study subjects. Figure 2 illustrates the mean nadir pH for each 30-min post-prandial study period. Evident in the figure, after the first 30-min period the nadir pH was

Table 1 | Demographics and clinical features of ten completed patients

Patient characteristic (n = 10)	Value
Age in years (s.d.); gender	48 (11.6) 5 male
Weight in kg (s.d.)	90.4 (15.4)
Number enrolled based on history of L A A esophagitis	4 (40%)
Number enrolled based on history of LA B esophagitis	4 (40%)
Number enrolled based on abnormal acid exposure on 48-h pH study	2 (20%)
Mean entry GerdQ score	9.5 (s.d. 1.2)

significantly greater in the Gaviscon studies and this effect persisted until 150 min post-prandially. Logically, the decreased oesophageal acid exposure observed during the Gaviscon studies was related to the decreased acidity of the refluxate during these periods.

Quantitative and qualitative characteristics of reflux events

Despite the decreased acidity of refluxate throughout most of the post-prandial period, the number of acid reflux events marginally failed to reach significance overall (Table 2). In all likelihood, this was related to small sample size. On the other hand, total reflux events (acid and weakly acidic) were quite similar between study conditions. Impedance data, also summarised in Table 2, show similar numbers of reflux events during Gaviscon and antacid studies. Similarly, there was no difference in the number of proximal reflux events (15–17 cm proximal to the LES). These observations were uniform throughout all 30-min periods of the study protocol suggesting no differences in either the propensity for reflux or the distribution of reflux in the oesophagus between study paradigms (Figure 3).

Table 2 | Post-prandial acid exposure and reflux data. Gaviscon Double Action Liquid vs. antacid.

	Gaviscon	Antacid	P
Distal acid exposure: median% (IQR)	0.7 (0–28.2)	8.0 (0–7.2)	0.001
Number of acid reflux events: mean ± S.E.M.	8.7 ± 3.0	12.4 ± 2.7	0.06
Total reflux events: mean ± S.E.M.	22.5 ± 4.9	25.1 ± 7.3	0.54
Proximal reflux events: mean ± S.E.M.	8.7 ± 4.4	6.4 ± 3.7	0.29

Mechanisms of reflux and reflux symptoms

When analysed by mechanism, most reflux events occurred by transient LES relaxation (Table 3) with no difference observed between study conditions.

Subjects reported relatively few reflux symptoms during the studies, again with no systematic differences between study conditions. It should, however, be noted that subjects were somewhat uncomfortable during the studies consequent of having two naso-oesophageal tubes in place, perhaps masking reflux-related symptoms.

DISCUSSION

This investigation compared the effectiveness of Gaviscon Double Action Liquid (alginate & antacid) to an equally potent antacid without alginate in controlling post-prandial acid reflux in GERD patients. Two 3-h post-prandial impedance pH recordings combined with HRM were done on each study participant in a double-blind crossover design. The major findings of the study were that Gaviscon was associated with significantly less distal oesophageal acid exposure than antacid and that this was related to a greater pH of the refluxate rather than to a decrease in the number of reflux events recorded in each study condition. The results suggest that the primary mechanism of efficacy for Gaviscon

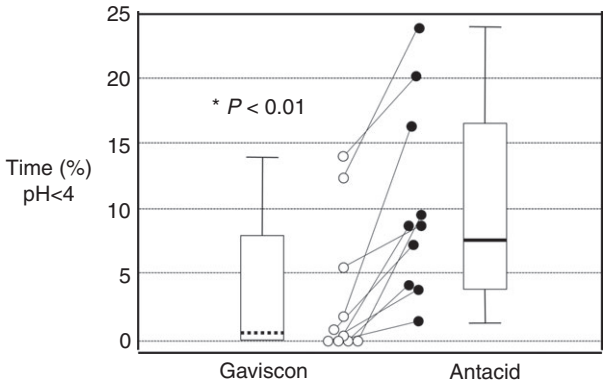

Figure 1 | Median, IQR, range (box plots) and paired (dots) acid exposure times for study subjects during Gaviscon Double Action Liquid (left, dashed line, white dots) and antacid (right, black line, black dots) studies. A consistent decrease was observed with Gaviscon compared to the antacid with corresponding significant decrease in the median (P < 0.01).

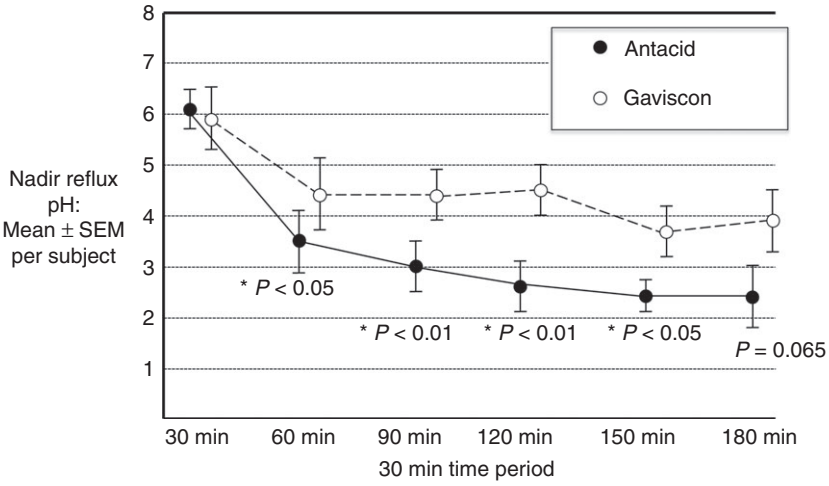

Figure 2 | Comparison of the mean nadir pH of refluxate during each 30-min post-prandial period during Gaviscon Double Action Liquid (white dots) and antacid (black dots) studies. After the first 30 min, the nadir pH of refluxate was significantly less acidic during the Gaviscon studies and this effect persisted until 150 min ($P < 0.05$, paired *t*-test).

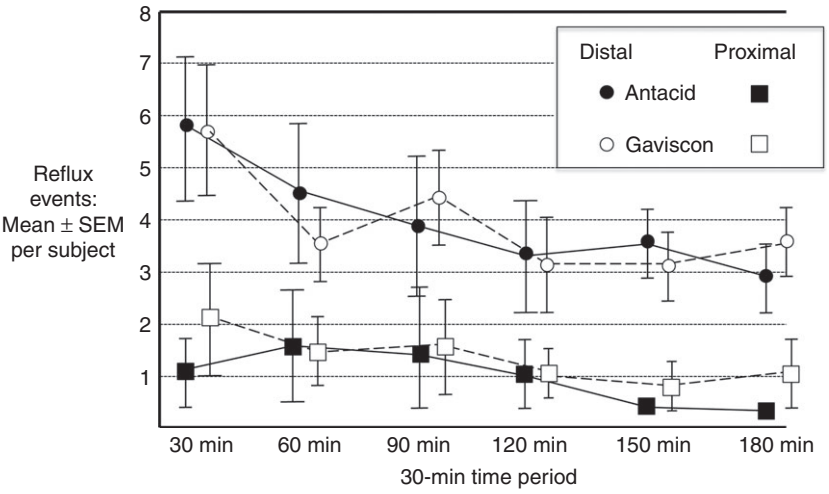

Figure 3 | Comparison of the number of reflux events (acid and weakly acidic) observed during the Gaviscon Double Action Liquid (distal events white dots and proximal events white squares) and antacid (distal events black dots and proximal events black square) studies. Similar numbers total and proximal events were observed throughout the duration of the recordings.

related to its demonstrated characteristic of localising with and displacing (or neutralising) the post-prandial acid pocket rather than serving as a mechanical barrier to reflux.

Although the acid pocket was described long ago,[13] its relevance to reflux disease is only now coming to light.[3] The initial observation was that the minimal pH of oesophageal reflux was lower than the concomitant pH recorded from within the stomach.[2] Ultimately, this paradox was resolved with the description of the acid pocket, the pool of newly secreted acid in the post-prandial period that layers on top of ingested chyme rather than mixing with it and serves as the reservoir for post-prandial acid reflux events within as little as 17 min of eating.[4] Subsequent observations were that ingested alginate co-localised with the acid pocket[10] and could displace or even neutralise it.[14] The current investigation adds to this with the demonstration that the effect of an alginate–antacid combination was above and beyond that of antacid after the first 30 min and persisted for at least 2.5 h after the meal. These observations support the persistence of the rafting effect of alginate also observed with 3D MRI imagery.[15]

An alternative mechanism of action proposed for alginates is of forming a barrier to reflux.[15–17] The hypothesis is that through molecular cross-linking, the polysaccharides form a cap over the gastric content and contains it within the stomach.[16] If this were the operant mechanism, one would anticipate a lesser number of

Table 3 | Mechanisms of reflux. No significant differences were seen between study paradigms. TLESR was the dominant mechanism with both medications. Data expressed as mean ± S.E.M.

Reflux mechanism	Gaviscon	Antacid	*P*
TLESR	10.9 ± 2.0	11.5 ± 1.2	0.6
Strain	8.8 ± 4.9	10.8 ± 7.8	0.3
Swallow	1.1 ± 0.5	1.6 ± 0.7	1.0
Hypotensive LES	1.7 ± 1.4	1.0 ± 0.6	0.6

reflux events in the Gaviscon condition than in the antacid condition. In this study, we observed only a trend in acidic reflux events number decrease likely due to the small sample size. One interesting finding of our study was a shift in the content of the refluxate to being less acidic suggesting that by displacing the acid pocket, it was now the alginate raft that was refluxing rather than gastric secretions. Comparing the Gaviscon to the antacid studies, no differences were seen in either the number of reflux events or in the number of reflux events that reached the proximal oesophagus. Furthermore, there was no difference in the mechanism of reflux, in each paradigm being dominated by transient LES relaxation. Nonetheless, there was substantially less oesophageal exposure on account of the increased pH of the refluxate during the Gaviscon studies.

Even though they had objectively less acid reflux, we observed no difference in the symptoms experienced by subjects during the Gaviscon studies. In fact, subjects reported relatively few symptoms with either treatment. This outcome is not surprising considering the complex instrumentation and multiple naso-oesophageal intubations. The experimental setup does not lend itself to detecting potentially subtle differences in reflux symptoms given the level of discomfort imposed by the experimental setup itself. A better experimental design to assess the impact of the medications on symptoms would be a simple crossover comparison done without any instrumentation with the outcome solely dependent on scoring a questionnaire such as the GerdQ. Such a study was recently conducted comparing Gaviscon Double Action Liquid to placebo finding substantial decrease in heartburn and regurgitation after Gaviscon administration.[18]

Limitations of this study include the immobility imposed on the study subjects by the experimental setup and, as already mentioned, the inherent discomfort of the instrumentation that probably negated our ability to analyse symptoms. Immobility potentially influences the outcome in that it makes it significantly less likely that reflux would occur by any mechanism other than transient LES relaxation and it may be that the alginate effect would be different with strain-induced or swallow-induced reflux.[19] Testing that hypothesis would, however, require an ambulatory manometry study, equipment that we do not have at our disposal.

In conclusion, we conducted a physiological study to compare the effectiveness of Gaviscon Double Action Liquid, an alginate-antacid combination, to antacid in controlling post-prandial acid reflux in a group of well-defined GERD patients. We found that Gaviscon decreased post-prandial acid exposure in the distal oesophagus and increased the nadir pH of the refluxate. The effect persisted for at least 2.5 h. Gaviscon did not, however, decrease the number of reflux events or the proximal extent of reflux within the oesophagus. These findings suggest that the dominant mechanism of action for the alginate-antacid combination is to displace and or neutralise the post-prandial acid pocket rather than mechanically constraining it. Nonetheless, the observations suggest a mechanism of action for the alginate-antacid combination uniquely suited to addressing post-prandial acid reflux.

AUTHORSHIP

Guarantor of the article: Peter J. Kahrilas, MD.

Author contributions: Peter J. Kahrilas coordinated drafting of the manuscript. A De Ruigh, S Roman and J Chen analyzed the data. All authors contributed to the writing, and provided critical revision. All authors approved the final version of the manuscript.

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