Duration of adhesion of swallowed alginates to distal oesophageal mucosa: implications for topical therapy of oesophageal diseases

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Summary

Background: We have previously shown, ex vivo, that alginate solutions can have a topical protective effect on oesophageal mucosal biopsies exposed to simulated gastric juice. Oesophageal mucosal impedance can measure the duration of mucosal adherence of ionic solutions since the impedance drops when the solution is present, and rises to baseline as the solution clears.

Aim: To investigate the in vivo duration of adhesion of swallowed alginate solution to distal oesophageal mucosa.

Methods: We studied 20 healthy volunteers and 10 patients with heartburn. A pH-impedance catheter was inserted, and baseline distal channel oesophageal impedance measured. Healthy volunteers received 10 mL of either sodium alginate (Gaviscon Advance), Gaviscon placebo (no alginate) or viscous slurry (saline mixed with sucralose), given in a randomised, single-blinded order over three visits. Patients received either sodium alginate or placebo on two visits. Initial impedance drop was measured, then 1-minute mean impedance was measured each minute until ≥75% recovery to baseline.

Results: In healthy volunteers, sodium alginate adhered to the oesophageal mucosa for longer than placebo or viscous slurry (10.4 [8.7] minutes vs 1.1 [1.6] vs 3.6 [4.0], P < 0.01). In patients, sodium alginate adhered to the oesophageal mucosa for longer than placebo (9.0 (5.4) vs 3.7 (4.1), P < 0.01).

Conclusions: Sodium alginate solution adhered to the oesophageal mucosa for significantly longer than placebo or viscous slurry. This demonstrates that alginates could confer a protective benefit due to mucoadhesion and can be a basis for further development of topical protectants and for topical drug delivery in oesophageal disease.
INTRODUCTION

The stratified squamous epithelium lining the luminal surface of the oesophagus has an essential role in protection from the passage of potentially noxious materials from the mouth to the stomach, and also from material refluxed from the stomach.

In normal circumstances, distal oesophageal mucosa is acidified due to gastro-oesophageal reflux up to approximately 4% of the time without any symptoms or injury. When reflux increases, the defensive barrier formed can be overcome. Typically, this results in heartburn as a symptom. In some cases, this is associated with macroscopic inflammation and erosion in the form of reflux oesophagitis. In the majority (perhaps 60%) there is no macroscopic injury (non-erosive reflux disease, or NERD). Despite macroscopic appearances, microscopic changes of inflammation are seen in NERD. Under electron microscopy, the oesophageal mucosa in patients with NERD can be seen to have dilated intercellular spaces (increase in the spaces between epithelial cells). These appear to be a morphological marker of impaired mucosal integrity, and are associated with greater permeability of the mucosa as measured by transepithelial epithelial resistance or intraluminal impedance. It is hypothesised that the increased permeability of the mucosa allows noxious material such as acid to permeate to afferent nerves within the mucosa, which are then stimulated to produce symptoms. In some cases (particularly in non-erosive reflux disease) these afferent nerves can be seen to lie very close to the luminal surface, and so are likely highly vulnerable to contact with noxious luminal contents.

Exposure to luminal contents is key to other oesophageal diseases, notably eosinophilic oesophagitis. Exposure to ingested food allergens (in the vast majority) results in eosinophilic infiltrate in the mucosa (and frequently deeper layers) in affected individuals, with dysphagia being the predominant symptom. Some investigators have suggested that acid reflux, and its subsequent impact on mucosal integrity, may play a role in eosinophilic oesophagitis pathogenesis.

The high prevalence of these oesophageal diseases, and the anatomical accessibility of the oesophagus, suggests that topical therapy would be desirable. Topical therapy in eosinophilic oesophagitis has already been successful. Swallowed dry powder inhalers, and a new budesonide orodispersible tablet have been used. Frequently, budesonide nebules have been mixed with thickeners (such as sucralose) to improve mucosal contact time. There remain a proportion of patients who inadequately respond to current treatment, and mucosal contact time of the drug may be a concern.

Topical therapy has been less commonly used in gastro-oesophageal reflux disease. Systemic therapy with anti-secretory therapy (proton pump inhibitors and histamine receptor 2 blockers) is the mainstay for all but mild disease. Patients have become increasingly concerned about potential long-term side effects of proton pump inhibitors. Furthermore, a significant proportion of patients with GORD have an unsatisfactory response to PPIs. Thus, there is a need for additional therapies, and topical treatments may have a future role.

AIM

To investigate the duration of adhesion of swallowed alginate solution to distal oesophageal mucosa in healthy subjects and patients with GORD.

METHODS

Twenty healthy volunteers and 10 patients with predominant heartburn symptoms were recruited between March and September 2019. Healthy volunteers were asymptomatic, scoring zero on the Reflux Disease Questionnaire (RDQ).

Patients were recruited after being referred to the upper GI physiology department of the Royal London Hospital for investigation of heartburn-predominant reflux symptoms. All had normal endoscopy.

Research Ethical Committee approval was obtained for conduct of the study (reference 15-LO-0935).

Study procedure

Healthy volunteers attended for three separate visits, all at least 24 hours apart. All were fasted for at least 6 hours prior to each visit. At visit 1, high resolution oesophageal manometry (Medtronic) was performed to exclude a major motility disorder and to locate the lower oesophageal sphincter. After removal of the manometry catheter, a pH-impedance catheter (OMOM, Jinshan Science and Technology) was inserted so that the most distal impedance segment was 3cm above
the lower oesophageal sphincter. Thirty minutes was allowed for the patient to equilibrate to the catheter and to establish a stable baseline impedance value. The volunteer was electronically randomised (www.randomizer.org) to swallow 10 mL (in one swallow) of test solution, either: (a) Viscous slurry (normal saline mixed with sucralose to the same viscosity as alginate solution), (b) Gaviscon placebo (liquid with same taste and consistency as Gaviscon Advance but without alginates, from Reckitt Benckiser) or (c) Sodium alginate solution (Gaviscon Advance; Reckitt Benckiser). Solutions were administered in a single-blinded fashion. After swallowing the solution subjects remained sitting for the duration of the study. They were asked not to eat and drink until the end of the measurement period, but normal swallowing of saliva was allowed. Impedance recording was continued for 1 hour, after which the catheter was removed, and the study visit was complete. Each of the test solutions were ingested once across the three visits.

Patients had two visits, receiving placebo and alginate in random order. On arrival to the department the high resolution manometry was completed, the pH-impedance catheter inserted and equilibrated, and test solution given and impedance recorded as described for healthy volunteers. After the hour measurement period the patient went home to complete the clinical 24-hour pH-impedance study according to our standard protocol. On return to the physiology unit, before removal of the catheter, the second test solution was given and measurements taken in the same manner. After the 1-hour measurement period the catheter was removed and the study complete.

3.2 | Measurements of impedance

All impedance measurements were made in the distal oesophagus 3 cm above LOS using proprietary software (AlphaLab, Jinshan Science and Technology). Baseline impedance was measured as mean impedance measurement of at least 10 minutes stable impedance during the 30 minutes equilibration period. The electronic ruler tool was used to measure impedance during the equilibration period, excluding swallows, reflux events and belches. Mean impedance of the measured segments was calculated.

After the test solution was swallowed, the impedance dropped, and 1-minute mean impedance was measured each minute. Clearance of the solution was considered when the impedance had recovered to ≥75% of baseline for two consecutive minutes (clearance time determined as the first of these minutes). Figure 1 illustrates the impedance analysis method, and Figure 2 is an example impedance tracing from the study. Analysis was performed (by PW) blinded to the nature of the test solution, with unblinding only occurring after the completion of analysis.

3.3 | Statistical analysis

Data are presented as mean (standard deviation). Comparison of baseline impedance between healthy volunteers and patients was made by unpaired t-test. Multiple comparisons are made using one-way ANOVA and Tukey’s multiple comparison test.

We used our previous ex vivo experiments to calculate sample size. These studies suggested that topical protection may occur 17% more effectively in alginate compared to control, and alginate appeared to adhere for at least 30 minutes ex vivo. We calculated that a sample size of 22 would be able to detect such a difference in vivo at a significance level of 0.05 and power of 0.8.

4 | RESULTS

4.1 | Healthy volunteers

Twenty healthy volunteers were aged range 25-63, mean age 42, 10 female.

![Figure 1](image_url)  
**Figure 1** Method of impedance analysis. Baseline impedance in the distal oesophageal channel is shown. After ingestion of the test solution there is an immediate fall in impedance. As the solution is cleared the impedance increases back towards baseline, and clearance was calculated as a 75% impedance recovery to baseline.
Baseline impedance during the 30 minutes equilibration period (for all visits) in healthy volunteers was 1820 (718) Ohms.

In healthy volunteers, the duration of adhesion for viscous slurry was 3.6 (4.0) minutes, for placebo 1.1 (1.6) minutes, and for alginate 10.5 (8.7) minutes (P < 0.01 for comparisons of placebo and viscous slurry with alginate, NS for placebo vs viscous slurry).

4.2 | Patients

Ten patients were aged range 32-62, mean age 46. 6 female.

Mean oesophageal acid exposure for patients was 9.6% (6.7). No patients had physiological acid exposure and positive symptom association. On manometry, four patients had normal motility, three patients had ineffective oesophageal motility, one patient had oesophagogastric junction obstruction, and one patient had hypercontractile oesophagus.

Baseline impedance in patients was significantly lower than in healthy volunteers at 1445 (579) Ohms (P = 0.03).

Mean nocturnal oesophageal baseline impedance calculated for patients 1361 (689) Ohms correlated excellently with the baseline impedance taken during the equilibration period prior to test solution ingestion 1445 (579) Ohms (r = 0.87, P = 0.001).

In patients the duration of adhesion for placebo was 3.7 (4.1) mins, and for alginate 9.0 (5.4) mins (P < 0.01).

Clearance of alginate in patients with normal motility was significantly faster compared to in patients with abnormal motility (duration of adhesion 5.2 [4.0] minutes vs 12.8 [3.6] minutes, P = 0.01) (Figure 3).

FIGURE 2  Example impedance tracing during alginate ingestion. Baseline impedance is measured, and ingestion of the alginate is marked on the tracing as a dashed line. Impedance falls, then gradually increases back towards baseline. Measurements were taken from the distal-most impedance tracing.

FIGURE 3  Duration of alginate adhesion in patients with normal motility and with abnormal motility (ineffective oesophageal motility = 3, OGJ obstruction = 1, hypercontractile oesophagus = 1). Duration of adhesion can be seen to be prolonged in the presence of abnormal oesophageal motility.
apy allows treatment with minimal systemic absorption. This results in reduction of systemic side effects of therapy and often increases patient satisfaction and tolerance. The second benefit is that a topical protectant can defend against all components of the refluxate. Anti-secretory therapies reduce gastric acid secretion but do not stop reflux occurring. Other components of the refluxate such as pepsin and bile acids may also play a significant role in symptoms and mucosal injury, and protection against all components may have additional therapeutic benefit. There are some limited previous data for topically applied therapy in reflux disease. Sucralfate is believed to bind to the oesophageal mucosa, particularly in ulcerated areas. It has been found to have equivalent heartburn resolution and oesophagitis healing to H₂RAs in two studies. More recently, a hyaluronic acid-chondroitin sulphate based bioadhesive formulation has been shown to have some benefit in PPI-refractory reflux disease. The mode of action of this may be via topical protection, although this has yet to be tested in vivo.

Previous data on mucosal adhesion for alginites are limited. Alginites are natural polysaccharide polymers isolated from brown seaweed. Chemically they are co-polymers of L-guluronic and D-mannuronic acid residues connected by 1:4 glycosidic linkages. In an acidic environment alginic salts and alginic acids precipitate within minutes to form a viscous gel and may have advantageous mechanical and adhesive properties over simple antacids. In addition to their mechanical properties at the gastro-oesophageal junction and on the acid pocket, alginites have been found to demonstrate bioadhesive potential, a property determined primarily by polymer chain length and the presence of ionisable groups rather than, for example, the viscosity of the gel used. Furthermore, they appear to become adhesive on hydration (as occurs in the gastrointestinal tract). In vitro porcine investigation of oesophageal mucosal retention has suggested a potential for alginate-mucosal adhesion. We have previously demonstrated human data in vitro and ex vivo that has suggested some adhesion may occur, but thus far in vivo human data were not available.

The duration of adhesion seen from alginate solution in our study, while being significantly longer than viscous slurry or placebo, is still short. Most gastro-oesophageal reflux occurs in the post-prandial period, so the addition of a short mucosal topical protection effect to the raft-formation properties of alginate solution in the tested form may contribute to its clinical efficacy in mild reflux disease, but is likely to be of lesser value in moderate to severe reflux. This is reflected by the limited clinical effect that alginites in their current form have in more severe GORD. Manipulation of the composition of alginites has potential to increase the adhesion time to more clinically significant durations.

An interesting finding in our study was that patients with abnormal oesophageal motility had a longer duration of adhesion than patients with normal motility. Abnormal motility, particularly ineffective oesophageal motility, is more common in GORD, suggesting that adhesion may be more somewhat prolonged in many patients compared to healthy volunteers. Another factor that may be clinically beneficial for alginites as topical protectants or as drug delivery vehicles is that the alginate solution, itself, may be refluxed back

4.3 Combined analysis

There were no significant differences in duration adhesion per-solution between healthy volunteers or patients.

When healthy volunteers and patients were taken together, the duration of adhesion for viscous slurry was 3.6 (4.0) minutes, for placebo 1.9 (2.9) minutes, and for alginate 10.0 (7.7) minutes (P < 0.001 for comparisons of placebo and viscous slurry with alginate, NS for placebo vs viscous slurry, Figure 4).

5 DISCUSSION

If alginate solutions can be shown to demonstrate a significant mucosal adherence in vivo, it could provide a basis for their further development as a topical protectant for GORD, and as a drug delivery medium for diseases such as eosinophilic oesophagitis.

Using a mucosal impedance technique, we evaluated the duration of mucosal adhesion for three solutions: a viscous slurry (similar to that used in treatment of eosinophilic oesophagitis), a Gaviscon placebo, and an alginate solution (Gaviscon Advance).

We found that, in both healthy volunteers and patients, alginate solution appeared to adhere for significantly longer than viscous slurry or placebo. We decided to test both patients and healthy volunteers as we were uncertain if microscopic changes in epithelial integrity seen in non-erosive reflux disease would have an impact on adhesion. However, no differences were seen in adhesion for any solution between our patient and healthy volunteer groups. The availability of an oesophageal topical protectant in the treatment of GORD is desirable. A significant minority of patients have inadequate response to PPI therapy, and patients are increasingly wary about taking them as a long-term systemic treatment. Topical treatment has two main potential benefits. The first is that topical therapy allows treatment with minimal systemic absorption. This results in reduction of systemic side effects of therapy and often increases patient satisfaction and tolerance. The second benefit is that a topical protectant can defend against all components of the refluxate. Anti-secretory therapies reduce gastric acid secretion but do not stop reflux occurring. Other components of the refluxate such as pepsin and bile acids may also play a significant role in symptoms and mucosal injury, and protection against all components may have additional therapeutic benefit. There are some limited previous data for topically applied therapy in reflux disease. Sucralfate is believed to bind to the oesophageal mucosa, particularly in ulcerated areas. It has been found to have equivalent heartburn resolution and oesophagitis healing to H₂RAs in two studies. More recently, a hyaluronic acid-chondroitin sulphate based bioadhesive formulation has been shown to have some benefit in PPI-refractory reflux disease. The mode of action of this may be via topical protection, although this has yet to be tested in vivo.

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into the oesophagus from the stomach. Alginate solutions displace the post-prandial acid pocket and can therefore substitute it as the reflux component in the post-prandial period, theoretically offering further periods of topical oesophageal coating.

The other therapeutic benefit of mucosal adhesion could be for drug delivery. In eosinophilic oesophagitis this has been shown to be an important therapeutic route for the oesophagus. Here, steroids are delivered to the mucosa with improvement of symptoms and histology. There remains, however, a proportion of patients in all studies who do not respond adequately to topical steroids in their current form. Symptoms also are less reliably improved than histological epithelial markers perhaps, in some cases, due to submucosal inflammation continuing. Increasing the mucosal contact time to the drugs may improve clinical response. Our study shows that the mucosal contact time for a viscous slurry made using sucralose may be limited, and that the contact time for the alginate solution was significant longer. This is in keeping with our previous ex vivo experiments which showed that simply increasing viscosity of the solution had only a small impact on mucosal protection. Topical drug delivery in GORD may also be an exciting route to explore. We know that acid sensitive receptors such as transient receptor villanoid type 1 (TRPV1) are present in the oesophageal mucosa and may be candidate nociceptive drug targets. Trials of systemic TRPV1 antagonist failed, but a possible reason for this is inability to deliver the drug to the mucosa at high enough concentration without systemic side effects, a problem topical therapy may circumvent. Given the superficial location of the nerves seen in NERD, other targets may also present themselves for topical therapy and this is an area of ongoing study for groups including our own.

Our study has limitations. The use of mucosal impedance is only a surrogate for mucosal adhesion, and may not fully reflect the duration of adhesion. However, impedance is sensitive to very subtle changes in the conductivity, and our previous in vitro studies suggest a lasting adhesion measurable by conductivity methods. The decision to consider clearance the solutions to have occurred when impedance had returned to 75% of baseline was fairly arbitrary. It does leave the possibility that protection would last longer than our measured duration if a small film of solution remains, but we believe our method mitigated impedance fluctuations that may have confounded the results. The duration of adhesion may be influenced by a number of mucosal factors, including inflammation. We had only a limited number of patients in our study, and there was no signal to suggest asymptomatic patients have a different duration of adhesion than healthy volunteers. We did not include patients with erosive disease or Barrett’s oesophagus. Clearance mechanisms are various and include swallowed saliva, number of swallows and oesophageal motility. The mechanisms of clearance were not extensively evaluated in this study. We did see, in a small sample of patients, that abnormal motility appeared to be a significant factor in clearance. Finally, each volunteer acted as their own control so intrindividual variability between different ingested solutions would be expected to be limited, but it is conceivable that saliva production, for example, could be influenced by the nature of the solution being ingested.

In summary, using in vivo oesophageal impedance techniques, alginate solution is shown to have a significantly longer-lasting oesophageal mucosal adhesion than non-alginate placebo and viscous slurry. These data have current potential for increasing topical drug exposure time in oesophageal diseases such as eosinophilic oesophagitis. Further manipulation of these alginate compounds could lead to exciting potential use as topical protectants in GORD.

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AUTHORSHIP
Guarantor of the article: Dr Philip Woodland.

Author contributions: SS performed the experiments, results analysis, and was involved in drafting the manuscript. CC was involved in concept and design of the study. DS was involved in study design and review of the manuscript. PW was involved in study concept and design, analysis and interpretation of results, and writing of manuscript. PW has served as a consultant and advisory board member for Dr Falk Pharma UK and Reckitt Benckiser UK. DS receives research grants from Reckitt Benckiser UK, Jinshan Technology China and Alfa Sigma, Italy.

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