

The Role for Liquid Alginate Suspension (Gaviscon Advance®) in the Protection of the Oesophagus Against Damage by Bile in the Refluxate

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INTRODUCTION

Bile acids are commonly found in the gastro-oesophageal refluxate and are implicated in the aetiology of oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma.¹ Cholic acid (CA), taurocholic acid (TCA), glycocholic acid (GCA) and deoxycholic acid (DCA) are the predominant bile acids found in oesophageal aspirates.^{2,3} In particular, TCA and DCA are noted to be the most damaging bile acids to the oesophageal mucosa.¹ The ability of each bile acid to cause cellular damage is linked to pH and at normal gastric pH (1-2) most bile acids are precipitated irreversibly out of solution. Postprandially, or with acid suppression, when gastric pH is greater than pH 4 then the potential for bile acids to enter the cells and cause damage is increased.^{4,6} The alginate-containing raft-forming oral suspension Gaviscon Advance (GA) contains 10% sodium alginate and acts as a barrier to reflux by preventing its entry into the oesophagus.⁷ The active component, alginate, has been shown to have beneficial effects on bile acid-induced molecular changes to oesophageal cell lines.⁸

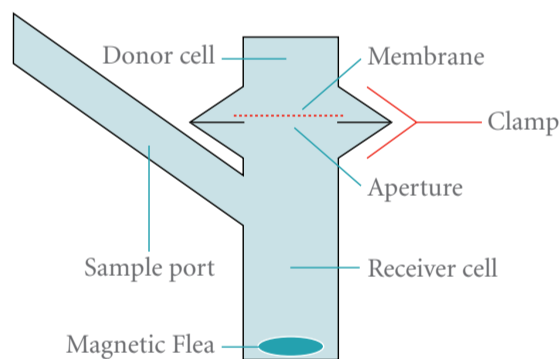
AIMS

The aim of this study was to investigate if an alginate raft-forming suspension (Gaviscon Advance) can be beneficial in preventing exposure of the oesophageal mucosa to bile acids.

METHODS

Gaviscon Advance (GA) (Reckitt Benckiser Healthcare (UK) Ltd), contains 10% sodium alginate and forms a buoyant, aerated raft on contact with gastric acid. *In vitro* diffusion of 1mM of bile acid solutions across an artificial membrane was measured using a horizontal Franz cell model (fig 1). The Franz cell apparatus has an approximately 5.0ml capacity receiver cell (filled with HCl of specified pH) and 1.5ml capacity donor cell with the provision to place a membrane (Whatman grade 4 filter paper) between the two phases when clamped together. The diameter of the aperture was 9mm giving an area for diffusion of 63.6mm². All experiments were maintained at 37°C with continual stirring. Detection of bile acids was by continual UV spectrometry of the receiver cell at 203nm with output onto a chart recorder.

Figure 1. Schematic diagram of the Franz cell model used to assess diffusion of bile acids.



The bile acids were all at 1mM concentration (a physiologically relevant concentration to that seen *in vivo*) in HCl at the specified pH and 0.5 ml was accurately added to the donor cell:

- Taurocholic acid (TCA) at pH 2 and pH 5
- Cholic acid (CA) at pH 5
- Glycocholic acid (GCA) at pH 5
- Deoxycholic acid (DCA) at pH 6

Diffusion of bile acids into the receiver cell was assessed over 30 minutes. A 0.1ml dose of GA (1.6mm layer) was added to the membrane and diffusion of bile acid measured. The percentage reduction in diffusion after 30 minutes was calculated.

RESULTS

The diffusion of 0.5ml of 1mM of each bile acid in HCl at the specified pH was assessed to provide the rate of diffusion without anything to influence it. Figure 2 shows the rate of appearance of TCA (pH 2) in the receiver cell over 30 minutes. Figure 3 demonstrates the large background generated from the release of material from GA into the receiver cell. Interestingly, more interference is observed from GA at pH 5 and 6 than at pH 2. The amount of interference at 203 nm by GA is 4 times greater than the actual bile acid signal (TCA pH 2).

Figure 2. Appearance of TCA across an artificial membrane into the receiver cell containing pH 2 HCl. Data are mean (SD) of n=8.

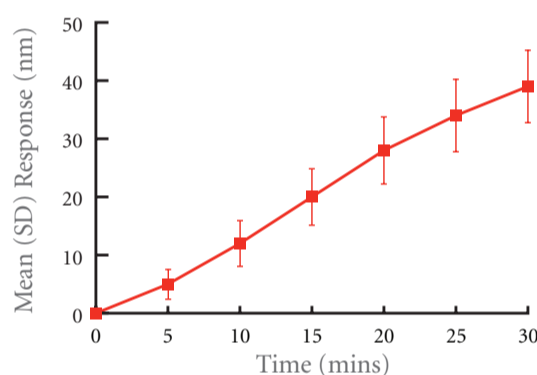
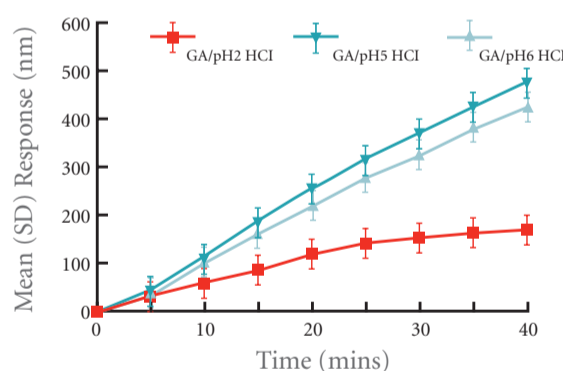


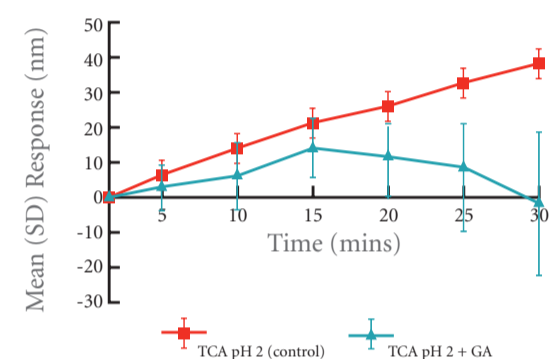
Figure 3. Influence of 0.1ml GA on the response at 203 nm in the receiver cell across an artificial membrane. Data are mean (SD) of n=3-6



It was necessary to subtract the mean background due to GA from all experimental data obtained for bile acid + GA. Figure 4 shows the rate of appearance of bile acid into the receiver cell in the presence of 0.1ml GA upon the artificial membrane using TCA pH 2 as the example. Table 1 gives the percent reduction in diffusion for each bile acid condition tested.

Figure 4.

Appearance of TCA across an artificial membrane in the presence of 0.1ml GA into the receiver cell containing pH 2 HCl. Data are mean (SD) of n=5 (n=8 for control). Owing to the high response due to GA alone (fig 3) the data in the presence of GA have high variability.



On average, 100% of the TCA in the refluxate is prevented from reaching the 'oesophageal cellular compartment' in this *in vitro* model.

Table 1.

Percent reduction in bile acid diffusion after 30 minutes in the presence of 0.1 ml GA for the five bile acid conditions evaluated in the Franz cell model.

Condition	Mean % reduction in diffusion	n=
TCA pH 2	100%	5
TCA pH 5	100%	3
GCA pH 5	94%	3
CA pH 5	100%	3
DCA pH 6	83%	4

CONCLUSION

- Gaviscon Advance has the ability to reduce the diffusion of a range of bile acids, common in the gastric refluxate, from crossing an artificial membrane and into the cellular compartment in an *in vitro* model.
- The effect is seen with a range of bile acids and at a range of pHs.
- *In vivo*, the mode of action of Gaviscon Advance is expected to give oesophageal protection from the damaging potential of bile acids.
- With regard to a wider clinical benefit, Gaviscon Advance, a non-systemic reflux treatment, is much more than a physical barrier to reflux.

References

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