

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

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INTRODUCTION

The gastric enzyme pepsin is a major component in the refluxate and is responsible for much of the erosive damage seen in the oesophagus. A reduction in the amount of pepsin that reaches the oesophageal mucosa may be a beneficial treatment for patients with reflux disease.

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.¹ The active component, alginate, has been shown to have multiple bioactive properties that could be of benefit in reflux disease.²

AIMS

Here we investigate whether GA can have an action to prevent pepsin reaching the oesophagus and to reduce the enzyme's activity *in vitro*.

METHODS

Gaviscon Advance (GA) (Reckitt Benckiser Healthcare (UK) Ltd), contains 10% sodium alginate and forms a buoyant, aerated raft on contact with gastric acid. A standard 10ml dose of GA was added to simulated gastric refluxate (SGR) containing 0.1M HCl and 1mg/ml porcine pepsin at 37°C. Pepsin protein in the SGR was measured by absorbance at 280nm.

To mimic a reflux event a volume of SGR was forced through a GA raft and the amount of pepsin retrieved measured by absorbance at 280nm after accounting for the contents of the raft that solubilised in the filtrate.

Dilute solutions of GA were tested for the ability to reduce proteolytic activity of porcine pepsin using a sensitive colorimetric N-terminal assay.³

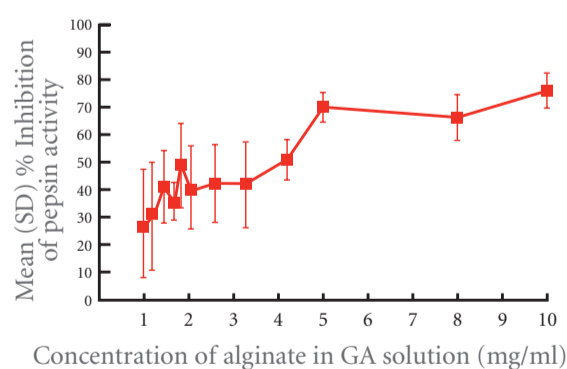
RESULTS – Pepsin inhibition by Gaviscon Advance

GA was shown to inhibit pepsin activity (fig 1). GA was tested at dilution of 1:10 (equivalent to a 10ml dose in 100ml gastric volume or 10mg/ml alginate) to 1:100 (equivalent to a 10ml dose in 1 litre gastric volume or 1mg/ml alginate).

A mean (SD) of 78(8)% of pepsin activity was inhibited at a dilution of 10mg/ml and there was a dose-dependent decrease in pepsin inhibition but even at 1mg/ml there was 28% inhibition of pepsin. Pepstatin was used as a positive control and inhibited all pepsin activity.

Figure 1.

Percent inhibition of pepsin proteolytic activity by aqueous solutions of GA. Data are mean (SD) of n=9-18. The x-axis is expressed as concentration of alginate in the GA solution. A 10ml dose of GA contains 1000mg alginate as the active ingredient, which is equivalent to 100mg/ml.



RESULTS

Entrapment of pepsin by Gaviscon Advance

GA (10ml dose) was able to entrap pepsin from the SGR into the forming buoyant raft. From 150ml of SGR a mean (SD) of 67(13)% of the pepsin was trapped by the GA raft (n=24).

The amount of pepsin removed was related to the dose of GA added (2-10ml). Table 1 shows the effect of varying the dose of GA added to SGR. The greater the dose the more pepsin is removed from the SGR. This is related to the amount of SGR surface that is covered by the GA dose.

With a standard 10ml dose of GA in 50ml SGR all pepsin was entrapped into the forming raft, regardless of the concentration of pepsin tested (Table 2). Pepsin was not released from the raft over the course of 4 hours. Newly secreted pepsin will remain in the stomach below the GA raft, where it is essential for the digestive process.

Table 1.

Proportion of pepsin removed by varying doses of GA added to SGR. n=3.

Condition	Mean	SD	% coverage
10ml GA	65%	4%	90%
8ml GA	52%	7%	80%
6ml GA	45%	7%	70%
4ml GA	46%	14%	50%
2ml GA	30%	11%	25%

Table 2.

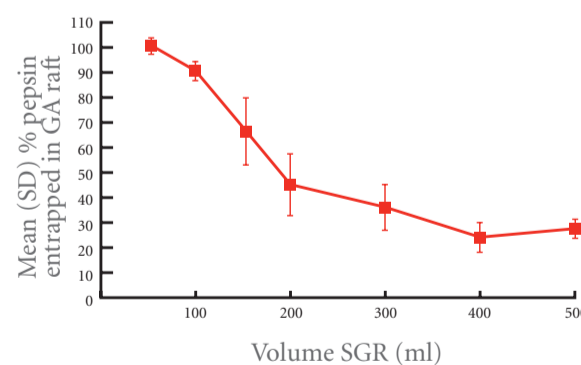
Proportion of pepsin removed from 150ml SGR by a 10ml dose of GA with varying concentrations of pepsin. n=3.

Condition	Mean	SD
1 mg/ml pepsin	96%	27%
5mg/ml pepsin	100%	7%
10mg/ml pepsin	98%	1%
20mg/ml pepsin	95%	2%

If the volume of the SGR was varied to approach that of a fed stomach (500ml) the amount of pepsin removed by a standard 10ml dose of GA was reduced, with 24% of pepsin in 500ml SGR being bound up in the raft as it forms (fig 2).

Figure 2.

Proportion of pepsin entrapped into a forming GA raft as a function of volume of simulated gastric refluxate (SGR). A 10ml dose of GA was added to SGR at 37°C and pepsin measured after 30 minutes. Data are mean (SD) of n=3.



RESULTS – Reflux simulation

An *in vitro* model of reflux events was established and GA rafts were able to remove all of the pepsin in a 5ml reflux event. The amount of pepsin removed from the simulated gastric reflux event was proportional to the volume of refluxate with 40% pepsin removed from a 50ml reflux event (fig 3).

Since patients who suffer reflux have multiple reflux episodes the ability of a single GA raft to accommodate pepsin from multiple reflux events was investigated. A single GA raft continued to be able to remove pepsin from repeated 5ml reflux events and after 10 reflux events, 56% of pepsin could still be entrapped (fig 4).

Figure 3.

The proportion of pepsin removed from a reflux event of varying volume by a preformed GA raft. Data are mean (SD) of n=3.

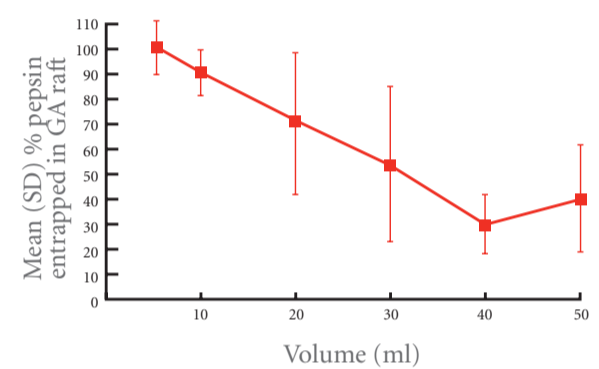
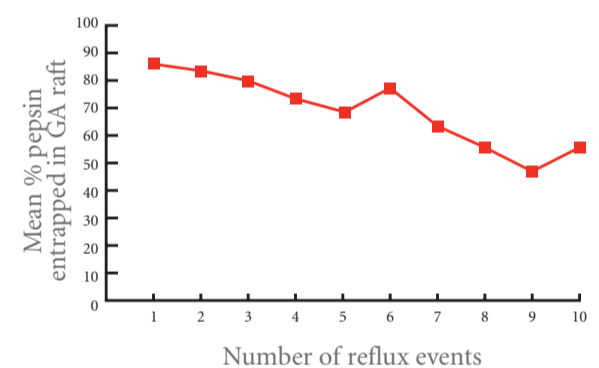


Figure 4.

The proportion of pepsin removed from successive 5ml reflux events by a preformed GA raft. Data are mean (SD) of n=3.



CONCLUSION

- Gaviscon Advance has the ability to inhibit the activity of pepsin, the broad acting gastric protease.
- Gaviscon Advance has the ability to entrap pepsin into the alginate raft structure that is formed on contact with the acidic stomach contents.
- Gaviscon Advance can remove pepsin from reflux events and has capacity to accommodate repeated reflux events.
- Gaviscon Advance can protect the oesophagus from the damaging potential of pepsin by preventing entry into the oesophagus and reducing the digestive potential of any pepsin that does reach the squamous mucosa.
- With regard to the wider clinical benefit, Gaviscon Advance, the non-systemic reflux treatment, is much more than a physical barrier to reflux.

References

1. Hampson et al. *Int J Pharm* 2005;294:137
2. Strugala et al. *Int J Pharm* 2005;304:40
3. Hutton et al. *Biochem Soc Trans* 1986;14:735