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Gastric distribution and residence time of two anti-reflux formulations

N. Washington [1], C. Washington [2] and C.G. Wilson [1]

[1] *Department of Physiology and Pharmacology, Queen's Medical Centre, Nottingham (U.K.)* and [2] *Department of Pharmacy, University of Nottingham, Nottingham (U.K.)*

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Summary

Two proprietary anti-reflux formulations "Liquid Gaviscon" and "Algicon Suspension" were characterized in vitro prior to an in vivo comparison in man. The raft strengths, pH profiles, time for raft formation and thickness of raft were measured over the normal gastric pH range. Ten ml of "Algicon" did not produce a raft in 125 ml hydrochloric acid below a concentration of 0.05 M. "Algicon" formed a weaker, thinner raft than "Gaviscon" in the in vitro tests, but there was no difference in speed of raft formation. "Gaviscon" produced a stronger raft than "Algicon" in the acid concentrations between 0.03 to 0.1 M hydrochloric acid. The standard Rossett and Rice test does not allow raft formation and partly releases antacid into the reaction mixture; "Algicon" (10 ml) maintained the pH above 3 for 23 min, but "Gaviscon" (10 ml) only raised the pH for 7 min. "Algicon" did not form a raft under the conditions of the experiment as described by Washington and coworkers (1986a) to measure the pH in and below the alginate raft. The gastric distribution and emptying were followed in 6 healthy female volunteers using gamma scintigraphy. Ten ml "Algicon" administered 30 min after a scrambled egg meal mixed and emptied with the meal, whereas the "Gaviscon" was found to empty significantly more slowly than the "Algicon" or food. Alginate and antacid therapy appear to be mutually incompatible in a single dose formulation.

Introduction

"Algicon Suspension" (Rorer Health Care, U.K.) is a new alginate-containing anti-reflux agent. It differs from the well-established anti-reflux agent "Liquid Gaviscon" (Reckitt and Colman, U.K.) because it contains antacid materials in addition to the bicarbonate required to elevate the raft. Previous in vitro studies conducted in our laboratories have indicated that the inclusion of antacid materials into "Liquid Gaviscon" decreases the raft strength, but increases the time at which the raft pH remains above 3 (Washington et al., 1986a).

"Liquid Gaviscon" and "Algicon Suspension" were tested over the physiological range of pH for raft strength, time for raft formation and thickness of the raft in vitro. The formulations were compared in vivo using the technique of γ-scintigraphy for distribution within the stomach and gastric residence time.

Correspondence: N. Washington, Department of Physiology and Pharmacology, Queen's Medical Centre, Nottingham NG7 2UH, U.K.

Materials and Methods

Materials

In vitro studies

"Liquid Gaviscon" (Reckitt and Colman, U.K., batch number EO6544).

"Algicon Suspension" (Rorer Pharmaceuticals, U.K., batch number 001L).

In vivo studies

Test meal:

Two eggs (60 g) labelled with 3 MBq technetium-99m [^{99m}Tc] sulphur colloid.

30 ml milk

25 g butter

2 slices toast

200 ml unsweetened orange juice.

(total calorific value of 1693 kJ.)

10 ml "Liquid Gaviscon" (Reckitt and Colman: batch number FO8547) labelled with 2 MBq indium-113 m alginate [^{113m}In]. .

10 ml "Algicon Suspension" (Rorer, U.K., batch number 001L) labelled with 2 MBq indium-113m alginate [^{113m}In].

The scrambled eggs were labelled by addition of the [^{99m}Tc] sulphur colloid to the ingredients before cooking. The integrity of this method of labelling had previously been evaluated by incubating the labelled scrambled eggs with simulated gastric juice (U.S.P. formulation) at 37 °C and monitoring the rate of release of the label into the liquid phase. It was found that the release of the label into the liquid phase correlated with the digestion of the egg by pepsin. The radiolabelled test meal has been used previously by Feldman and coworkers (1984) to measure gastric emptying. 4 MBq in 0.1 ml of [^{113m}In] chloride solution in 0.04 M HCl was mixed with 25 mg of sodium alginate powder and this was stirred until a uniform gel of alginic acid formed. This was added to 10 ml of either "Liquid Gaviscon" or "Algicon Suspension" and mixed thoroughly by stirring. The activity was calculated to provide 2 MBq per subject at the time of administration.

The suitability of the label for "Liquid Gaviscon" is well established (May et al., 1984; Bennett et al., 1984), and the effectiveness of this method of labelling "Algicon Suspension" was tested in vitro prior to the study. 10 ml of the radiolabelled preparation was added to 125 ml simulated gastric juice (USP formula) and this was incubated for 1 h at 37 °C. The distribution of label between the alginate and liquid phase was measured. More than 80% of the label was found to be associated with the alginate phase.

Methods

(a) Neutralization properties

Neutralization profiles for the "Algicon Suspension" and "Liquid Gaviscon" were measured using both the technique described by Rossett and Rice (1954), and the modification to the test described by Washington and coworkers (1985) which allowed the pH measurements to be obtained in both the raft and bulk phases. When the pH was measured in the raft, the rate of acid addition was reduced from 4 to 2 ml/min to improve correlation with in vivo data (Washington et al., 1985).

(b) Raft strength

The raft strengths were measured over an acid range of 0.03–0.15 M. The strength of a raft was measured using the following procedure: 125 ml of hydrochloric acid in a 250 ml beaker was warmed to 37.5 ± 1 °C, 5 ml of antacid was added, and the mixture was gently stirred. The wire probe was then inserted into the mixture before the raft had formed. The mixture was returned to the water bath for 10 min to allow the raft to form completely. The raft strengths were then measured as previously described (Washington et al., 1986a). The results were corrected for the force required to lift the probe through the same distance in water.

(c) Raft thickness and time for raft formation

The time required for all the alginate material to rise to the top half of a 250 ml beaker, containing 125 ml HCl at 37 °C was measured. The beaker was then placed in a water bath to maintain the temperature and 20 min later the thickness of the raft produced was measured at 4 places and the results averaged.

(d) In vivo study

Six healthy female volunteers were fasted overnight and on the morning of the trial given the radiolabelled scrambled egg breakfast. Thirty minutes later the subjects were either given 10 ml of radiolabelled "Liquid Gaviscon", or 10 ml of radiolabelled "Algicon Suspension". The allocation to the treatment group was randomised and a cross-over study was performed one week later.

The γ-camera (GEC Maxicamera II) was fitted with a medium energy (140 keV maximum energy) parallel hole collimator. Anterior and posterior images of 30 s duration were recorded at 15 min intervals until the stomach was empty. The ^{99m}Tc and ^{113m}In images were recorded simultaneously, but stored separately on the camera for subsequent analysis.

Each image was analysed by creating two regions of interest, one around the whole stomach and the second to assess background activity. An additional region of interest was created around the upper half of the stomach. The count rates from the regions of interest were corrected for background and decay. The ^{99m}Tc count rates were also corrected for ^{113m}In overlap into the technetium channel. The geometric mean of the activity in the regions of interest in the anterior and posterior images was calculated to correct for attenuation (Hardy and Perkins, 1985).

Results

"Liquid Gaviscon" produced only a short total neutralization time in the unmodified Rossett and Rice test which destroyed the raft. The pH rapidly reaching a peak of 4.6, and falling below pH 3 within 7 min (Fig. 1. This agrees with previously published data by our group (Washington et al., 1985). The neutralization profile obtained for "Algicon Suspension" is also shown in Fig. 1. The formulation maintained the pH above 3 for 23 min and attained a peak pH of 6.1.

The modified test confirmed that "Liquid Gaviscon" did not produce any detectable neutralization below the raft. The raft, however, maintained a pH elevated to above 3 for 60 min, which also agreed with previously published results (Washington et al., 1985). "Algicon Suspension" did not form a raft under the conditions used in the modified Rossett and Rice test, hence the pH in and below the raft could not be measured.

The raft strengths for "Liquid Gaviscon" and

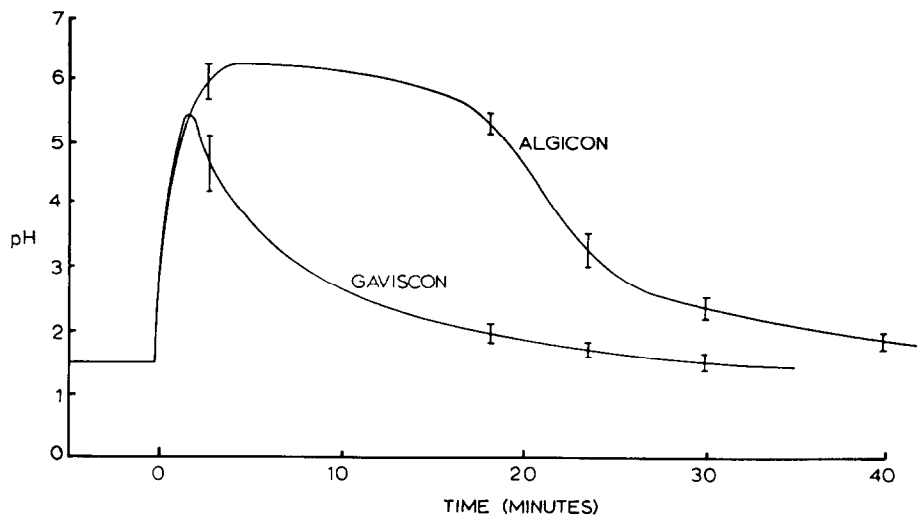

Fig. 1. Neutralization profiles for 10 ml "Liquid Gaviscon" and "Algicon Suspension" in the standard Rossett and Rice test ($n = 5$, mean ± S.D.).

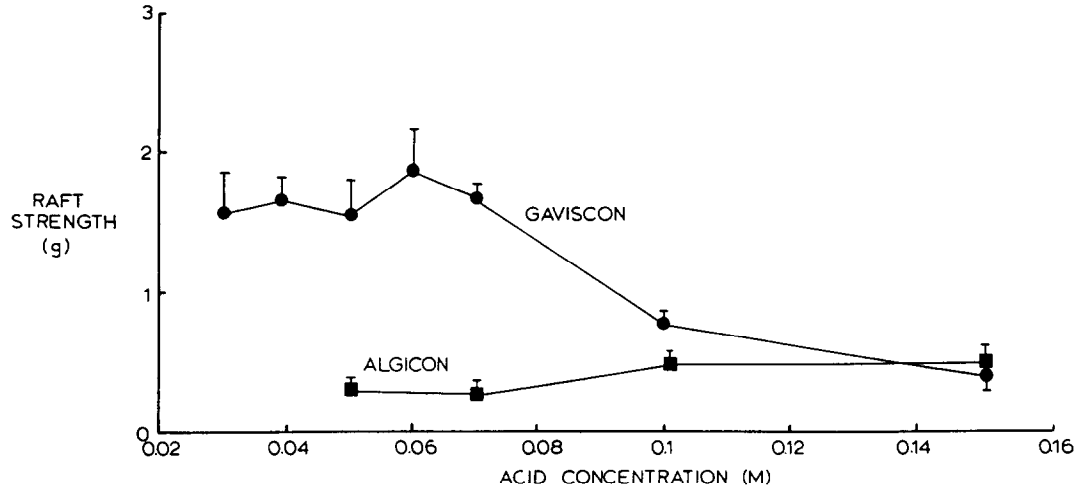

Fig. 2. Raft strength of "Liquid Gaviscon" and "Algicon Suspension" at varying acid concentrations ($n = 5$, mean ± S.D.).

"Algicon Suspension" were measured using a range of acid concentrations from 0.03 to 0.15 M. The results are presented in Fig. 2. The raft strength of "Liquid Gaviscon" remained in the region 2–2.5 g in the acid concentration range 0.03–0.07 M, then decreased with increasing acid concentration to 0.5 g at 0.15 M. "Algicon Suspension" would not form a raft under the conditions of the experiment in acid weaker than 0.05 M. The raft formed by "Algicon Suspension" had a strength of 0.3 g in 0.05 M acid, which rose to 0.5 g in 0.15 M acid.

The time for raft formation and raft thickness for the formulations in varying acid strengths are shown in Figs. 3 and 4. Although the time for raft formation decreased with increasing acid strength, the thickness of the raft also decreased.

The mean gastric emptying curves for "Liquid Gaviscon" and "Algicon Suspension" are shown in Figs. 5 and 6, respectively. T_{50} values for each subject are shown in Table 1. The "Liquid Gaviscon" emptied significantly more slowly from the stomach than the "Algicon Suspension" ($P < 0.01$,

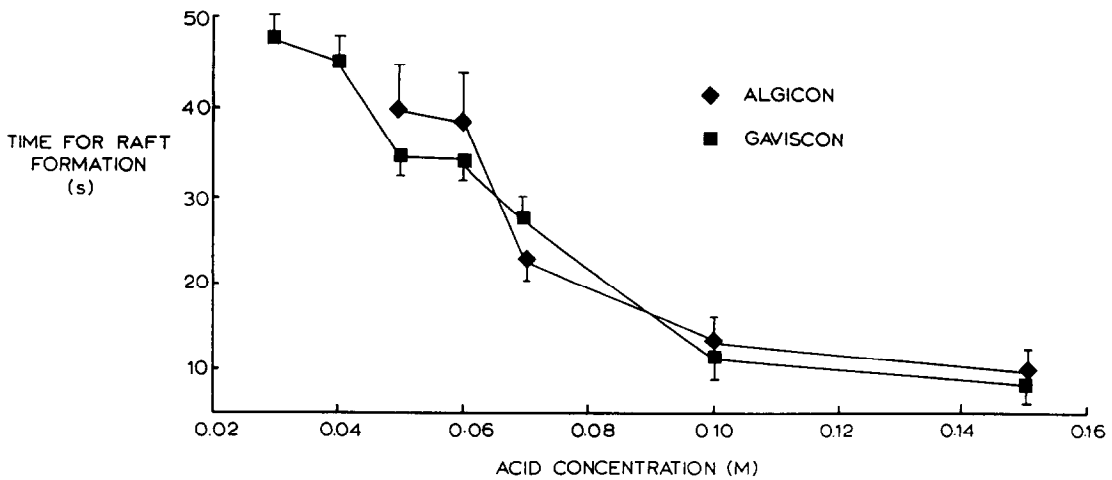

Fig. 3. Time for raft formation of "Liquid Gaviscon" and "Algicon Suspension" at varying acid concentrations ($n = 5$, mean ± S.D.).

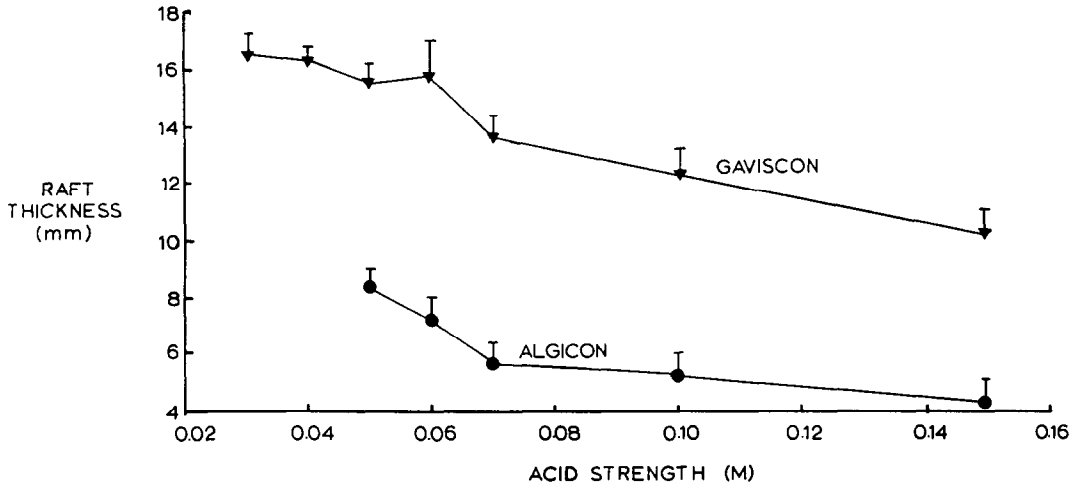

Fig. 4. Raft thickness of "Liquid Gaviscon" and "Algicon Suspension" at varying acid concentrations ($n = 5$, mean ± S.D.).

paired t-test). Examining the distributions of the two formulations in the top half of the stomach (Figs. 7 and 8) clearly shows that "Algicon Suspension" did not form a raft, but mixed and emptied with the food, whereas "Liquid Gaviscon" persisted in the upper half of the stomach. The emptying curve for "Liquid Gaviscon" was significantly different from that of the corresponding meal ($P < 0.01$, paired t-test) while there was no significant difference between the emptying of "Algicon Suspension" and the corresponding meal.

TABLE 1

Time (hours) taken to half-empty stomach (T_{50})

Subject	Formulation		Food	
	Gaviscon	Algicon	Gaviscon	Algicon
A	1.8	1.2	1.8	1.7
B	2.6	2.4	2.2	2.6
C	2.2	–	1.9	–
D	2.0	1.3	1.7	1.8
E	2.4	2.1	1.8	1.6
F	2.9	2.0	1.9	2.4
Mean ± S.E.M.	2.3 ± 0.2	1.8 ± 0.3	1.9 ± 0.1	2.0 ± 0.2

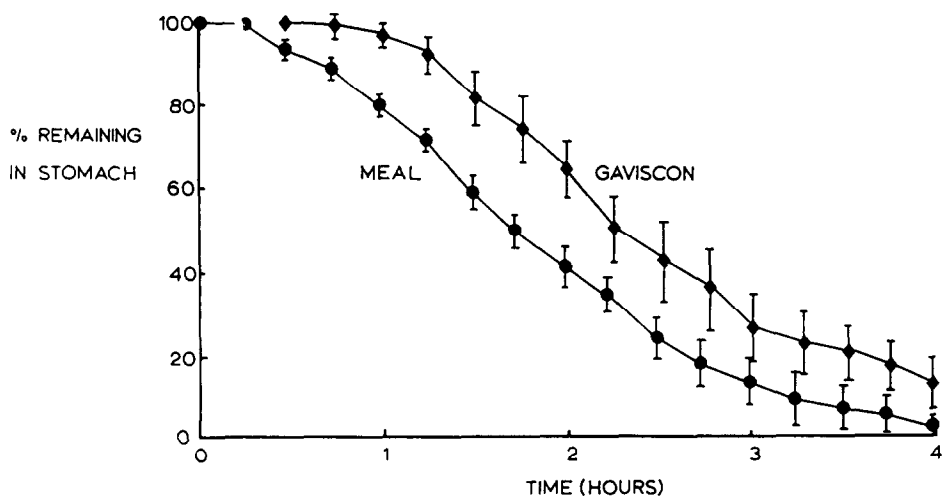

Fig. 5. Percentage of "Liquid Gaviscon" and the meal remaining in the stomach with time ($n = 6$, mean ± S.E.M.).

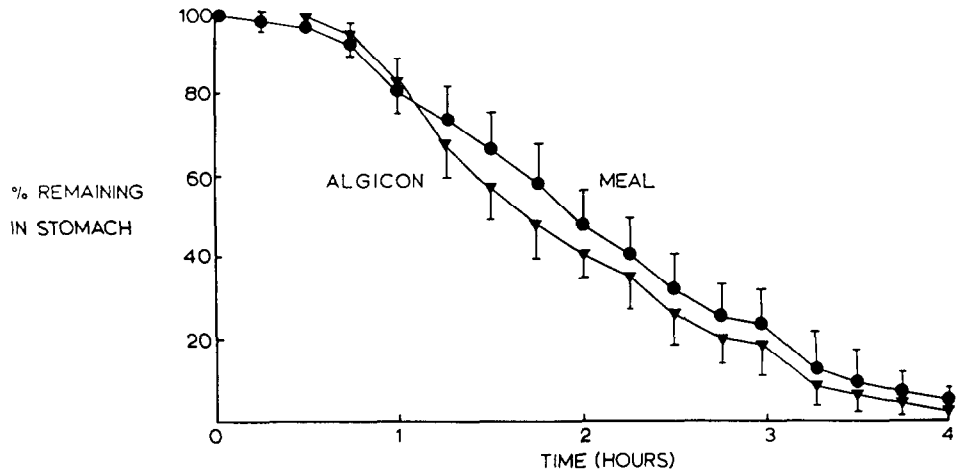

Fig. 6. Percentage of "Algicon Suspension" and the meal remaining in the stomach with time ($n = 5$, mean ± S.E.M.).

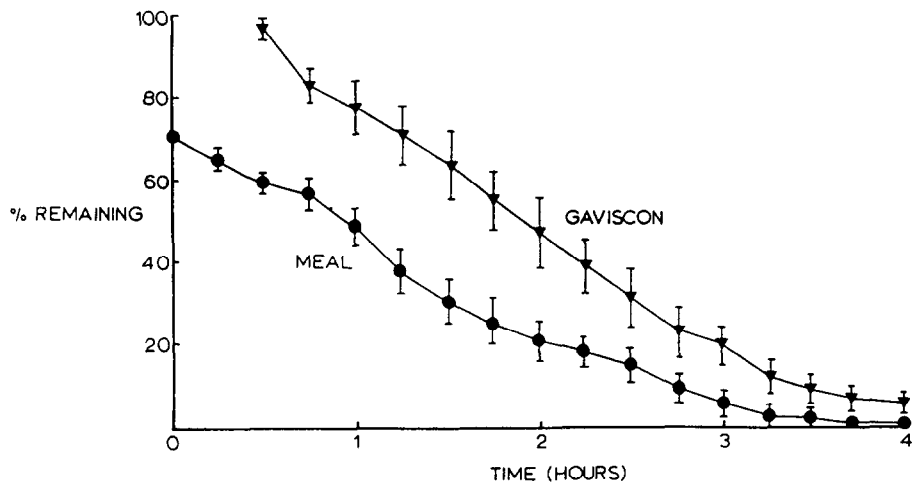

Fig. 7. Percentage of "Liquid Gaviscon" and the meal remaining in the fundus with time ($n = 6$, mean ± S.E.M.).

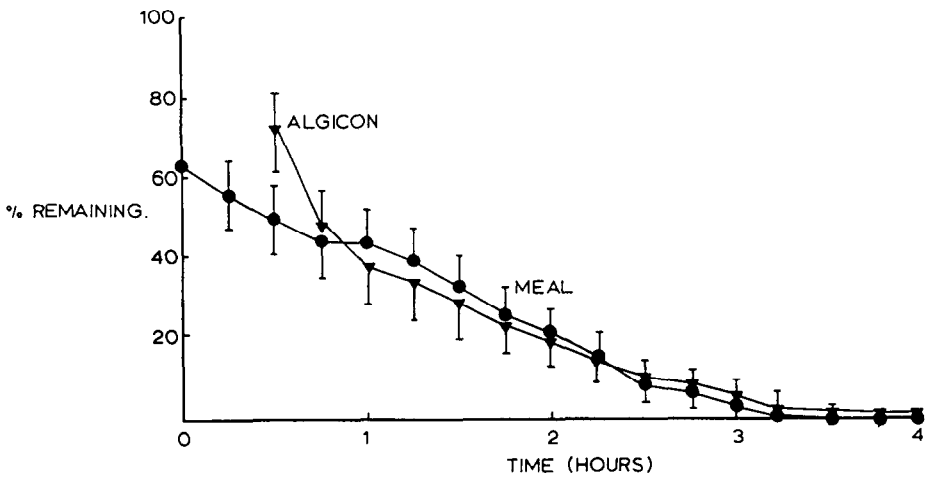

Fig. 8. Percentage of "Algicon Suspension" and the meal remaining in the fundus with time ($n = 5$, mean ± S.E.M.).

There was no difference between the emptying of the meal given before the "Liquid Gaviscon" to that given before "Algicon Suspension" ($P < 0.2$, paired t-test).

Subject C withdrew from the study because the taste and smell of the "Algicon Suspension" led to nausea and subsequent vomiting.

Discussion

Previous studies have demonstrated that the inclusion of particulate antacids into "Liquid Gaviscon" reduced both the raft strength and the neutralization capacity of the antacid in vitro (Washington et al., 1986a).

The transient neutralization produced by "Liquid Gaviscon" when the raft was destroyed was due to the release of the bicarbonate into the reaction mixture. Although "Algicon Suspension" produced a longer neutralization profile, the buffering capacity was less than would be expected for the antacid content. A greater neutralization profile would be expected if the alginate domains were broken down further to release a greater amount of the entrapped antacid into the reaction mixture.

The failure of 'Algicon Suspension' to form a raft under the conditions used in the modified Rossett and Rice test may be due to the additional antacid in the formulation competing with the potassium bicarbonate for the available H^+ ions. The pH measured in and below the raft for "Liquid Gaviscon" confirms the previous studies by Washington and coworkers (1986a and b). "Liquid Gaviscon" produces a very strong gel-like raft and it can be postulated that acid diffusion through such a system would be slow. Consequently, the raft maintained an elevated pH even though there was only sodium bicarbonate present. If the rate of acid diffusion is primarily governed by the available surface area at the acid/alginate interface, this in turn would be dependent upon the structure of the raft. A very weak, floccular raft with a high antacid content, e.g. the "Liquid Gaviscon" formulation manufactured by Marion Laboratories (U.S.A.), demonstrated a short time for which the raft pH remained above 3 since the acid diffused very rapidly through the alginate structure (Washington et al., 1986b).

'Liquid Gaviscon' produced a strong raft in acid of concentration 0.03–0.07 M. Pure parietal cell secretion has an H^+ concentration of 0.15 M, which is diluted into the range 0.02 to 0.06 M by non-parietal cell secretion (Johnson, 1985). Consequently 'Liquid Gaviscon' would be expected to form a strong raft over the majority of the physiological range. At higher acid concentrations, in the range 0.08–0.15 M, the raft became progressively weaker. 'Algicon Suspension' did not form a raft under the conditions of the experiment below an acid concentration of 0.05 M. The strength increased slightly with greater acid strengths. Over the physiological range, the raft formed by 'Algicon Suspension' was approximately a factor of 4 times weaker than that formed by 'Liquid Gaviscon'.

Although there was no difference in the time for raft formation for the two formulations, the rafts which formed in higher acid concentrations were thinner. It appeared that the faster the rafts formed, the less carbon dioxide was trapped within the alginate and hence the raft thickness decreased. The entire process of raft formation relies upon the presence of acid, both for the conversion of the alginate salt to the alginic acid gel and for the release of carbon dioxide from the bicarbonate. The relative rates at which the two reactions occur would be expected to be critical, both for raft formation and for determining the characteristics of the raft formed. 'Algicon Suspension' did not form a raft in vivo when administered 30 min after a scrambled egg meal, whereas distinct raft formation was shown by 'Liquid Gaviscon', although 'Liquid Gaviscon' and 'Algicon Suspension' are both described as anti-reflux agents. Any initial preference of 'Algicon' for the upper part of the stomach could be ascribed to stratification in the stomach before mixing occurred. Within 15 min, the 'Algicon' and food appeared identically distributed within the stomach.

There has been much discussion as to whether anti-reflux agents act as mechanical barriers to prevent reflux or whether the neutral alginate is refluxed in preference to the acidic gastric con-

tents. Originally the apparatus to measure raft strength was developed to provide an index for the possible barrier effect of a raft; however, the coherence of the raft reflected by its strength may be an important factor in maintaining the raft intact against the forces of gastric mixing. This theory is supported by the observation that in vivo "Liquid Gaviscon", which forms a strong coherent raft, persisted well in the stomach; however, the weak floccular raft formed by "Algicon Suspension" mixed rapidly with the stomach contents and emptied with them. During the first half-hour after a meal, peristaltic activity in the stomach is very weak (Vander et al., 1975) and food passes through the stomach to the pyloric antrum roughly in the order in which it is swallowed. However, a dense material sinks to the floor of the stomach passing through the gastric contents (Bechgaard et al., 1985). The alginate material is initially more dense than gastric contents after a liquid meal and [^{113m}In] 'Liquid Gaviscon' (U.K.) has been observed to sink to the bottom of the stomach before rising to form a raft. Raft formation can be distinguished from stratification when two distinct layers persist for longer than half-an-hour after administration of the material.

Despite an extensive literature search, no evidence could be found for abnormal gastric motility patterns or fundal pressures in reflux patients. Consequently, the raft should be subjected to normal intragastric motility patterns in the fundus. Gastric and oesophageal motor activity are independent of each other (Henderson, 1976) and hence the tertiary spasms which arise in the oesophagus in response to irritant materials are not propagated into the stomach, nor do they originate from it. Normally, the pressure gradient between the stomach and duodenum forces the chyme into the small intestine because the oesophagus is effectively closed, but if the lower oesophageal sphincter is incompetent, the chyme could be propelled upward producing the reflux. Thus, if an alginate raft is located in the fundus, it would be expected to withstand the normal gastric resting pressure of 5–10 mm Hg. The pressure gradient between the body of the stomach and the oesophagus has been measured in the fasting state, during phase III of the migrating myoelectric complex (Dent et al., 1983) and it was estimated to be of the order of 60 mm Hg. Antral pressures up to 43 mm Hg have been measured during trituration of food (Quigley and Brody, 1950). Pressure in this region would be expected to be the highest in the stomach during the fed mode, since the antrum is responsible for grinding of food particles. It appears that in normal subjects the coherence of the raft is of primary importance in resisting gastric motility.

The raft-forming materials not only require sufficient gastric volume for the raft to be correctly positioned in the fundus, but also gastric secretion has to overcome the buffering effects of the meal to produce sufficient free H^+ ions for proper raft formation. Additional particulate antacids added to raft-forming materials will compete for available gastric acid and consequently initial gastric pH will have to be lower for adequate raft formation. Since gastric emptying occurs continuously, gastric volume may be insufficient to hold the raft in the correct position. There is surprisingly little in the literature concerning buffering capacities of food and future studies are planned in this field. The 'Algicon' formulation demonstrates the problem of competition for available acid local to the raft, between the bicarbonate required to elevate the raft and entrapped antacid component. This was shown in a study by Knight and coworkers (1986) who found that an antacid–alginate formulation failed to form a raft when administered after 300 ml of water. It was necessary to acidify the gastric contents with 150 ml of 0.1 N HCl + 150 ml of apple juice to obtain raft formation in vivo.

The rationale for the inclusion of antacid materials in raft-forming antacids is to gain the benefits of both, i.e. a mechanical barrier which impedes reflux episodes, and neutralization of the gastric contents by the aluminium hydroxide. In the event of a reflux episode, the alginate and any gastric contents would both be of high pH. It has been demonstrated in vitro that particulate antacids significantly reduced the strength of the raft which results in decreased resistance to gastric mixing in vivo. The alginate trapped the antacid making it unable to neutralize the bulk of the gastric contents, and reduced its neutralizing power even if the reflux episode was sufficiently severe to

totally destroy the raft. Consequently alginate and antacid therapy appear to be mutually incompatible in a single-dose formulation.

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