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The effect of inclusion of aluminium hydroxide in alginate-containing raft-forming antacids

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Summary

The effect of the inclusion of aluminium hydroxide on the neutralization profiles and raft strength of alginate-based antacid formulations was investigated using in vitro techniques. The results indicate that the aluminium hydroxide remains associated with the raft material and does not neutralize the acid layer below. The physical strength of the raft produced by the formulation on reaction with acid was reduced by the inclusion of aluminium hydroxide.

Introduction

Antacid formulations consisting of sodium bicarbonate, with alginic acid and/or sodium alginate, are advocated for the treatment of gastro-oesophageal reflux. The sodium alginate is converted to alginic acid in the acid conditions of the stomach. The alginic acid absorbs water to form a swollen gel-like precipitate. Reaction of sodium bicarbonate with gastric acid releases carbon dioxide which becomes entrapped in the gel, making the alginic acid layer buoyant and causing it to float on the gastric contents.

Various mechanisms of action have been postulated to explain the symptomatic benefit associated with these preparations. Firstly, the material may be preferentially refluxed into the oesophagus, providing a coating for the epithelial lining (Malmud et al., 1979). The neutral raft material would be expected to be less damaging to the compromised mucosa than the gastric acid. Secondly, the material may provide a mechanical barrier to reflux, thus reducing the number of reflux episodes. A therapeutic goal may be to combine the benefits of the barrier with neutralization of the gastric contents beneath, or to increase the neutralizing capacity of the raft. Thus the inclusion of additional antacid materials such as aluminium hydroxide or magnesium carbonate might be beneficial. These ingredients are present in a number of proprietary alginate–antacid formulations.

The neutralizing capacity, or rate of reaction of antacid formulations with hydrochloric acid, may be tested using a number of different types of apparatus. These tests, such as that described by Rossett and Rice (1954), are unsatisfactory for

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testing raft-forming preparations since they destroy the integrity of the raft and do not simulate the in vivo behaviour of this type of antacid preparation. A modification of the Rossett and Rice test (Washington et al., 1985c) has been used to measure the neutralization–time profile of the raft-forming preparation 'Liquid Gaviscon'. It has been suggested that any antacid component incorporated in a raft-forming preparation remains associated with the alginate layer and does not significantly affect the gastric pH (Beckloff et al., 1972; Hasan, 1980). To test this hypothesis the effect of the inclusion of aluminium hydroxide on 'Liquid Gaviscon' was investigated. The effect of the additional antacid components on the breaking strength of the raft was investigated using a microcomputer-controlled force balance which pulled a wire probe through the alginic acid layer (Washington et al., 1985a and b). This was also used to measure the strengths of the rafts formed by 'Gaviscon Granules', 'Gaviscon Tablets' (Reckitt and Colman), 'Pyrogastrone (Winthrop Laboratories), and 'Gastrocote' (M.C.P. Pharmaceuticals).

Materials and Methods

Materials

Proprietary antacid preparations. All antacids were used as supplied from the hospital pharmacy in their original packs; these were 'Liquid Gaviscon', 'Gaviscon Tablets', 'Gaviscon Granules', (Reckitt and Colman Pharmaceuticals, Hull), 'Pyrogastrone' (Winthrop Laboratories, Surrey) and 'Gastrocote' (MCP Pharmaceuticals, West Lothian).

Preparation of alginate–aluminium hydroxide mixtures. A suspension of aluminium hydroxide BP in water (10% w/v) was evaporated to a stiff paste containing approximately 40% solids w/v using a rotary evaporator. This was added to 'Liquid Gaviscon' to obtain final concentrations of 0–10% w/w aluminium hydroxide–alginate mixture. The preparation was left for 48 h with regular thorough shaking to ensure even distribution of the two materials.

Methods

Neutralization properties

Neutralization profiles for the 'Gaviscon' and aluminium hydroxide mixture, and for the aluminium hydroxide component alone, were measured using the technique described by Rossett and Rice (1954), and the modified test (Washington et al., 1985c) allowing measurements to be obtained in both the raft and bulk phases.

Raft strength

The relative force required to break the rafts was measured with a microcomputer-controlled apparatus developed specifically for that purpose (Fig. 1). A horizontal wire probe 25 mm long and 0.6 mm diameter was suspended under the raft from one arm of a beam balance. A chain was suspended from the opposite arm of the balance to supply the force required to raise the probe. The length of free chain, and hence the force applied to the beam, was controlled by a stepping motor. The deflection of the beam, and hence the probe height, was measured by sensing the transmission of a graded optical neutral density filter attached to the beam. A BBC microcomputer controlled the stepping motor, monitored the beam position sensor signal, and performed all calibration, data collection, storage and plotting. The probe position could be measured to within 0.3 mm and the applied force to within 10 mg.

Solid preparations were first ground to a smooth paste with 5 ml of distilled water. The strength of

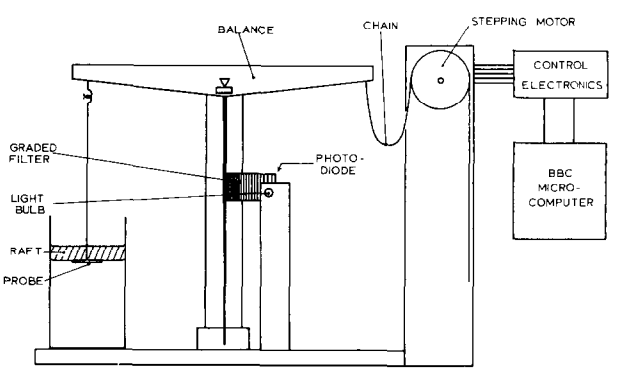

Fig. 1. Apparatus for measuring raft breaking strengths.

the barrier formed by the alginate-containing antacid was compared by using half the minimum recommended dose of each preparation. Comparisons are complicated by the differing compositions of the formulations. This method was chosen as it appears to be more clinically relevant to compare the effect of the recommended dose of each formulation than that of a particular component.

The strength of a raft was measured using the following procedure: 125 ml of 0.03 M 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. 5 min were allowed for the raft to form completely. The probe was then attached to the balance arm and the force required to break the raft was measured. The results were corrected for the force required to lift the probe through the same distance in water.

Results and Discussion

The total neutralization profile of 'Gaviscon' containing varying amounts of aluminium hydroxide was measured using the Rossett and Rice test (Fig. 2). Addition of 0.5% aluminium hydroxide caused no detectable change in the neutralization profile of 'Gaviscon'. Increasing concentrations of aluminium hydroxide caused the magnitude of the initial high pH produced by the sodium bicarbonate to be progressively depressed. The neutralization profile shows a second pH maximum due to the aluminium hydroxide component which does not appear until the neutralization caused by the bicarbonate has nearly finished. This second component of the curve is more prolonged than the first, and the peak pH is lower.

Fig. 3 shows the neutralization profiles caused by aluminium hydroxide alone, in the same concentrations as used for the experiments with 'Gaviscon'. Aluminium hydroxide at 0.5% is insufficient to produce measurable neutralization in the Rossett and Rice test. Higher concentrations buffer the mixture to pH 3.8. 5% w/v aluminium hydroxide maintains this pH for 60 min, and 10% w/v aluminium hydroxide for more than 130 min. In all cases the initial rise in pH is rapid.

These data show that the neutralizing effects of aluminium hydroxide is delayed when added to acid in the presence of the sodium bicarbonate/alginate mixture. All the curves obtained from the 'Gaviscon'–aluminium hydroxide mixtures pass through a common point at 35 min, after the bicarbonate neutralization phase finished, but before the aluminium hydroxide has started to react. The presence of sodium bicarbonate buffers the acidic medium and so reduces the rate of reaction of the aluminium hydroxide. This mechanism appears to be independent of any effects due to entrapment of the aluminium hydroxide within the alginate. However, the presence of the alginate alters the duration of action of the aluminium hydroxide as may be seen by comparison of Figs. 2 and 3.

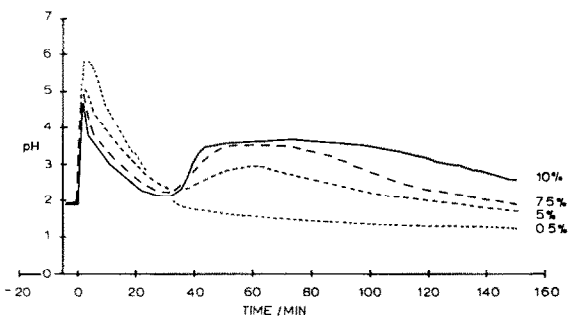

Fig. 2. Neutralization profiles for 'Liquid Gaviscon' containing varying amounts of aluminium hydroxide, obtained from the Rossett and Rice test (n = 5, S.D. less than 0.25 of a pH unit in all cases).

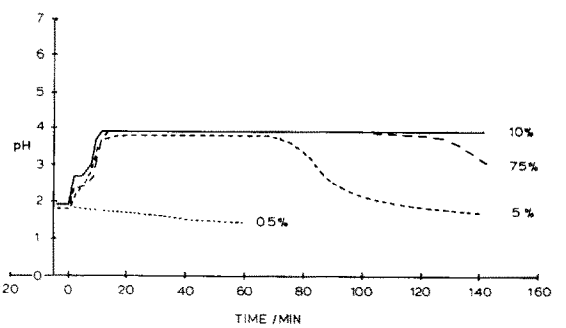

Fig. 3. Neutralization profiles for varying amounts of aluminium hydroxide, obtained from the Rossett and Rice test (n = 5, S.D. less than 0.25 of a pH unit in all cases).

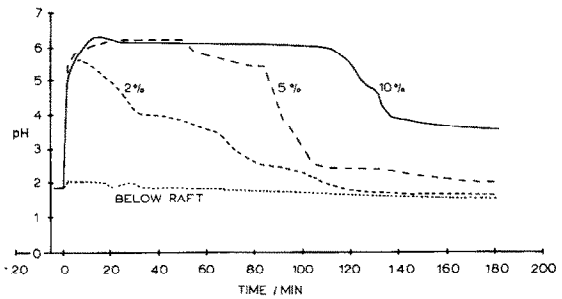

Fig. 4. Neutralization profiles for 'Liquid Gaviscon', above and below the raft, containing varying amounts of aluminium hydroxide, obtained from the modified Rossett and Rice test (n = 6, S.D. less than 0.3 of a pH unit in all cases).

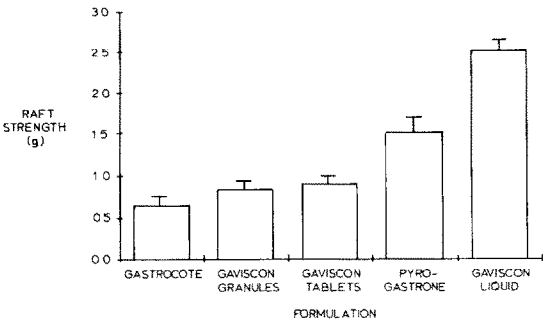

Fig. 6. Relative breaking strengths of the rafts formed by a number of proprietary alginate-containing formulations (n = 5).

The pH measured in the aluminium hydroxide–'Gaviscon' raft using the modified technique is elevated to between 5.5 and 6.0 (Fig. 4). There is little difference between the in-raft neutralization of 'Gaviscon' (Washington et al., 1984, 1985c) and that caused by the addition of 2% aluminium hydroxide. Further increases in the percentage of aluminium hydroxide increases the time at pH 6.0. No neutralization is observed below the raft, indicating that the majority of the antacid component is associated with the alginate raft.

The contribution of sodium bicarbonate to the overall neutralization decreases as the concentration of aluminium hydroxide is increased (Fig. 2). This effect is actually less marked than the graph suggests, since the pH scale is a logarithmic one, and the amount of neutralization on a linear scale varies only by a few percent. This can be attributed to the slight dilution of the bicarbonate in the 'Gaviscon' by the addition of the aluminium hydroxide.

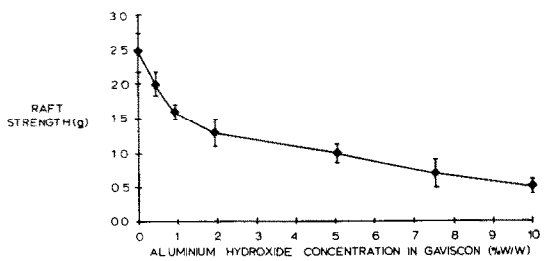

Fig. 5. Relative breaking strengths of the rafts formed by 'Liquid Gaviscon' containing varying amounts of aluminium hydroxide (n = 5).

The strength of the raft is weakened by the addition of increasing amounts of aluminium hydroxide (Fig. 5). The aluminium hydroxide is physically very bulky, since it contains a large amount of adsorbed water. This has a diluting effect on the raft, which reduces its strength. In addition, alginate gels are strengthened by the Ca^{2+} ion, which is present in most commercial grades of alginate. This is due to the formation of an 'egg-box' cross-linked structure (Rees, 1972). The Al^{3+} ion may compete for these binding sites, and since it is physically smaller than the Ca^{2+} ion, and trivalent, may disrupt the cross-linked structure.

The forces required to break the rafts formed by a number of proprietary formulations are shown in Fig. 6. The strongest raft was formed by 'Liquid Gaviscon'. The rafts formed from the solid formulations are weaker, possibly because dissolution of the alginates is slow or incomplete. In addition, all the solid preparations investigated in this study contain additional materials, aluminium hydroxide and magnesium trisilicate being common to all. The list of major components of the formulations included in this study are shown in Table 1.

The rationale for the inclusion of aluminium hydroxide 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. Unfortunately, this is not the case since the aluminium hydroxide significantly reduces the strength of the

TABLE 1

COMPOSITION OF RAFT-FORMING PREPARATIONS STUDIED

Product	Quantity tested	$NaHCO_3$	Sodium alginate	Alginic acid	$Al(OH)_3$	Mg trisilicate	Other materials
Gaviscon liquid	5 ml	133	250	–	–	–	Saccharin
Gaviscon tablet	Half-tablet	85	–	250	50	12.5	Sucrose + Mannitol
Gaviscon granules	Half-sachet	88	260	240	104	26	Sucrose
Pyrogastrone	Half-tablet	105	–	300	120	30	Carbenoxolone Na
Gastrocote	1 tablet	70	–	200	80	40	

raft and weakens the barrier to reflux. In addition, the alginate traps the aluminium hydroxide making it unable to neutralize the gastric contents, and reduces its neutralizing power even if the reflux episode is sufficiently severe to totally destroy the raft.

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