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The neutralization capacity of magnesium trisilicate BP and magnesium trisilicate mixture BP

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Summary

The in vitro neutralization properties of magnesium trisilicate mixture BP and its ingredients have been examined using the Rossett and Rice test. It is concluded that the inclusion of the principal component, magnesium trisilicate, in the mixture is unwarranted due to the failure to demonstrate a significant neutralizing action. This appears to be due to the extremely slow rate of reaction of this compound with hydrochloric acid.

Introduction

Antacids based on magnesium trisilicate are widely used, especially by anaesthetists and obstetricians, as a preoperative procedure for the prevention of Mendelson's syndrome, i.e. acid aspiration into the lungs leading to pneumonia (Taylor and Pryse-Davis, 1966). Magnesium trisilicate mixture BP has been found to possess good neutralization both in vitro (Williams and Crawford, 1971) and in vivo (Peskett, 1973; Holdsworth, 1978; Husemeyer and Davenport, 1980; O'Sullivan and Bullingham, 1984).

In contrast, pure magnesium trisilicate fails to meet the requirements for non-prescription antacids and all over the counter preparations containing solely this antacid material have been withdrawn in the United States (Harvey, 1980). Magnesium trisilicate BP also has been reported to perform poorly in an in vitro test (Gore et al., 1953).

However, the results in the latter study were obtained at room temperature and the observed reaction rates would be expected to be slower than that obtained in vivo. Magnesium trisilicate mixture BP contains substantial amounts of both sodium bicarbonate and magnesium carbonate as well as magnesium trisilicate. The contribution of each component to the total neutralization capacity of magnesium trisilicate mixture BP has been studied using the in vitro technique described by Rossett and Rice (1954).

Materials and methods

All materials used were BP grade and were used without further purification. Fresh magnesium tri-

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silicate mixture BP was provided by the Hospital Pharmacy, Queen's Medical Centre (Nottingham) from the normal suppliers (Raymed, Leeds). The components in each 10 ml dose of the suspension are magnesium trisilicate (500 mg), sodium bicarbonate (500 mg) and light magnesium carbonate (500 mg) BP grade. Samples of the individual components were used to prepare the mixture with and without magnesium trisilicate in distilled deionized water.

Ten ml batches of antacid were added to 100 ml of 0.03 M hydrochloric acid at 37.5°C in a Rossett and Rice (1954) apparatus. 0.1 M hydrochloric acid was pumped in at rates of 4, 1, 0.5 and 0 ml/min and the mixture stirred continuously. In the modified test the volume of the reaction mixture was kept constant by a second pump (Washington et al., 1985). The pH was measured with a pH electrode and the output continuously recorded. The duration of action of the antacid was defined as the time for which the reaction mixture was held above pH 3.0. Each test was carried out 5 times and the mean profile determined.

Results and Discussion

Magnesium trisilicate mixture BP (10 ml) reacted rapidly with acid in the Rossett and Rice test and the system reached a maximum pH of 7.4 within 4 min (Fig. 1, trace a). In contrast, 500 mg magnesium trisilicate BP did not produce any significant pH change in the Rossett and Rice test until the rate of acid addition was reduced from 24 mmol H^+/h (4 ml/min) to 3 mmol h^+/h (0.5 ml/min) (Fig. 2). At an input rate of 3 mmol H^+/h, the magnesium trisilicate powder BP increased the pH to above 3 for approximately 20 min. The same weight of magnesium trisilicate BP increased the pH of the fixed volume of hydrochloric acid (100 ml, 0.03 M) to 7.5 when no additional acid was added (Fig. 2.), taking at least 40 min to reach a maximum. These tests demonstrate that this amount of antacid is sufficient to neutralize the initial quantity of acid, but the rate of reaction is extremely slow.

At higher rates of acid addition (between 6 and 24 mmol H^+/h), the rate of reaction of magnesium trisilicate BP was not sufficiently rapid to neutralize the added acid, and consequently no significant rise in pH was observed. Thus a 500 mg dose of magnesium trisilicate would not be able to affect the acidity significantly in the stomach if acid secretion is increased above 6 mmol H^+/h; the normal basal rate of acid secretion in the stomach is approximately 4 mmol H^+/h which rises to rates of 40 mmol H^+/h when maximally stimulated.

In the fasting subject, the small volume of

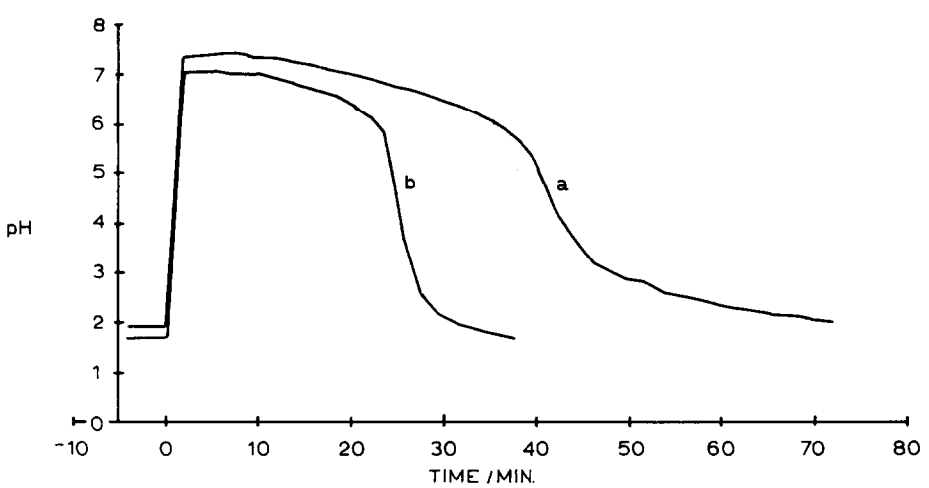

Fig. 1. Mean pH neutralization profile for 10 ml magnesium trisilicate mixture BP (a) in the Rossett and Rice test at an input of 4 ml 0.1 N HCl per minute; and (b) in the modified Rossett and Rice test with input equal to output (n = 5, S.D. < 0.1 pH unit).

antacid has been shown to be rapidly emptied from the stomach (Jenkins et al., 1983). Even in the presence of a meal, the liquid phase empties continuously during digestion, gradually removing unreacted antacid. Thus, a slowly reacting antacid would be largely emptied unused from the stomach. A modification to the Rossett and Rice test can be made to hold the reaction volume constant. This has been shown to produce better in vitro and in vivo correlation of antacid action (Washington et al., 1985), possibly because it in part mimics gastric emptying of unreacted antacid. The effect of this modification (Fig. 1, trace b) was to reduce the duration of action of magnesium trisilicate mixture from approximately 46 min to 27 min while only slightly reducing the peak pH from 7.4 to 7.0.

In order to establish the contributions of each antacid component in magnesium trisilicate mixture BP to acid neutralization, sodium bicarbonate (500 mg) and magnesium carbonate (500 mg) were also examined singly and in combination (Fig. 3) in the Rossett and Rice test at an acid input rate of 4 ml/min, corresponding to 24 mmol H^+/h. Sodium bicarbonate caused a rapid rise to pH 6.4 within 1 min and with a duration of action of 11 ± 1 (S.D.) min. Magnesium carbonate increased the pH rapidly to 7.2 within 3 min and had a duration of action of 22 ± 1 (S.D.) min. The addition of sodium bicarbonate to the magnesium carbonate (500 mg of each) raised the pH rapidly to 7.4 and altered the duration of action from 22 ± 0.7 (S.E.M., $n = 5$) min to 41 ± 0.7 (S.E.M., $n = 5$) min which is highly significant increase in neutralization (unpaired t-test, $t = 20.0$, $P < 0.001$). Lord (1984) has suggested that the sodium bicarbonate is the most important constituent of the magnesium trisilicate mixture, but the present data demonstrate that it is the combination of the two components, sodium bicarbonate and magnesium carbonate, which produces the prolonged neutralization profile in the Rossett and Rice test.

In the final set of studies, 500 mg of magnesium trisilicate BP was added to the other two components and the pH–time profile of the mixture was measured (Fig. 4). The duration of action of the mixture was also found to be 42 min, with a peak neutralization of 7.2. This mixture behaves almost identically to that with no magnesium trisilicate, indicating that the magnesium trisilicate has no useful addition neutralizing action. This system showed that the neutralization capacities of the components gave a similar neutralization profile to a sample of the commercial magnesium trisilicate mixture BP (Fig. 1).

These data suggest that the neutralization capacity of magnesium trisilicate mixture BP is

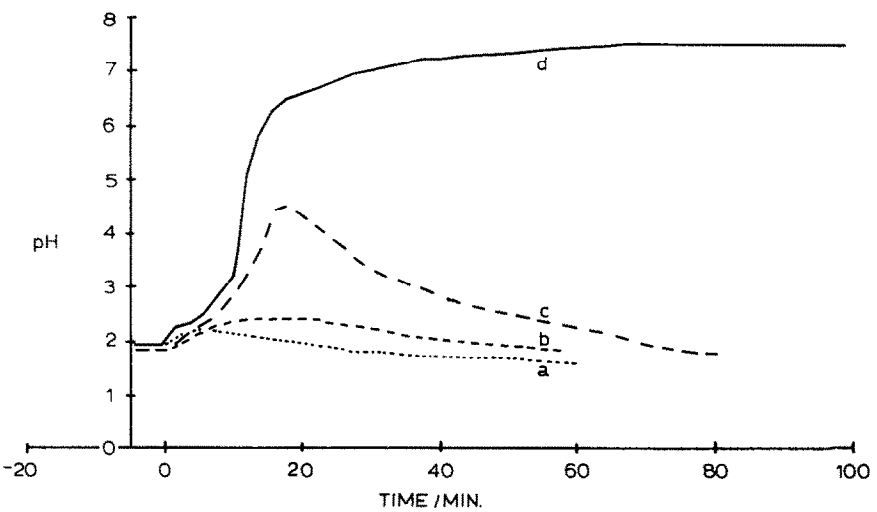

Fig. 2. Mean pH neutralization profiles for 500 mg magnesium trisilicate in the Rossett and Rice test at H^+ inputs of: (a) 24 mmol H^+/h; (b) 6 mmol H^+/h; (c) 3 mmol H^+/h; and (d) no acid input ($n = 5$, S.D. < 0.1 pH unit).

due only to the sodium bicarbonate and magnesium carbonate components, and the addition of magnesium trisilicate is of questionable value.

Within the literature there are reports that magnesium trisilicate is a useful antacid material. Armstrong and Martin (1953) reported that magnesium trisilicate BP displayed good in vitro neutralization, using a test similar to the Rossett and Rice test. The authors, however, were not explicit concerning the preparation used, which could have been magnesium trisilicate compound oral powder, containing both sodium bicarbonate and magnesium carbonate. This is probable since the neutralization profile is virtually identical to that obtained in the Rossett and Rice test for magnesium trisilicate mixture BP, and unlike that obtained for the magnesium trisilicate alone. Other reports suggest that magnesium trisilicate BP (i.e. the pure material) has poor neutralizing properties (Gore et al., 1953; Lahiri et al., 1973) in agreement with the data obtained in the present study.

The failure of magnesium trisilicate mixture BP to neutralize gastric contents has been reported by a number of investigators, and several explanations have been suggested. A primary cause may be the usage of an incorrect dosing regimen, as the schedule is rather nursing-intensive. An accepted pre-operative schedule is 15 ml of magnesium trisilicate mixture at two-hourly intervals and a final 15 ml dose 15 min prior to the induction of anaesthesia (Holdsworth, 1978; Crawford and Potter, 1984). The final dose of antacid before anaesthesia is often overlooked and it has been proposed that this is the critical dose to elevate the gastric pH during the surgical procedure.

Matts et al. (1965) have described a study of the effectiveness of magnesium trisilicate for the treatment of gastric and duodenal ulcer, but found that the material did not affect gastric pH. However, the assay method used was questionable as all the gastric juice was aspirated 30 min after administration of the antacid, thus removing any antacid material remaining. Not surprisingly, further aspirations to examine the effect of the antacid on pH did not reveal striking effects. The patients were pretreated with the antacid for 1 month prior to the study, but the dosing schedule was not optimized as the patients were instructed to take the antacid before meals. The duration of action of the antacid is prolonged if it is taken 1 h after meals due to the slowed gastric emptying caused by food, which is a critical factor in the action of slowly reacting antacids.

A second factor affecting the antacid's efficacy is the change in the mixture which occurs on storage. Magnesium trisilicate forms an aggregate which cannot be dispersed on shaking after 2 months of storage at 37°C (Crawford and Potter,

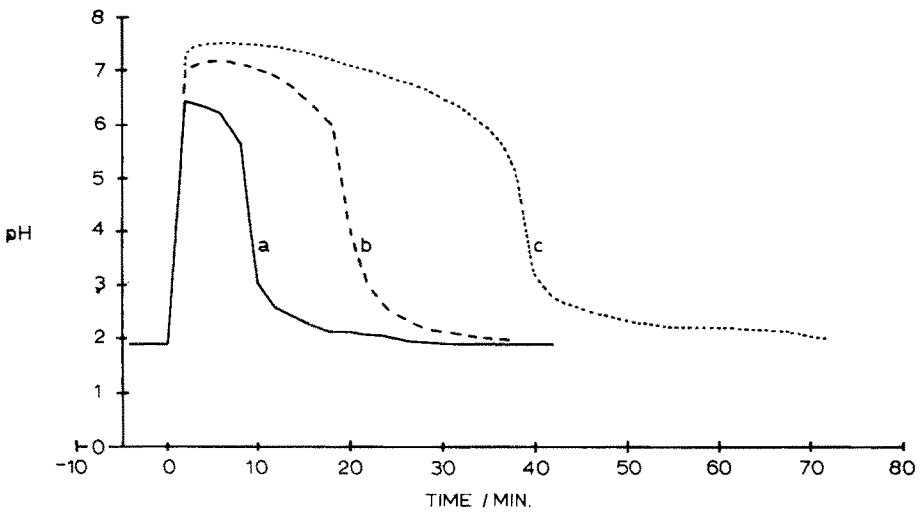

Fig. 3. Mean pH neutralization profiles in the Rossett and Rice test of: (a) sodium bicarbonate 500 mg; (b) magnesium carbonate 500 mg; and (c) sodium bicarbonate 500 mg + magnesium carbonate 500 mg (n = 5, S.D. < 0.1 pH unit).

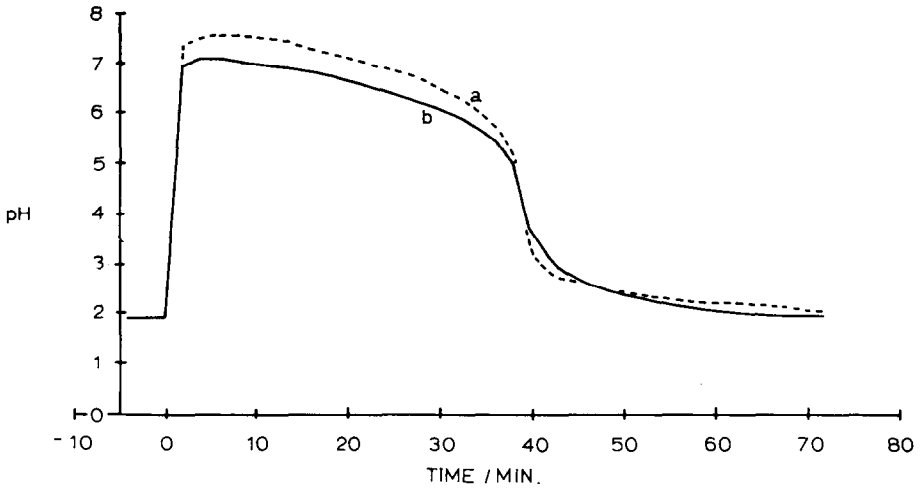

Fig. 4. Comparison of mean pH neutralization profiles of: (a) sodium bicarbonate 500 mg + magnesium carbonate 500 mg; and (b) sodium bicarbonate 500 mg, magnesium carbonate 500 mg + magnesium trisilicate 500 mg (n = 5, S.D. < 0.1 pH unit).

1984) whilst sodium bicarbonate solution slowly decomposes losing carbon dioxide (Lord, 1984). The British National Formulary recommends that the mixture should be used soon after preparation.

A final factor complicating the interpretation of the behaviour of magnesium trisilicate containing preparations may be variability in the physical form of the compound. Brindle (1953) found considerable variation of the in vitro neutralization of different samples of magnesium trisilicate, which were suggested to be due to the existence of two forms (light and heavy) of the compound.

The failure to demonstrate any useful antacid action of the principal ingredient calls into question the rationale for the inclusion of magnesium trisilicate mixture BP on the present 'white list' of prescribable antacids. The magnesium trisilicate component has no useful action, and may even produce siliceous stones, although persistent antacid use is necessary for this. The question of alternative preparations for pre-operative use should be addressed. Recently there has been a move towards the use of non-particulate antacids as pre-operative treatments to avoid aspiration of particulate material into the lung. Sodium citrate has been suggested as a suitable alternative. Of the particulate preparations, magnesium carbonate mixture, a non-systemic antacid, may be a more consistent preparation for use where optimum performance must be guaranteed. It does, however, contain a larger proportion of sodium bicarbonate. Magnesium hydroxide mixture could also be a useful preparation, as it does not release any gas on reaction. Finally, it should be noted that most antacid preparations will be at their most reactive when freshly prepared, before the particles begin to aggregate.

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