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Evaluation of 'raft-forming' antacid neutralizing capacity: in vitro and in vivo correlations

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

[1] *Department of Pharmacy, University of Nottingham, Nottingham NG7 2RD; and*
[2] *Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Nottingham, NG7 2UH (U.K.)*

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Summary

pH telemetry has been employed to measure the in vivo neutralization–time profile of two antacid formulations, 'Asilone Suspension' and 'Gaviscon Liquid', in man. The results from this investigation were compared with those obtained in the Rossett and Rice in vitro test (1954) of acid neutralizing capacity. For both antacids, the test gave a poor prediction of the duration of action in vivo. The in vitro test was modified to improve the correlation with the in vivo results, both for raft-forming and conventional antacids.

Introduction

The commonly used antacids contain a mixture of weakly basic ingredients such as the hydroxyaluminium compounds, and stronger bases such as magnesium hydroxide or sodium bicarbonate. The neutralizing capacity of the antacid ingredients varies according to the method of manufacture and the product age, and thus must be standardized within and between products.

Correspondence: C.G. Wilson, Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH, U.K.

Antacid neutralization capacity may be measured conveniently by a variety of in vitro tests, including those which simply measure total available neutralizing capacity, through methods which provide varying amounts of kinetic (i.e. reaction rate) information, to those which attempt to measure performance under conditions which bear some resemblance to those occurring in vivo. These include pH stat methods, the method of Holbert et al. (1947), and the Fuchs test (1949).

The Rossett and Rice test (1954) adds a sample of the antacid to 100 ml of 0.03 M hydrochloric acid, and measures the pH as further acid is added at 4 ml/min. This provides some indication of how the antacid may be expected to behave in vivo. However, gastric emptying of antacids may greatly reduce the period of time available for acid neutralization (Jenkins et al., 1983). Smyth et al. (1976) modified the Beekman procedure (Beekman, 1960) by pumping reactants out of the reaction vessel at a constant rate, and found a good correlation between in vitro and in vivo antacid activity.

None of the standard tests are applicable to antacids and mucosal protectives which form a floating 'raft', such as those based on alginates. The agitation employed in conventional tests destroys the raft and may alter the rate of reaction of the entrapped ingredients.

In the present study modifications of the Rossett and Rice test were investigated in an attempt to mimic the pH–time profiles recorded in vivo in man using the technique of pH telemetry (Watson, 1981) for a floating and a conventional antacid formulation.

Materials and Methods

Materials

Two antacid preparations were studied: 'Asilone Suspension' (Berk Pharmaceuticals, Shalford), containing 840 mg aluminium hydroxide, 140 mg light magnesium oxide and 270 mg activated dimethicone in 10 ml, and the same volume of 'Gaviscon Liquid' (Reckitt & Colman Pharmaceuticals, Hull), which contains 500 mg sodium alginate and 267 mg sodium bicarbonate. 'Clinifeed-ISO' (Roussel Laboratories, Wembley Park) (375 ml) was used as a liquid meal having an energy content of 1575 kJ.

Methods

(a) In vitro studies

The apparatus used was a modification of that described by Rossett and Rice (1954). In the original test, 10 ml of the antacid under test was added to 30 ml of 0.1 M hydrochloric acid and 70 ml distilled water. 0.1 M hydrochloric acid was pumped into the beaker at a rate of 4 ml/min. This was stirred and the pH was monitored continuously. The test was carried out at 37°C. The apparatus was modified by the addition of a stationary collar of wide bore glass tubing around the stirrer shaft to prevent vortex mixing of the raft as shown in Fig. 1. A second pump was introduced

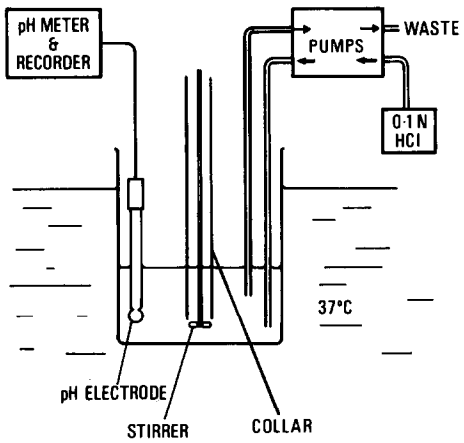

Fig. 1. Apparatus for the Rossett and Rice test, with modifications shown.

to remove the reaction mixture at the same rate (2 or 4 ml/min) as the addition of the acid. The output from the pH electrode was recorded on a 10 mV flatbed chart recorder.

(b) In vivo studies

Eleven healthy subjects, 8 male and 3 female, age range 19–38 years, participated in this study after giving written informed consent. Approval for the study had previously been obtained from the Nottingham University Hospital Ethical Committee. A pH-sensitive radiotelemetry capsule (model 7006, Medici Developments) was calibrated in buffer solutions of pH 1, 4 and 7 prior to and immediately after use. The pH capsule was prepared with a fine polythene tether fixed to the outside of the capsule with a rubber retaining ring, and the whole assembly was sterilized by immersion in a 5–10% solution of 'Hibiscrub' (I.C.I., Macclesfield) prior to its administration to the subject. The position of the lower oesophageal sphincter was established in each subject by manometry on a previous occasion. The pH capsule was swallowed with 20 ml of water and the tether adjusted to position the pH capsule 5 cm from the cardia. The signal was detected by an inductive loop aerial worn in a belt. The aerial was connected to a receiver (model 7040, Rigel Research). The pH output from the receiver was recorded by a chart recorder (Grass Instruments, model 79D).

The subjects were fasted overnight and on the morning of the experiment were given initially the 'Clinifeed-ISO' meal (375 ml) and 1 h was allowed for the stomach pH to reach a basal level; 10 ml of antacid were then administered, and the pH was recorded for 90 min until the basal pH was again reached. For the subjects who received 'Gaviscon' the pH capsule was repositioned 10 cm from the cardia and the basal pH monitored for 30 min. The experiment was then repeated as before. Pilot studies conducted on three volunteers after administration of 'Asilone' showed no differences in pH profiles observed with the pH capsule in the body of the stomach

(10 cm from cardia) and at the top of the stomach (5 cm from cardia). The experiment was, therefore, not repeated in subjects who received the 'Asilone'.

Results and Discussion

The unmodified Rossett and Rice test shows distinct differences between the pH–time profiles obtained for the two formulations. 'Asilone Suspension' (10 ml) produced a prolonged neutralization of the reaction mixture, maintaining the pH above 3 for more than 70 min (Fig. 2). In the case of 'Gaviscon', the raft structure formed initially by the product on contact with acid was broken up, releasing the entrapped bicarbonate. Consequently the pH rose rapidly to 5.6, and then decreased to below 3 after 14 min (Fig. 2).

In the in vivo studies it was necessary to administer the 'Clinifeed' meal approximately 1 h before conducting the pH telemetry experiment in order to allow time for the buffering action of the 'Clinifeed' to be overcome by acid secretion, thereby reducing the pH to near basal levels. It can be predicted that during this time, approximately 50% of the stomach contents would have emptied into the small intestine (May et al., 1984). Allowing for acid secretion, the residual volume can be estimated to be approximately 200 ml, which is sufficient to allow raft formation and discrimination of two phases, as observed by May et al. (1984).

Following administration of 'Asilone' (10 ml) to the subjects, the mean pH rose from 1.9 to a plateau of just greater than 4. Gastric emptying and secretion of acid reduced the mean pH to below 3 after 38 min (Fig. 3). For 'Gaviscon', distinct differences in the pH profile were noted with the capsule tethered at 5 cm and 10 cm

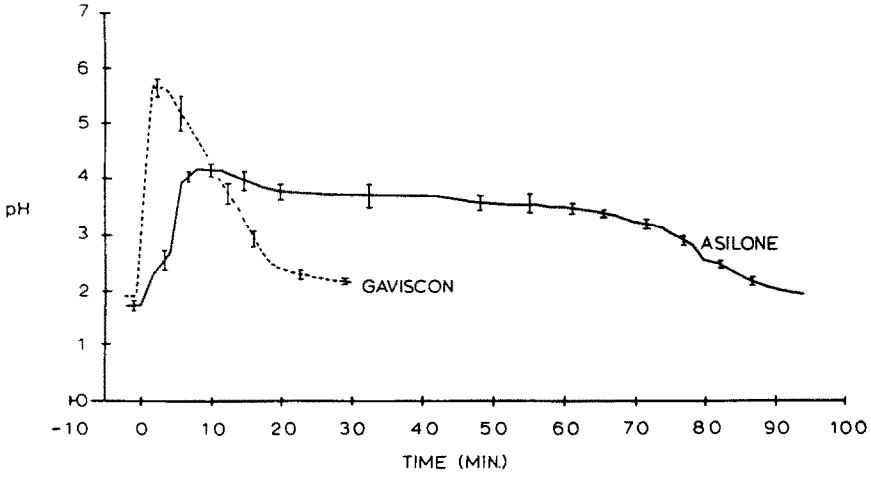

Fig. 2. Antacid neutralization traces for 10 ml 'Asilone' suspension and 10 ml 'Liquid Gaviscon' in the Rossett and Rice test. Mean ± 1 S.D.; n = 5 and 6, respectively.

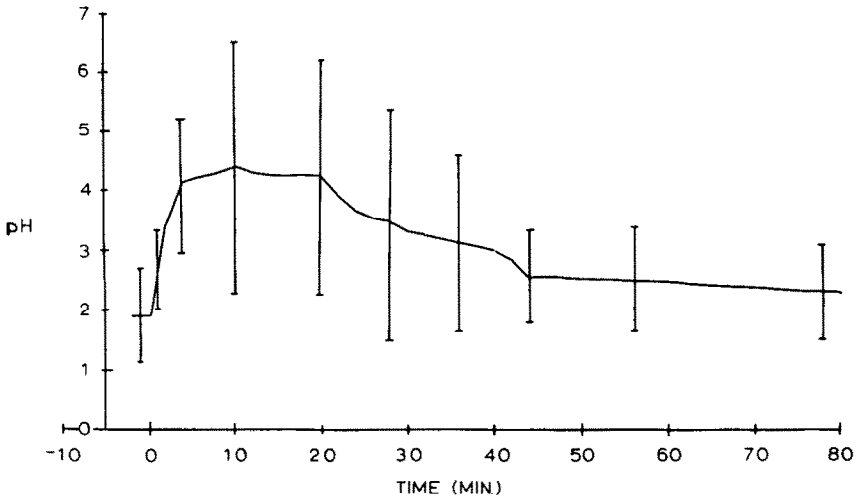

Fig. 3. Measurement of stomach pH after administration of 10 ml 'Asilone' suspension. Mean ± 1 S.D.; n = 6.

below the cardia. With the capsule positioned in the raft, the mean pH was observed to rise from a basal level of 2.5 to a maximum of 5.8. The duration of action (time for which the pH was greater than 3) was 42 min. When the capsule was positioned at the bottom of the stomach, the mean pH remained at, or near, basal levels for the duration of the experiment (Fig. 4).

The modification of the Rossett and Rice test to keep the reaction volume

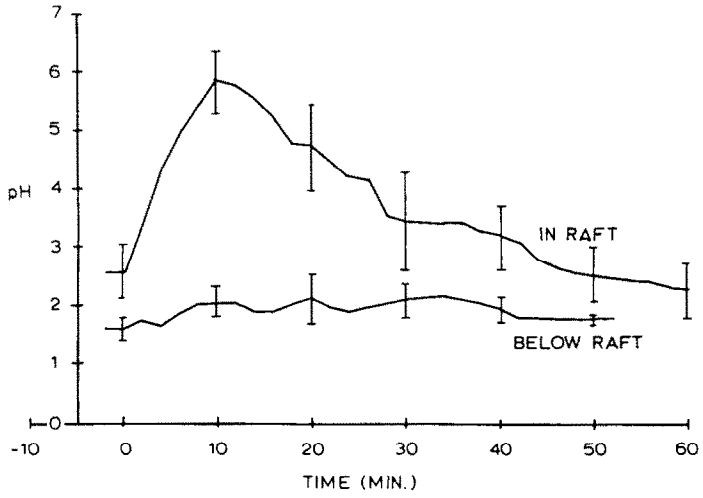

Fig. 4. Measurement of stomach pH after administration of 10 ml 'Liquid Gaviscon' (Mean ± 1 S.D.; n = 5).

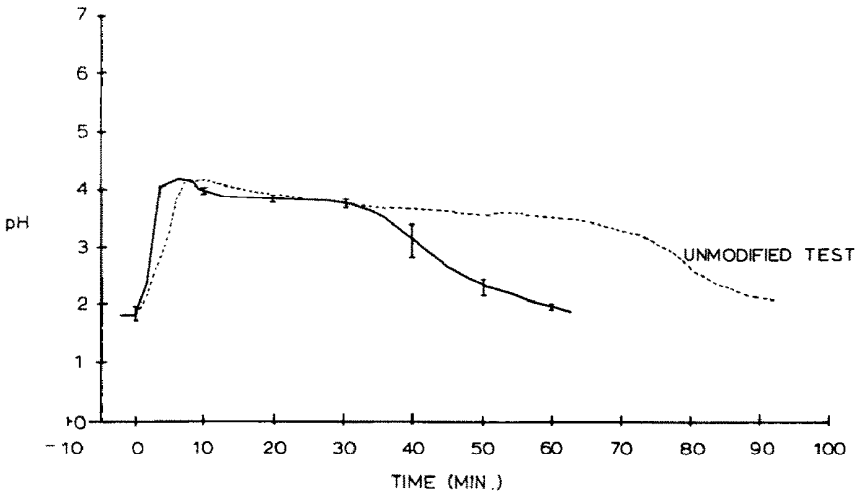

Fig. 5. Antacid neutralization trace for 10 ml 'Asilone Suspension' in the modified Rossett and Rice test. Mean ± 1 S.D.; n = 5.

constant reduced the duration of action of 'Asilone' to a similar value to that observed in vivo (Fig. 5) (38 min in vivo, 39 min in vitro). The peak pH, and the general shape of the neutralization profile, were unchanged by the modification of the test. By positioning the pH electrode in the 'Gaviscon' raft, a trace similar to that observed in vivo at the top of the stomach was obtained. However, the maximum pH in vitro was lower (4.2) than that found in vivo and the time above pH 3 approximately half that found in vivo (Fig. 6).

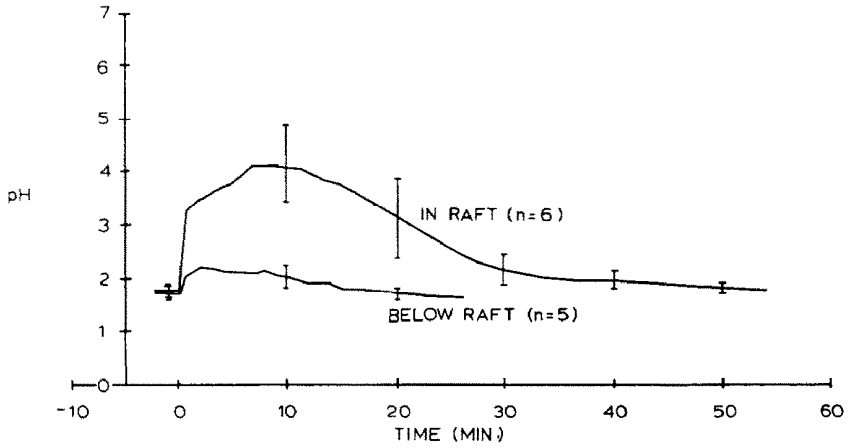

Fig. 6. Antacid neutralization trace for 10 ml 'Liquid Gaviscon' in the modified Rossett and Rice test. Mean ± 1 S.D.; n = 5.

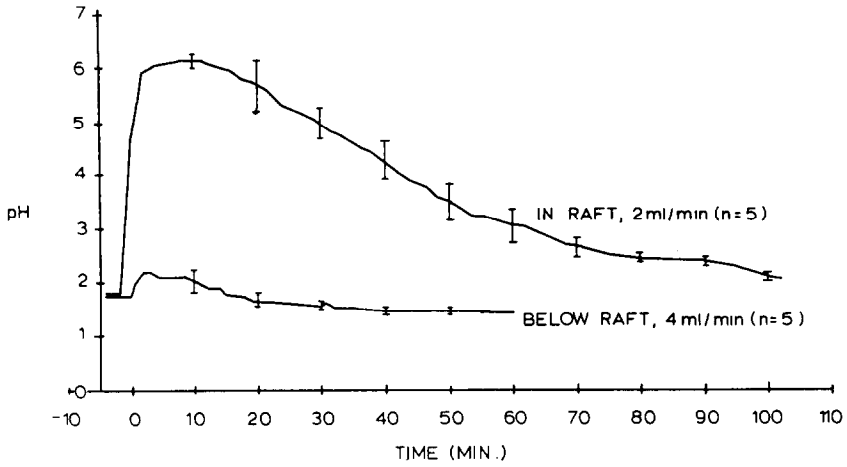

Fig. 7. Antacid neutralization trace for 10 ml 'Liquid Gaviscon' in the modified Rossett and Rice test; rate of acid turnover 2 ml/min. Mean ± 1 S.D.; n = 5.

The majority of the acid-secreting cells occur in the body of the stomach, decreasing towards the fundus. Since there is a relationship between the number of parietal cells in human gastric mucosa and the acid output (Card and Marks, 1960), it can be postulated that the buffering action of a floating formulation may be more prolonged when the bulk of the antacid formulation is positioned in the fundus. The parietal cell density at the top of the stomach is about half to two-thirds of that in the body of the stomach, and the total acid output at peak rates of secretion would be 24 mmol H^+/hour. Consequently the acid addition rate was reduced to 2 ml/min to mimic conditions in the fundus. The result of this experiment is shown in Fig. 7. Comparison of Figs. 4 and 7 shows that the in vivo results fall between the in vitro pH–time profiles obtained with acid addition rates of 2 and 4 ml/min.

In conclusion, modification of the Rossett and Rice test in the manner described produced better in vitro/in vivo correlation than the original test both for liquid and 'raft-forming' antacids. This indicates that such a test provides better prediction of in vivo performance in the design and quality control of antacid formulations.

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