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Effect of Alginate and Alginate-cimetidine Combination Therapy on Stimulated Postprandial Gastro-oesophageal Reflux

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Abstract

This randomized, single-blind cross-over study compared the effectiveness of a conventional alginate reflux barrier formulation (20 mL single dose of Liquid Gaviscon; sodium alginate, sodium bicarbonate, calcium carbonate) with a 20 mL single dose of an alginate-cimetidine combination formulation (Algitec Suspension; sodium alginate, cimetidine) in the suppression of food and acid reflux into the oesophagus after a test meal in 12 healthy volunteers.

Subjects were fasted overnight before the study. A pH electrode and gamma detector were accurately positioned 5 cm above the cardia. The volunteers received a ^{99m}Tc-labelled meal designed to provoke reflux and then either remained untreated, or 30 min later were given either Algitec Suspension or Liquid Gaviscon. Reflux of both food and acid into the oesophagus was measured for 3 h. There was a seven day wash-out period between each treatment.

Food reflux in the control group was 22 878 ± 14 385 counts × 10^3 and this was significantly suppressed by both Liquid Gaviscon (174 ± 128 (s.e.) counts × 10^3; $P = 0.003$); however, although the reduction of food reflux to 3812 ± 2322 counts × 10^3 observed after Algitec treatment was considerable, this did not reach statistical significance ($P > 0.05$) due to the large intersubject variation. Liquid Gaviscon was significantly better at reducing food reflux than Algitec ($P = 0.001$). Gaviscon also significantly reduced acid reflux when compared with the control group (1.08 ± 0.73 vs 5.87 ± 3.27% recording time oesophageal pH < 4, respectively) ($P = 0.03$). The slight reduction in acid reflux after Algitec treatment (3.25 ± 1.82% recording time oesophageal pH < 4) also did not reach statistical significance. The difference between Algitec and Gaviscon treatment was also not significant.

Sandmark & Zenk (1964) demonstrated that a tablet containing alginic acid, sodium bicarbonate and antacids when chewed would form a near neutral foam or raft which floated on the gastric contents. This was highly effective in relieving the symptoms of oesophagitis in patients with hiatus hernia and this was the beginning of a new type of therapy for gastro-oesophageal reflux, the anti-reflux agents. Subsequently there have been numerous variations of the original formulation.

Liquid Gaviscon is unique among these formulations in that it does not contain particulate antacids such as aluminium hydroxide and consequently it forms a strong cohesive raft. Interestingly, once a raft has formed within the stomach, although the raft itself may have a high pH, the pH of the bulk of the gastric contents remains unchanged (Beckloff et al 1972; Goodall et al 1977; Hasan 1980). Inclusion of conventional antacid materials such as aluminium hydroxide into the alginate in an attempt to neutralize gastric acid not only markedly decreases the physical strength of the barrier and floatation of the raft, but entrapment of the antacid by the alginate renders it unavailable for neutralization (Washington et al 1986). The overall result is that the antacid-alginate suspensions perform poorly in-vivo, forming neither a floating raft on the gastric contents nor suppressing reflux of gastric acid or food into the oesophagus (Washington et al 1987, 1992).

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It has been suggested that co-prescription of an H_2-antagonist and anti-reflux agents, or an H_2-antagonist-alginate combination formulation, would provide an alternative means to antacids of reducing gastric acid concentrations during alginate therapy. The present study has been carried out to assess the efficacy of an H_2-antagonist-alginate combination (Algitec Suspension, SmithKline Beecham) in the suppression of postprandial reflux, using Liquid Gaviscon (Reckitt and Colman Products) as a positive control. This was performed using a technique developed at Nottingham, which simultaneously measures oesophageal pH using a conventional nasogastric pH probe, and the reflux of radiolabelled food using an externally mounted collimated gamma detector, in ambulatory subjects.

Materials and Methods

Volunteer selection

The study was performed in 12 normal, healthy non-patient volunteers recruited from the Nottingham University student population. Age range was 19 to 30 years. All subjects were screened by a fully qualified medical practitioner for fitness to participate in the study before entry. The physical examination included heart rate, height, weight, blood pressure, respiratory rate and general examination. A full medical history was taken. Blood samples were taken for haematological and clinical chemistry analysis and a urine analysis was performed using Clinitest test strips. A screen for drugs of abuse was performed. On each study morning,

females were given a pregnancy test and were only accepted into the study if the result was negative.

Written and verbal information as to the nature of the experiment was provided for the volunteers before entry into the trial. The volunteers gave written and informed consent to participate in the trial. They were advised that they were free to leave at any time throughout the duration of the trial. Approval for the trial was granted from the Nottingham University Ethical Committee and the Department of Health. The study was conducted in accordance with the Declaration of Helsinki. The total effective radiation dose equivalent for each subject for the completed study was 0·18 mSv.

Study medication

Liquid Gaviscon comprised 1000 mg sodium alginate, 534 mg sodium bicarbonate and 320 mg calcium carbonate per 20 mL dose (Reckitt and Colman Products, Batch no JO8686). Algitec Suspension comprised 1000 mg sodium alginate and 400 mg cimetidine per 20 mL dose (SmithKline Beecham, Batch No BN77443).

The study medication was supplied in standard bottles from which 20-mL doses were dispensed immediately before administration. The subjects took the medication from calibrated syringes, so that the full dose was delivered in each case, regardless of the viscosity of the formulation.

Raft strength

The raft strength of the Algitec Suspension and Liquid Gaviscon was measured in-vitro using the apparatus described by Washington et al (1986).

Study procedure

A pH probe (Radiometer, Copenhagen) was calibrated at pH 1·68 and 7·0, according to the manufacturer's instructions, and sterilized. It was then marked 5 cm from the end using approximately 0·5 MBq ^{99m}Tc dried onto a 5-mm square of filter paper, and secured using waterproof tape.

Subjects fasted overnight if the study was carried out in the morning, or for 6 h before an afternoon study. Upon arrival in the department, the pH probe was passed nasogastrically into the stomach. Using the change in pH between the stomach and oesophagus, the tip was positioned approximately 5 cm from the cardia. Accurate positioning of the pH probe was then carried out in front of a gamma camera (IGE Maxicamera II) which was fitted with a low energy collimator and optimized for ^{99m}Tc. The subjects swallowed 100 mL water, labelled with approximately 0·5 MBq ^{99m}Tc-diethylenetriaminepentaacetic acid, whilst standing in front of the gamma camera in order to outline their stomach. The pH probe was then adjusted to position the marker on the probe 10 cm above the cardia, i.e. to position the tip 5 cm above the cardia. A small external source of ^{99m}Tc was used to locate a position on the chest wall approximately 5 cm from the cardia (i.e. directly over the tip of the pH probe). The external gamma detector was placed in this position and the source removed; the detector was then secured using an elasticated belt. Both the pH probe and the gamma detector were connected to a two-channel solid-state recorder (Novo Memolog; Vertec Scientific Ltd, Reading), the timebase was set to 15 s and baseline values were recorded for 20 min.

Subjects ingested the radiolabelled meal (Washington et al 1992, 1993a) and were then either left untreated, or 30 min after the meal they were given 20 mL of either Liquid Gaviscon or Algitec Suspension. The subjects were then free to resume their normal activities. Recording of data took place for a minimum of 3 h after which the equipment was removed and the calibration of the pH probe was checked. The cross-over studies between the two treatments and control were performed one week apart and allocation to the treatment group was randomized.

Data assessment

At the end of the recording period, the data were transferred to an Apple Macintosh computer for analysis. The time for which the oesophageal pH was below 4 after the meal was consumed was calculated as a percentage of the total postprandial recording time. All calculations were carried out using the spreadsheet Excel (Microsoft).

The refluxed activity was corrected for decay and a baseline rejection was performed using the algorithm described in previous studies (Washington et al 1992, 1993a). The total food refluxed during the experiment was represented by the area under the activity-time curve, once the baseline rejection had been performed.

Data was not normally distributed, and a range of common transformations (such as the addition of a small constant and log transformation) did not normalize the data. Consequently all comparisons were made using a Wilcoxon Signed Rank test.

Results

Raft strength measurement

The comparative raft strengths for 10 mL Algitec and 10 mL Gaviscon raft were $1{\cdot}36 \pm 0{\cdot}68$ and $2{\cdot}86 \pm 0{\cdot}51$ g (mean ± s.d.), respectively.

Demographic data

Seven male and five female subjects were entered into the trial (Table 1).

Evaluation of acid and food suppression

There was no detectable correlation of food and acid reflux events. Liquid Gaviscon significantly suppressed the reflux of the radiolabelled food (174 ± 128 (s.e.) counts $\times 10^3$) when compared with the control group ($22\,878 \pm 14\,385$ counts $\times 10^3$; $P = 0{\cdot}003$) and the Algitec-treated group (3812 ± 2322 counts $\times 10^3$) ($P = 0{\cdot}001$). The reduction of food reflux observed after Algitec treatment compared with controls did not reach statistical significance ($P > 0{\cdot}05$). Gaviscon significantly reduced acid reflux when

Table 1. Demographic data of subjects in the trial.

	Age (years)	Weight (kg)	Height (cm)
Mean ± s.e.m.	22·1 ± 0·9	68·5 ± 2·7	174·8 ± 2·0
Range	19–30	51–83	161–188

compared with controls (1·08 ± 0·73 and 5·87 ± 3·27% recording time pH < 4) ($P = 0·03$). There was no significant change in acid reflux after Algitec treatment (3·25 ± 1·82% recording time pH < 4, $P > 0·05$) and the difference between Algitec and Gaviscon treatment was also not significant ($P > 0·05$).

No adverse effects were reported in the study.

Discussion

The poor correlation of food and acid reflux observed in this study has also been reported using conventional gamma scintigraphy and interestingly, more reflux is observed with scintigraphy than with simultaneous oesophageal pH monitoring, particularly during the first half-hour period after feeding. It has been suggested that the two techniques explore different phases of reflux with scintigraphy detecting the reflux of buffered gastric contents (Tolia et al 1990; Shay et al 1992; Vandenplas et al 1992; Orenstein et al 1993). The phenomenon of independent food and acid reflux implies incomplete mixing of food and acid in the stomach, and further shows the inadequacy of reflux diagnosis methods that depend on pH detection alone (Washington et al 1993a).

In the current study, Liquid Gaviscon significantly reduced reflux of both radiolabelled food and acid to 0·5 and 17%, respectively, of control values. This is in agreement with previously published data from our group (Washington 1990; Washington et al 1992), which demonstrated that the same dose of Liquid Gaviscon reduced food and acid reflux to 1·3–10 and 0·88–16% (interquartile range), respectively, of control values.

The large variation in the data and that of the controls, did not allow a conclusion to be made on the effect of Algitec Suspension on food and acid reflux. It is possible that a regular dosing regimen of a cimetidine-containing formulation may raise gastric pH sufficiently to enhance the trends observed. Four hundred milligrams of cimetidine given intravenously at 6-h intervals will raise gastric acidity from a median of pH 1·8 to 4·7 (Reynolds et al 1987). Unfortunately, anti-reflux medications are often used by the general public to provide symptomatic relief and are not taken regularly; hence formulations of this type should be effective on a single-dose basis if they are to be of clinical benefit.

There is some evidence to suggest that addition of cimetidine to anti-reflux agents reduces acid exposure to the oesophagus more effectively than either of the treatments alone (Bennett et al 1988; Ericksen et al 1988a, b). The combined alginate-cimetidine formulation has no additional benefit over cimetidine alone in the healing of oesophagitis, but it has been shown to produce better symptomatic relief, despite the fact that there is only half the dose of cimetidine in the alginate-cimetidine formulation compared with the standard cimetidine treatment (Kennedy & Keeling 1988; Cooperative Oesophageal Group 1991). Cimetidine-alginate combinations are also reported to provide better symptomatic relief than alginic acid-antacid combinations (Lennox et al 1988).

The degree of cross-linking within the alginate by calcium controls the raft strength but it also affects the rate of release of cimetidine; indeed alginate is commonly used within the pharmaceutical industry as a matrix base for controlled and sustained release formulations. There is some evidence that cimetidine absorption from the combined alginate-cimetidine formulation is decreased and slowed (Boyko & Lamb 1988). In an earlier study, co-administration of cimetidine and Liquid Gaviscon in two separate formulations did not affect the bioavailability of the cimetidine (Britton et al 1991). The raft strength of Algitec (1·36 ± 0·68 g) was approximately half that of Liquid Gaviscon and this could explain the relative efficacies of the formulations in reducing food reflux

The behaviour of alginate-H_2-receptor antagonist combinations is likely to be significantly more complex than that of simple alginate or alginate-antacid combinations for a number of reasons. For example, a study carried out by Goodall & Temple (1980) reported that cimetidine increased lower oesophageal sphincter tone in patients with reflux oesophagitis; however, this was not observed in normal subjects. The reduction of food reflux observed in the present study could be a combination of suppression of reflux produced by the alginate raft and delivery of the cimetidine to the lower oesophageal sphincter by the refluxed raft material in sufficient concentration to produce increased pressure in the normal subjects. Ranitidine also increases sphincter pressure after intravenous administration of the drug, possibly via a cholinergic-like mechanism (Bertaccini et al 1981).

Concern was expressed that, if used in the long term, the inhibition of acid secretion by cimetidine would interfere with Gaviscon's ability to form a raft, since it requires gastric acid to achieve floatation. A recent study by this group demonstrated that Liquid Gaviscon still formed a raft after 7 days pretreatment with cimetidine (400 mg, four times daily (Washington et al 1993b)). Single-dose users of these formulations are unlikely to experience these problems since the sodium alginate reacts with the gastric acid within minutes of dosing (Washington et al 1987). It will thus be appreciated that the H_2-receptor antagonist and the alginate may interact in a complex manner. The alginate may influence the delivery or bioavailability of the cimetidine component, which in turn may affect gastric acidity and thus raft floatation.

The present study has demonstrated that Liquid Gaviscon is superior to Algitec in the prevention of reflux in a single-dose situation, which is important since alginate formulations are used largely to provide symptomatic relief on an as-needed basis. Indeed, the maximum potential efficacy of these materials is often not assessed for this reason. In the case of the alginate-cimetidine combination, a rigorous dosing schedule may give rise to improved benefit from the medication.

Conclusions

The addition of an H_2-receptor antagonist to an alginate provides a reduction in food reflux when given as a single dose, but this is not as great as that produced by the alginate alone. Due to the large variability in the data obtained after cimetidine-alginate treatment, the reduction in acid reflux was not significantly different between the two treatments. It is likely that several doses of cimetidine are required to

achieve full benefit of the medication, whereas the formation of a physical barrier on the gastric contents by the alginate allows an immediate action.

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