An Antacid Preparation in the Treatment of Duodenal Ulcer

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Gaviscon is an antacid preparation containing alginic acid, sodium alginate, sodium bicarbonate, magnesium trisilicate and aluminium hydroxide. It forms a viscous, alkaline foam that floats on the gastric contents and significantly reduces post-prandial and night pain in patients with gastro-oesophageal reflux (Barnardo *et al.*, 1975). The pH of the gastric contents below the foam is unaltered (Beckloff *et al.*, 1972) so the effects of Gaviscon may be due to placement of the antacid foam at the lower end of the oesophagus (Beeley and Warer, 1972; Stanciu and Bennett, 1974).

Since the epigastric pain associated with duodenal ulceration can be reproduced by acid in the lower end of the oesophagus (Earlam, 1970), Gaviscon might be expected to give symptomatic relief as a result of its antacid action at this site – especially as the presence of acid in the oesophagus stimulates acid production by the stomach (Ward *et al.*, 1970). One clinical trial has suggested that Gaviscon increases the rate of healing of duodenal ulcers as well as relieving symptoms (Moshal, 1973), but the data were insufficient to allow the report to be evaluated. The present trial was designed to test the hypothesis that Gaviscon gives symptomatic relief from the pain of duodenal ulcer, even though it does not alter the pH of the gastric contents below the foam.

Patients and Methods

Patients were admitted to the trial during exacerbations of the pain of a duodenal ulcer that had been diagnosed radiologically or endoscopically within the previous 3 years. Patients with hiatus hernia, concomitant gastric ulcer, low intelligence, or those taking regular anti-inflammatory drugs or corticosteroids were excluded. Patients who were subsequently admitted to hospital for complications of ulcer, or who failed to complete correctly the assessment forms were withdrawn.

The trial was designed to compare Gaviscon firstly with a tablet of identical composition except for the alginate and alginic acid – this, we called a placebo even though it contained as

much antacid as the standard Gaviscon tablet – and secondly with magnesium trisilicate compound tablets BPC. Patients were instructed to chew 2 tablets 4 times daily after each meal. Trial preparations were made to look and taste the same but were presented in foil packs of distinctive colours. This made the patients aware of those days during the trial when the treatments were similar and so helped him form an opinion about them. To prevent the physicians from identifying the treatments the correspondence between the colour of the foil packs and their contents was varied from patient to patient. Each day's treatment was packaged separately and labelled sequentially to improve patient compliance.

If the ability of Gaviscon to relieve pain is due to its ability to increase the pH at the lower end of the oesophagus, any beneficial effect should appear within an hour of starting treatment. Twenty-four hours was chosen as the length of a treatment period because of the diurnal variation in symptoms and the speed with which the effect of treatment was established.

To increase the number of within-patient comparisons each of the 3 treatments was given for periods of one day in 8 blocks of 3 days in an incomplete Latin square designed to minimize the effects of order.

Patients were allowed free access to 'rescue' antacid tablets of magnesium trisilicate compound. Although identical in composition to the trial antacid treatment, these rescue tablets were smaller and were supplied separately in a bottle. Patients were told to take their trial tablets regularly and as many rescue antacid tablets as they needed to keep themselves free from pain. They were given a diary card on which they recorded the number of rescue antacids taken for each day of the trial, the presence of indigestion, heartburn and acid regurgitation into the throat during the day and night, and the overall severity of their indigestion on a visual analog scale (Earlam *et al.*) They were also asked to record their comments about treatment in response to the question 'We need to know if the tablets are agreeing with you. Is there anything else you would like to tell us about your treatment this week?'

Wilcoxon and Mann-Whitney U tests were used for within and between patient comparisons respectively. Two-tailed tests were used throughout and the significance level was preset at $2\alpha=0{\cdot}05$.

Results

Five centres contributed a total of 62 patients – 21 women and 41 men. Nineteen patients failed to complete the trial or returned diary cards that were unsuitable for analysis. There were no significant differences between centres either with respect to the numbers of patients withdrawn or the severity of symptoms in those who completed the trial.

Overall Severity of Indigestion

There was no difference between any of the treatments with respect to global indigestion rating on the analog scales. Some of the patients were unable to keep themselves pain-free even if they took more than 100 rescue antacid tablets per week. Others persistently recorded symptoms of severe indigestion but took few rescue antacids. In general the patients who took the greatest number of rescue antacids also recorded the most severe indigestion.

Consumption of Rescue Antacids

The distribution of individual differences for rescue antacid consumption between the Gaviscon, placebo and antacid groups were skewed; they were therefore expressed as median rather than mean differences. During the whole of the 8 Gaviscon treatment periods the median rescue antacid consumption was 3 tablets less than during the placebo period and one less than during the antacid period. During treatment with trial antacid the patients took one fewer rescue antacid tablet than during the placebo period.

The difference between Gaviscon and placebo was significant ($p<0{\cdot}05$); neither of the other differences reached significance at this level. Rescue antacid consumption showed a tendency to fall towards the end of each week of the trial, but this effect was not seen in patients whose symptoms were still persisting at the end of the trial period (fig. 1). The data also suggested that patients with persistent symptoms got better relief from Gaviscon than those whose attacks of pain were brief ($p=0{\cdot}06$).

Patients' Comments

The number of spontaneous reports fall into the 4 categories shown in figure 2. Since each patient took every treatment on 8 occasions, there is a maximum of 8 possible reports for each patient for each treatment for the categories 1 to 3. Gaviscon was associated with a significantly greater total number of unwanted effects than

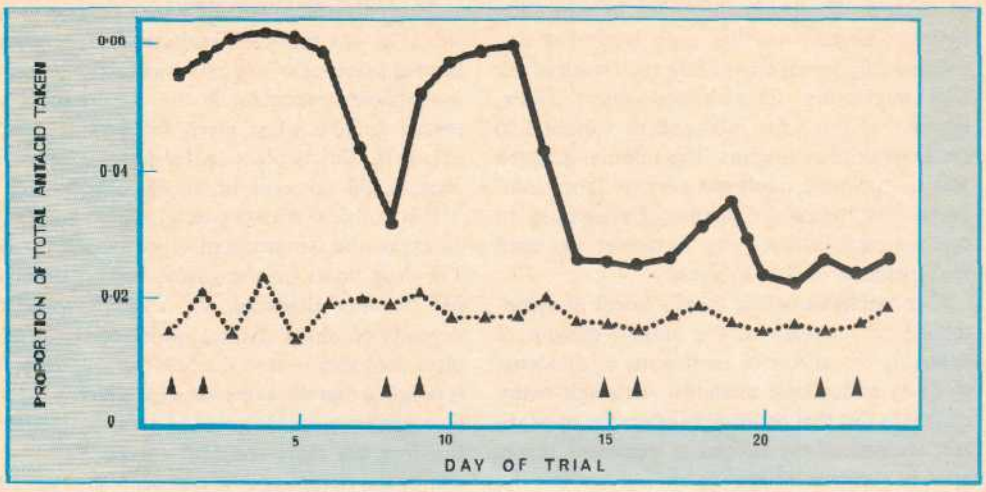


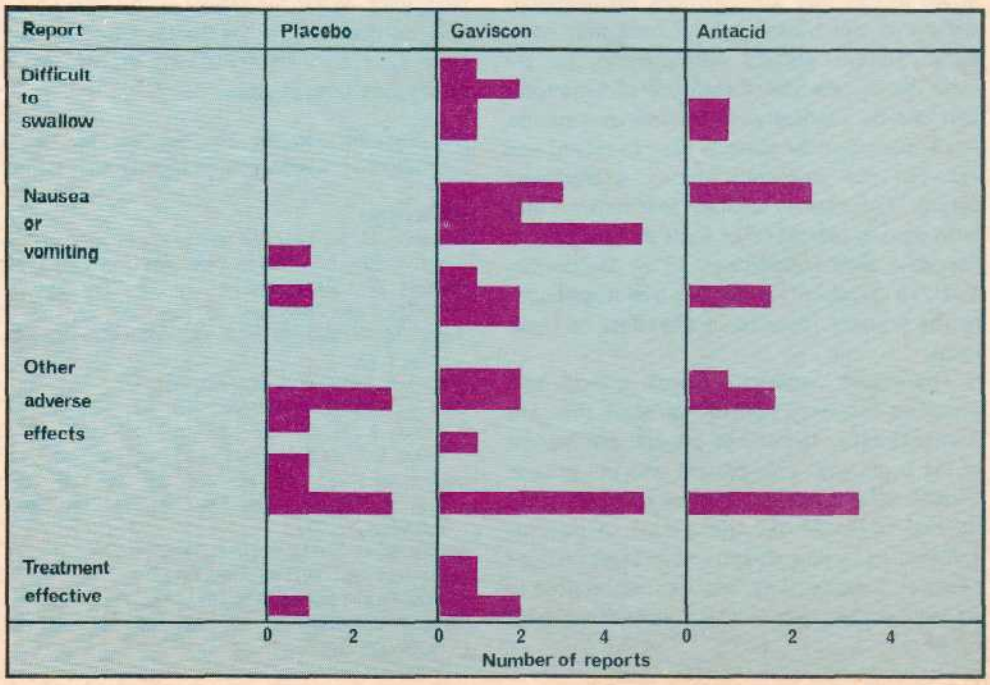
FIG. 1 – Proportion of the total 'rescue' antacids consumed for each day of the trial

either of the other two treatments. Nausea and vomiting were significantly more common. There was, however, no difference between the treatments with respect to waking at night. The response to Gaviscon was not influenced by the length of history, age or site of the pain. Patients who complained of heartburn and acid regurgitation responded no better than those without.

Discussion

Clinical trials are designed to give every treatment an equal chance of success. Most exacerbations of the pain of a duodenal ulcer last less than 3 weeks. Treatments given during the early period of the exacerbation when the symptoms are worsening stand a smaller chance of giving relief than those taken later when the patient is recovering. If the 3 treatments used in this trial had been given for periods of one week they would not all have been given an equal chance

FIG. 2 – Number of spontaneous reports about 4 categories of treatment effect. Each row represents the reports of one patient. Patients who made no reports are not represented



of success. Balancing the order of allocation between patients so that each treatment was used equally frequently during each week of the trial might not have helped much either, because of the large inter-patient variation in the severity of symptoms. The solution adopted was to make the treatment periods short compared with the rate of change of symptoms so that for each patient every treatment was used for symptoms of similar severity.

Our emphasis on the measurement of symptoms runs contrary to the present custom of assessing the effects of treatments in duodenal ulcer by endoscopic methods. Although many clinicians feel that endoscopy offers the most direct evidence of the benefits of treatment, this is open to question. In routine clinical practice the decision to treat these patients usually depends entirely on symptoms and not on the endoscopic appearances. It is for this reason that asymptomatic patients are not subjected to repeated endoscopy. A treatment that gives better relief of pain is preferred by the patient and by the physician. Endoscopic appearances are of secondary interest.

Measurement of symptoms by visual analog scales has not been widely applied in gastroenterological trials. The 'global indigestion' rating used in our trial proved disappointing probably because of its lack of specificity and poor standardization. The analysis of data collected in this way also provides mathematical difficulties which have not yet been fully overcome. Rescue antacid consumption, on the other hand, provides a measure of symptoms that can be handled as a continuous variable, has unequivocal meaning, is easy to record and can be used frequently during a treatment period. The rescue antacid consumption has been used in several other trials of treatment in duodenal ulcer (Landecker, 1976; Multicentre Trial, 1975) and in the present trial it was used as the primary measure of the effect of treatment.

The overall pattern of rescue antacid consumption showed a periodic variation that was lowest towards the end of a week and highest at the beginning. This pattern was not seen in patients whose symptoms were still present at the end of the 24-day trial period. A possible explanation is that patients with exacerbations of short duration may be more susceptible to environmental stresses which vary throughout the week.

The only treatment difference to emerge in this trial was between Gaviscon and its placebo; the presence of alginate was responsible for a significant reduction in the consumption of rescue antacid when given for periods of 24 hours. In clinical practice the duration of treatment would, however, be considerably longer.

It is not clear why Gaviscon should have any effects on the symptoms of duodenal ulcer at all. The drug floats on the gastric contents whose pH remains unaltered. Its neutralizing effect depends on direct contact, which for duodenal ulcer probably occurs for brief periods only. It is possible that the symptoms for which patients took rescue antacids arose in an area to which the drug has more constant access. The lower end of the oesophagus is one such site, yet patients with symptoms of heartburn and acid regurgitation showed no more benefit than those without. However, it seems that the total acid output during pentagastrin stimulation may be reduced after single doses of Gaviscon (Moshal, 1973) and that increasing the pH of the oesophagus may reduce gastric acid output (Ward *et al.*, 1970). We have no data that might associate a fall in acid output with a reduction in antacid consumption. It may be that the effect of Gaviscon is unrelated to its local neutralizing ability but lies in some property of the alginate which has not yet been described or it may possibly act on the duodenal ulcer itself. While the results of this trial do not help us decide how Gaviscon works in duodenal ulcer, they are sufficiently encouraging to justify long-term studies.

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