Is antral gastrin important in the resistance of duodenal ulcers to H2 receptor antagonists or in recurrent ulceration after highly selective vagotomy?

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Abstract
Basal serum gastrin, integrated gastrin response to a meal, and integrated gastrin response to insulin induced hypoglycaemia were measured in 60 patients with duodenal ulcer before and after elective highly selective vagotomy to determine whether antral gastrin has a role in resistance to H2 receptor antagonist treatment which the patients had received before surgery or in the development of recurrent ulceration after vagotomy.

The basal gastrin, integrated gastrin response to a meal, and the integrated gastrin response to insulin were similar in patients whose ulcers healed after H2 receptor antagonist treatment or were refractory to at least three months of this treatment. The same parameters measured before or after highly selective vagotomy were similar in patients who eventually developed recurrent ulceration compared with those who did not. As expected the basal and meal stimulated (but not insulin stimulated) serum gastrin values increased after highly selective vagotomy. Ulcer patients with particularly high gastrin values (whether basal or stimulated) were not more resistant to H2 receptor antagonist treatment or prone to develop ulcer recurrence after highly selective vagotomy.

This study suggests that antral gastrin is not important in ‘resistance’ of duodenal ulceration either to H2 receptor antagonist treatment or to highly selective vagotomy.

In 1972 Polak described a patient with duodenal ulceration, hypergastrinaemia of antral origin, and hyperplasia of the antral G cells.1 She thus raised the possibility that gastrin may have a role in the pathophysiology of duodenal ulcer disease, other than in those patients with the rare Zollinger Ellison syndrome. Although there have been subsequent reports2 that seem to support the existence of such a syndrome, the role of gastrin in ordinary peptic ulcer disease remains uncertain.4

The treatment of duodenal ulceration has changed dramatically in recent years since the advent of H2 receptor antagonists. These powerful drugs are effective in suppressing gastric acid secretion and most duodenal ulcers can now be healed by medical treatment.5 Patients whose duodenal ulcers will not heal are frequently referred for surgical treatment but there is some evidence that they have a high incidence of recurrent ulceration after elective surgery,6 7 though other authors would not agree.8 9 This uncertainty makes it clinically important to know whether a patient’s ulcer will heal after treatment with H2 receptor antagonists and whether the ulcer will recur after surgical treatment, should this prove necessary.

To clarify the role of antral gastrin in resistant duodenal ulcers, we have performed a prospective study of basal, meal stimulated (luminal stimulus), and insulin stimulated (vagal stimulus) serum gastrin before and after highly selective vagotomy performed electively for duodenal ulceration.

Patients and methods
We studied 60 patients with duodenal ulceration confirmed by endoscopy who had been referred for elective surgery. Forty nine were men and 11 were women. Their mean age was 42 (17–69) years. In 24 of the patients the ulcer had failed to heal in spite of three months’ treatment with an H2 receptor antagonist in full dosage (cimetidine 1 g per day or ranitidine 300 mg per day). In the remaining 36 patients surgery was performed because of frequent, early, symptomatic ulcer relapses when the H2 receptor antagonist treatment was stopped. All 60 patients had a highly selective vagotomy performed as described previously10 and were then followed up for four to six years at a gastric follow up clinic to detect symptomatic recurrence. Asymptomatic recurrence was not sought by routine gastroduodenoscopy.

The patients in this study are a sub-group of a larger population reported in more detail elsewhere in whom highly selective vagotomy has been performed.11

GASTRIN STUDIES
Basal (fasting) serum gastrin, meal stimulated, and insulin stimulated gastrin were measured before and again after surgery. In the case of insulin stimulated gastrin, the measurement was repeated seven days after operation, but the meal test was not performed until one to two months had elapsed.

A meal stimulated gastrin test was performed after an overnight fast. Blood samples for gastrin assay were taken before the test meal and at 15, 30, 45, 60, 90, and 120 minutes after the meal using an indwelling cannula in a large antecubital fossa vein. The test meal consisted of steak and potatoes containing 34 g of protein, and was consumed over 15 minutes. A blood sample was taken for gastrin assay before the performance of a combined insulin
pentagastrin test (see below) and after giving insulin. Samples were also taken at 15, 30, 45, 60, 90, and 120 minutes. All samples were allowed to clot at room temperature and were then centrifuged to separate the serum. Samples were stored at −20°C until assayed.

Gastrin was measured by radioimmunoassay using antiserum AB4562 (kindly provided by Professor Rehfeld, Copenhagen) and synthetic gastrin 17 (National Institute of Biological Standards and Control) as control. The antiserum showed a 70% cross reactivity with gastrin 34 but less than 5% cross reactivity with cholecystokinin.

A combined insulin pentagastrin test was performed before and seven days after operation as described previously.11

ANALYSIS OF DATA
The integrated gastrin response to the meal and to insulin was calculated from the area under the curve, in which the serum gastrin was plotted against time. Statistical analysis was carried out on an Amdahl computer using SAS software. Non-parametric statistical methods were used throughout.

Informed consent was given by each patient before the performance of these studies.

Results
The results of the gastrin studies performed before surgery are shown in Figures 1 to 3 and are subdivided according to whether the patients’ ulcers were resistant to or healed after treatment with H2 receptor antagonists. No significant differences were found between the basal, meal-stimulated, and insulin-stimulated gastrin values of patients whose ulcers healed in response to treatment and those who had refractory ulcers. There was no evidence that patients with gastrin values near the upper end of the normal range were more likely to belong to the refractory group than patients whose gastrin values were average or low.

The serum gastrin values in patients with and without recurrent ulceration after follow up of at least five years after highly selective vagotomy are shown in Figures 4 to 6. The results of the tests performed both before and after surgery are shown. Both basal and meal stimulated gastrin values increased significantly after highly selective vagotomy (p<0.001) but the response to insulin remained unchanged. No difference was found between the serum gastrin values of patients who developed recurrent ulceration and those of patients who did not. Patients with the highest gastrin values showed no significant tendency to recurrent ulceration.

The results of the gastric secretory studies in these patients are essentially as reported elsewhere.7 To determine whether there was any relation between serum gastrin and gastric acid secretion, multiple comparisons were made between the results of the gastrin studies (basal, meal, and insulin stimulated) and the results of the gastric secretory studies, using Spearman’s rank order correlation. The data used in these comparisons were basal acid output, peak acid response to insulin, and peak acid response to pentagastrin, both before and after surgery, and also the percentage reductions of each of these parameters after highly selective vagotomy. In none of these comparisons was any statistically significant correlation identified between serum gastrin and gastric acid output before or after surgery.

Discussion
These results do not establish a prominent role for antral gastrin in either resistance of duodenal ulcers to treatment with H2 receptor antagonists or the development of recurrent ulceration after highly selective vagotomy. Before surgery, the basal, meal stimulated, and insulin stimulated serum gastrin values of patients whose ulcers healed after treatment with H2 receptor antagonists were similar to the values in patients with refractory ulcers. After highly selective vagotomy, too, serum gastrin values were similar in patients with and without recurrent ulceration. This was true of the gastrin studies performed both before and after surgery.
The methods used to elicit a serum gastrin response were as simple as possible—either allowing the patient to eat a standard meal or by insulin-induced hypoglycaemia. The meal test provides a luminal stimulus to gastrin release in the main, although vagal and other influences may play some part in the response. Similarly, insulin-stimulated hypoglycaemia elicits a response that is mainly vagal in origin, though the local effects on antral mucosa of the acid released by the stimulus and circulating adrenaline may both play some part. No attempt was made to regulate intragastric pH during these studies, as has been done by others who used the technique of intragastric titration during instillation of a standard fluid meal. Our technique for assessing the gastrin response to a meal, however, is at least physiological, and although some subtleties of the relation between gastric acid and gastrin may not have been explored by this technique, the results obtained provide a good indication of the gastrin responses of patients who are eating normal meals. In addition, detailed examination of our data does not suggest that refinements in investigative techniques would support a role for gastrin in the resistant ulcer, since patients with the highest gastrin values tended to be in the groups who responded well to both H₂ receptor antagonist treatment and to highly selective vagotomy.

All the patients in this series required surgical treatment. It may therefore be argued that the basal and stimulated gastrin values may be abnormally high for the group as a whole when compared with patients with less resistant ulcers. This, in turn, could influence the relapse rate while on medical treatment and thus the need for surgery. Our limited observations on the gastrin values in patients who do not require surgery for their duodenal ulcers suggest, however, that this is not the case. More importantly, the various reports on basal and meal stimulated gastrin values in duodenal ulcer patients and reviewed by Walsh show mean basal values between 13 and 91 pg/ml. Although variations in assay systems make comparisons difficult, the overall mean of these series is virtually identical to our own. Similarly the meal stimulus, although calculated as a peak rather than an integrated response, is very similar to that observed in our own patients.

How the finding that some patients with duodenal ulceration have raised gastrin values relates to the previously proposed G cell hyperplasia/hyperfunction is unclear. It has often been shown that, as a group, the basal and meal-stimulated gastrin values do not differ between normal subjects and patients with duodenal ulcers. Some authors have suggested, however, that there exists a distinct subgroup of duodenal ulcer patients who are hypergastrinaemic. In our study it was noticeable that the patient with the highest basal gastrin value (302 pg/ml) also had the highest responses to the test meal and to insulin (1021 and 448 pg/ml respectively). Since there were only a few hypergastrinaemic patients in this series, however, it was not possible to determine whether this finding had any statistical validity. Certainly, for the group of patients as a whole, no significant correlation was found between basal gastrin values and the gastrin responses to a test meal or insulin. It seems likely that there is a continuous range of stimulated serum gastrin values in duodenal ulcer patients, from concentrations considered to be normal to values at which some previous authors have postulated the existence of a specific disease entity which has been called G cell hyperplasia. It is one of the principal findings of this study that the gastrin value is of little importance since the finding of high concentrations of gastrin does not indicate that an ulcer is likely to prove resistant to medical treatment or to recur after highly selective vagotomy. The only importance of a high basal gastrin value is that it raises the possibility that the patient may have a gastrinoma. This was not to be the case in any patient in this study.

The basal and meal-stimulated gastrin values increased after highly selective vagotomy. This is a well-recognised phenomenon, although it does not always seem to be related to a reduction in intragastric acidity and may be related to the destruction of some vagal inhibitory fibres. It is also well recognised that, in man, insulin-stimulated serum gastrin values do not increase after highly selective vagotomy.

We conclude that measurements of serum gastrin are of little value in the clinical management of patients with duodenal ulcer disease, except in those who suffer from the Zollinger-Ellison syndrome.

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