Gastric acid secretion and gastrin production in the short bowel syndrome

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SUMMARY Excess gastric acid secretion and gastrin production may occur in patients with the short bowel syndrome but the two measurements have never been made simultaneously in man in response to a food stimulus. Using the technique of intragastric titration, this was carried out in eight patients after extensive small bowel resection resulting mainly from vascular occlusion and in eight matched normal control subjects. Basal acid output and peak acid output in response to pentagastrin was also measured separately. Although peak and integrated serum gastrin concentrations were significantly greater in patients ($450 \pm SE 109$ pg/ml; $113 \pm 2.9 \times 10^{-3}$ pg/ml/min) compared with control subjects (174 ± 98 pg/ml; $6.1 \pm 2.0 \times 10^{-3}$ pg/ml/min $p < 0.05$), no concomitant increase in acid secretion was shown either during intragastric titration or in response to pentagastrin. These findings indicate that there is no rationale for treating these patients with long term anti-ulcer therapy.

Excessive secretion of gastric acid has been shown after extensive small bowel resection in both man and experimental animals.¹⁻⁴ This abnormality is considered to play an important role in the short bowel syndrome because it impairs intraluminal digestion. The low pH inactivates lipase, precipitates bile salts and damages small bowel mucosa.⁵ The effects of acid hypersecretion are considered to be so deleterious that in the past some surgeons recommended that vagotomy should be carried out simultaneously with the intestinal resection.^{6,7} With the advent of H_2 receptor antagonists a more conservative approach is now suggested.⁸

The acid hypersecretion is usually explained on the basis of raised concentrations of serum gastrin which have been found by some investigators.⁹⁻¹¹ This explanation can only remain a supposition, however, as these two measurements have never been made simultaneously in man in response to a meal stimulus.

The present study has used the method of intragastric titration¹² to achieve this aim. In addition the opportunity was taken to confirm a previous report⁴ which showed in man that acid hypersecretion occurred in response to pentagastrin.

Patients who had undergone extensive small

bowel resection were compared with a group of normal control subjects. In view of the possible influence that residual Crohn's disease in the small bowel might have on gastric secretion, most of the patients studied had undergone resection as a result of vascular occlusion.

Methods

PATIENT AND CONTROL SUBJECTS

Informed consent was obtained from all subjects. Eight patients (four men and four women) were studied and compared with eight normal subjects (four men and four women) without gastrointestinal disease, matched carefully for age (patients $60 \pm SE 4.5$ years; normal subjects 63 ± 4 years) and body weight (patients 62 ± 3.0 kg; normal subjects 64 ± 4.6 kg). Each patient had undergone extensive resection of the distal small bowel, a mean of 5.3 years (range 1-16 years) previously. The reason for excision was vascular occlusion either because of thrombus or embolus (five patients), strangulation within an incisional hernia (one patient) or pressure from a mesenteric cyst (one patient). One patient who was considered to have ischaemic bowel at operation, has since been shown to have Crohn's disease. The mean length of bowel resected was 2.3 metres (range 1.4-3.8 m) as measured at operation and 1.6 metres (range 1.0-3.0 m) as measured from the pathological specimen. Most patients had been

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maintained on total parenteral nutrition for a variable period after operation although this had ceased at the time of the study. Each patient did, however, complain of chronic diarrhoea.

INTRAGASTRIC TITRATION STUDY

After an overnight fast, a double lumen nasogastric tube was passed into the stomach and its position verified by the water recovery test. Basal gastric secretion was aspirated by continuous suction at 7–12 mm Hg negative pressure with a vacuum pump. Residual juice was collected for 15 minutes and discarded, basal secretion was then collected for four 15 minute periods. Basal acid concentration was determined by titration of 0.2 ml of juice with 0.2 N NaOH to pH 7.0.

A liquid test meal was prepared¹² by dissolving four standard red Oxo cubes (Brooke Bond Group plc) in 400 ml of water at 37° giving a 6.25% wv solution. The pH was adjusted to 5.5 by addition of 0.2 N NaOH if required. Validation experiments showed that the osmolality of the meal and the concentration of its constituents were reproducible. The coefficients of variation in the content of sodium, fat and nitrogen after solution, were 2.3%, 7.8% and 4.3% respectively.

Each meal was instilled into the stomach through one limb of the nasogastric tube by gravity over two minutes. After each meal, gastric acid secretion was measured for 60 minutes by the technique of intragastric titration¹³ as modified by Lam *et al*¹⁴ (Fig. 1).

Briefly this involved continually mixing the gastric contents by removing and reinserting 30 ml aliquots seven times per minute with an automatic syringe. The gastric contents were passed over a combined pH and reference electrode and intragastric pH was maintained at 5.5 with an automatic titrator which instilled 0.5 mol/l NaOH from an automatic burette through the other limb of the nasogastric tube. The number of mmol of HCl secreted was assumed to be equal to the number of mmol of NaOH necessary to maintain intragastric pH at 5.5.

After 60 minutes gastric contents were completely aspirated and the residual volume measured. Six millilitre samples of blood were taken from an antecubital vein at 0, 5, 10, 15, 30, 45, and 60 minutes. Each specimen was allowed to clot in a glass tube for one to two hours at room temperature. The clots were rimmed, the tube centrifuged and an aliquot of serum was stored at -20°C for subsequent assay. The procedure used was that described by Stadil *et al*¹⁵ and under these conditions no alteration in gastrin content occurs because of either temperature or protease activity before separation and storage.¹⁶ Serum gastrin was measured by radio immunoassay using the unique high

Fig. 1 Technique of intragastric titration.

titre antiserum (AB4362) found by Rehfeld.¹⁷ This antibody has a high specificity for both the G₁₇ and G₃₄ forms of gastrin.

ASPIRATION STUDY

On a separate day basal acid output (BAO) was measured as previously described and in addition pentagastrin acid output (PAO) in response to 6 µg/kg of pentagastrin administered subcutaneously was determined.¹⁸

STATISTICAL ANALYSIS

Differences in serum gastrin concentration and acid output between the two groups were analysed by the Wilcoxon's sum of ranks test for unpaired data. Correlation between measurements were analysed by Spearman's rank correlation.¹⁹ All results were expressed as mean ± SE.

Results

INTRAGASTRIC TITRATION STUDY

Acid output

The mean cumulative acid outputs are shown in Figure 2. There was a linear increase in acid output per unit time in both groups of subjects but no significant difference was demonstrated between them. The maximum acid output – that is, the total

Fig. 2 Cumulative acid output during period of intragastric titration. No significant difference between the groups.

acid secreted throughout the 60 minute period, in the patients was 12.3 ± 3.4 mmol and in the control subjects was 12.4 ± 3.2 mmol.

Serum gastrin concentrations

Mean fasting level of gastrin in patients was greater than in control subjects 107 ± 59 pg/ml: 14.9 ± 7.8 pg/min respectively ($p < 0.06$).

After ingestion of the meal, serum gastrin increased and reached a peak in both patients and controls at 5–10 minutes (Fig. 3).

The integrated gastrin response (calculated as the change in gastrin $\times$ time in minutes) was significantly greater in patients compared with controls, $113 \pm 2.9 \times 10^{-3}$ pg/ml/min and $6.1 \pm 2.9 \times 10^{-3}$ pg/ml/min respectively ($p < 0.05$).

Fig. 3 Serum gastrin concentrations during period of intragastric titration. Integrated and peak responses were significantly greater ($p < 0.05$) in patients after resection compared with control subjects.

Fig. 4 Significant correlation between maximum acid output and serum gastrin response in normal subjects $\square$ but not in patients after resection $\circ$. Correlation, however, in the normal subjects depends on one 'outlier'.

The same was true for the peak gastrin responses 450 ± 109 pg/ml in patients compared with 174 ± 98 in controls ($p < 0.05$).

Correlation of acid output and gastric concentration

There was a significant positive correlation between maximum acid output and integrated gastrin response in normal subjects ($p < 0.05$), but this was clearly dependent on one outlier (Fig. 4). There was no correlation in the patients.

Residual volumes

There was no significant difference in volumes of gastric contents remaining in the stomach after 60 minutes in control subjects or patients. Volumes were 151 ± 36.2 and 125 ± 23 ml respectively.

ASPIRATION STUDY

Mean BAO in control subjects was 3.8 ± 1.6 mmol/h and in patients was 3.7 ± 1.7 (NS). Mean PAO response to pentagastrin was 25.9 ± 3.5 mmol/h in control subjects and in patients was 19.9 ± 5.5 mmol/h (NS).

The results described above include the one patient with Crohn's disease. Exclusion of this patient does not affect the statistical conclusions.

Discussion

It is generally believed that after extensive resection of the small intestine in man there is an increase in the amount of gastric acid secreted. The abnormality has been explained by the finding that serum gastrin is raised in these patients. The results of our study although confirming the rise in serum gastrin

previously observed have been unable to show that this is associated with a concomitant increase in acid secretion.

The evidence for increased acid production has primarily been derived from animal experiments.^{1 3 20-22} Although several case reports document acid hypersecretion after extensive small bowel resection in man few studies have measured acid production in a controlled manner. Thus, Aber *et al*² carefully documented gastric secretion, urinary net hydrogen ion excretion and extracellular acid base state in one patient and concluded that acid hypersecretion resulted from resection. Similar conclusions were drawn by Krone *et al*²³ who found that the pH of jejunal contents in six patients after intestinal resection was low. Fielding *et al*⁴ in a more detailed study showed that BAO and PAO in response to pentagastrin were significantly increased in eight male patients who had had 60 cm or more of their distal ileum resected for Crohn's disease compared with four patients who had an intact gastrointestinal tract. It is not stated if the two groups were similar with respect to age, sex, or body weight, factors which are of great importance in the interpretation of data from acid secretion studies.²⁴

Our results are at variance from those reported by Fielding *et al*⁴ in so far as no significant difference in BAO and PAO could be shown between our two groups of subjects. Differences in study design might explain this discrepancy. First, our patients and control subjects were very carefully matched not only for age and sex but also for body weight. In addition seven of our eight patients did not have Crohn's disease and if the one exception is excluded the conclusions remain unchanged. In studies which include patients with Crohn's disease it is not possible to be sure if observed differences between groups are because of resection of small bowel or because of the presence of residual disease. It should be noted, however, that although acid studies do not seem to have been undertaken in patients with Crohn's disease, several studies have shown normal fasting and postprandial concentrations of gastrin.^{25 26}

Although several canine studies^{3 27-29} have examined acid output in response to a meal stimulus after small bowel resection, similar studies have not previously been done in man. Using the technique of intragastric titration we were able to do this, but as with measurements of PAO and BAO, we were unable to confirm those animal studies which showed hypersecretion. Although the method used did not utilise a solid meal, the meal stimulus did contain a balanced proportion of nutrients which are known to stimulate acid production by similar mechanisms.³⁰ The technique of intragastric titra-

tion can naturally be criticised as it manipulates intragastric pH and maintains it at a constant level. Nevertheless, it is more 'physiological' than aspiration techniques because not only can it measure acid secretion in response to food but it is not affected by changes in gastric emptying.³¹ The latter is of particular relevance in patients after ileal resection as recent studies suggest that the distal small bowel may control emptying by an inhibitory feedback mechanism.^{32 33} It is of interest that in a recent canine study which used a similar method of intragastric titration to measure acid secretion in response to liver extract, massive small bowel resection caused gastric acid hyposecretion. In addition the same study showed that pentagastrin stimulated acid secretion remained unchanged after resection.

Since some reports^{22 27 28 34 35} have shown that proximal resection was more likely to increase acid output than distal resection it might be considered that any discrepancy between our results and those of others was related to this factor. Most of our patients, however, had considerable lengths of small bowel removed and although the distal ileum had always been resected a significant proportion of jejunum had also been excised. With regard to the length and site of resection, therefore, our patients were similar to experimental animals that showed hypersecretion.^{36 21} Furthermore, in Fielding's study in man,⁴ hypersecretion occurred after 60 cm or more of distal small bowel had been resected. Allied to this point are the findings of Windsor *et al*³ who could not correlate the extent of resection with the hypersecretion which occurred in their patients.

The finding of increased concentrations of serum gastrin are in agreement with other studies.^{9 11} The cause is obscure. The fact that the concentration of gastrin is greater in arterial blood than in mesenteric veins draining the distal small bowel³⁷ suggests that the small bowel may be necessary for the metabolism of gastrin and that raised gastrin concentrations may be secondary to impaired degradation in this part of the gut. This hypothesis, however, seems unlikely. If there was a decreased degradation rate of gastrin in the patients there would be a prolonged delay involving the peak gastrin concentration and in its return towards basal levels. Yet the peak gastrin concentrations were achieved at the same time as in the control group and the subsequent fall off appeared similar in the two groups. Similar findings were noted by Strauss *et al*⁹ who, in fact, postulated that the cause for the hypergastrinaemia in their four patients might be because of the absence of an inhibitor in the small intestine. The likely candidates were considered at that time to be secretin, gastrointestinal inhibitory polypeptide and

cholecystokinin (CCK). As the former two hormones have been shown to be localised primarily in the duodenum and proximal jejunum^{37,38} it seems unlikely that they are implicated. On the other hand CCK has recently been shown to be present throughout the small bowel^{39,40} and this hormone may be culpable. Similarly, somatostatin, another inhibitor of gastrin⁴¹ which is found throughout the ileum may also be involved.³²

Whatever the cause of the raised concentrations of gastrin it is clear that in our patients they were not associated with acid hypersecretion. On the face of it this conclusion is further emphasised by the finding that whereas in normal subjects a positive correlation between serum gastrin and acid output existed this was not the case in the patients. Because, however, the correlation between these measurements in normal subjects was dependent on the one 'outlier' we are reluctant to draw firm conclusions from these data. The finding that acid secretion in response to exogenous pentagastrin was no different in patients and controls suggests that the fault is not an insensitivity of the parietal cell mass to endogenous gastrin. It may be that either an inhibitory substance to endogenous gastrin is present after resection or that the gastrin that is released is ineffective. The assay we used measured both G₁₇ and G₃₄. Because G₁₇ is mol for mol six times more potent in stimulating acid secretion than G₃₄,⁴² a rise in the latter of the magnitude found in our patients without a concomitant rise in G₁₇ would be unlikely to significantly affect acid secretion. This explanation would of course be dependent on the half lives of the two gastrins being identical in the resected group and the control group. This situation has been found to be the case in patients with chronic renal failure.⁴³

It is difficult to understand the purpose of the raised serum gastrin in these patients. It was considered at one time that because gastrin was trophic to gastrointestinal mucosa,^{44,45} it might play a role in the compensatory changes which occur in the residual small bowel.^{46,47} Current evidence, however, suggests that gastrin does not fulfil either a physiological or pathophysiological role in the medication of these changes.^{48,49}

From a clinical standpoint our findings are clear. Although no comment can be made about changes in the short term after extensive small bowel resection, in the long term acid hypersecretion does not occur. This finding also receives support from the fact that there is no clinical evidence which suggests an increased incidence of peptic ulceration in these patients. It therefore seems unnecessary to keep patients who have undergone this type of surgery on maintenance anti-ulcer therapy.

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