Serum gastrin in duodenal ulcer

M. G. KORMAN, C. SOVENY, AND J. HANSKY

From Monash University Department of Medicine, Prince Henry's Hospital, Melbourne, Australia

Part I Basal levels and effect of food and atropine

SUMMARY Fasting serum gastrin has been measured by radioimmunoassay in 72 patients with duodenal ulcer and compared with that in normals, patients with gastric ulcer, and with the Zollinger-Ellison syndrome. The mean ($\pm$ SEM) gastrin levels were 15.7 ± 1.5 pg/ml in the duodenal ulcer group, 32.1 ± 4.3 pg/ml in normals, 118 ± 18.1 pg/ml in gastric ulcer, and between 450 and 2,000 pg/ml in the Zollinger-Ellison syndrome. There were no difficulties in distinguishing simple ulcer from the Zollinger-Ellison syndrome as the presence of hyperchlorhydria in combination with hypergastrinaemia led to a confident diagnosis of the latter disease.

The effect of protein, glucose, and cream feeding with and without atropine was also assessed in a group of these patients with duodenal ulcer. As in normals, there was no stimulation of gastrin release by either atropine alone, distilled water, glucose, or cream. However, protein alone produced a greater rise in serum gastrin levels compared with that in normals and prior atropinization augmented this response greatly in duodenal ulcer. This indicates an increased amount of releasable gastrin in the latter disease, the release of which, under basal conditions, is suppressed by the high acidity in the antrum.

Although the precise aetiology of duodenal ulcer is unknown, many patients with this disease have increased acid secretion from the stomach (Baron, 1963) and the parietal cell mass is increased (Card, 1962). Gastrin is a potent stimulant of acid secretion (Gregory and Tracy, 1961) and serum gastrin levels can now be measured using sensitive radioimmunoassays (McGuigan, 1968; Hansky and Cain, 1969). Elevated gastrin levels have been reported in the Zollinger-Ellison syndrome (McGuigan and Trudeau, 1968), pernicious anaemia (Hansky, Korman, Soveny, and St John, 1971a), and certain forms of gastritis (Korman, Strickland, and Hansky, 1971a). However, in peptic ulcer the levels have been controversial, some groups finding low to normal levels (Hansky and Cain, 1969; Trudeau and McGuigan, 1970), others variable levels (Walsh, Yalow, and Berson, 1971), and one group has reported high levels in this disease (Byrnes, Young, Chisholm, and Lazarus, 1970a).

Employing a radioimmunoassay for gastrin based on antibodies to synthetic human gastrin I (SHGI), this report presents data on serum gastrin levels in a group of patients with active duodenal ulcer both in

the fasting state and after stimulation by food and atropine.

Material and Methods

Seventy-two patients with duodenal ulcer were studied. All patients had recent symptoms consistent with this diagnosis and radiology was positive. Age ranged from 22 to 76 years, with a mean of 44 years, and the male to female ratio was 3:1. Following an overnight fast, peripheral venous blood was drawn and the serum separated by centrifugation and stored at -20°C until assayed.

Five patients were then investigated after an overnight fast. A 19 gauge needle was inserted into a forearm vein and patency ensured by frequent flushing with a solution of heparin 1,000 units in 20 ml of 0.9% sodium chloride. This solution has been shown not to affect serum gastrin levels. Each patient had gastrin measured after a protein meal with and without a prior intramuscular injection of atropine sulphate (0.6 mg) and also in response to atropine sulphate alone. Blood was drawn at -60, -30, 0, 15, 30, 45, 60, 75, 90, and 120 minutes. The protein meal comprised steak, cheese, and milk, the

Received for publication 11 August 1971.

contents being protein 60 g, fat 51 g, and carbohydrate 11 g.

Two patients from this group then had their gastrin responses assessed to fresh cream (250 ml: protein 7 g, fat 99 g, carbohydrate 9 g) and glucose (80 g in 250 ml water) with and without prior atropine sulphate. In addition their response to distilled water (250 ml) was estimated.

Fasting serum gastrin levels were also measured in seven patients with a clinical history and acid secretory studies suggestive of the Zollinger-Ellison syndrome (Zollinger and Ellison, 1955), as well as in 18 patients with chronic lesser curve gastric ulcer in whom endoscopy, radiology, and cytology suggested a benign lesion. The levels of serum gastrin in these groups were compared with those in 93 subjects with no known gastrointestinal disease.

Serum gastrin was estimated in duplicate by radioimmunoassay as previously described (Hansky and Cain, 1969; Hansky, Soveny, and Korman, 1971b). Statistical analysis of group means was performed by Student's *t* test on unpaired samples using standard formulae (Snedecor and Cochran, 1967).

Results

The Table compares the mean age, basal serum gastrin levels, and basal intragastric pH in duodenal ulcer patients with normal subjects, patients with gastric ulcer, and patients with the Zollinger-Ellison syndrome. The mean age of the duodenal ulcer and normal group is almost the same but the fasting gastrin (mean $\pm$ SEM) in duodenal ulcer is 15.7 ± 1.5 pg/ml compared with the normal level of 32 ± 4.3 pg/ml. Although there is overlap between these groups in gastrin levels (range for duodenal ulcer 0–44 pg/ml and for normals 0–300 pg/ml) the mean values are significantly lower in duodenal ulcer compared with normals ($P < 0.005$).

Patients with gastric ulcer are older than the

Fig. 1 Serum gastrin in response to a protein meal, a protein meal with prior atropinization, and intramuscular atropine 0.6 mg alone.

preceding groups and have a significantly higher serum gastrin level (118 ± 18.1 pg/ml) than normals or patients with duodenal ulcer ($P < 0.0005$). In patients with the Zollinger-Ellison syndrome, gastrin levels were easily distinguished from either of the three preceding groups (450 to 2,000 pg/ml). Fasting intragastric pH in duodenal ulcer was 1.5 ± 0.03 , in normals 3.7 ± 0.36 , and in gastric ulcer 4.2 ± 0.5 .

Figure 1 shows the response to a protein meal, with and without prior atropine, and to atropine alone in five patients with duodenal ulcer. With protein alone, there is a significant rise from a mean basal level of 17 ± 3.0 pg/ml to a peak of 94 ± 15.7 pg/ml at 45 minutes ($P < 0.0025$) with a gradual fall to normal. With a prior injection of atropine, serum gastrin rises from 15 ± 3.0 pg/ml to 122 ± 17.3

Group	No.	Age (years)	pH (units)	Serum Gastrin (pg/ml)
Normals	93	40.3 ± 2.0	3.7 ± 0.36 (1.3 – 7.8)	32.1 ± 4.3 (0 – 300)
Duodenal ulcer	72	44.2 ± 2.1	1.5 ± 0.03 (1.1 – 2.2)	15.7 ± 1.5 (0 – 44)
Gastric ulcer	18	57.7 ± 3.5	4.2 ± 0.5 (2.2 – 6.8)	118 ± 18.1 (36 – 330)
Zollinger-Ellison syndrome	7	49 ± 3.2	< 1.3	450 – 2,000

Table Age, basal pH, and basal serum gastrin levels in normals, patients with duodenal ulcer, gastric ulcer, and Zollinger-Ellison syndrome¹

¹All values mean $\pm$ SEM (range)

pg/ml at 75 minutes ($p < 0.0005$). The response to atropine alone revealed no significant differences from basal levels.

Distilled water, glucose, and cream alone produced no significant change from basal levels (a change from 2 to 6 pg/ml, 4 to 9 pg/ml, and 8 to 16 pg/ml respectively) but prior atropinization increased the response to glucose and cream slightly (a rise from 7 to 13 pg/ml and 7 to 20 pg/ml respectively). These changes were not significant.

Discussion

These studies indicate that basal serum gastrin in duodenal ulcer is in the low part of the normal range when measured by an immunoassay based on antibodies to synthetic human gastrin I. That mean values are significantly lower in normals, whilst patients with gastric ulcer have a higher mean gastrin level, suggests that the gastrin measured by this assay is sensitive to pH changes within the stomach. It is known that in dogs, gastrin secretion is inhibited at a pH of between 1 and 3 (Elwin and Andersson, 1966). In the basal state, the pH of gastric contents in duodenal ulcer is usually less than 2, in normals it is variable, and in gastric ulcer it is often higher than 3.

The results of this study support a direct relationship between intragastric pH and serum gastrin with an increase in serum gastrin concomitant with a rise in pH. We have found that patients with achlorhydria and autoimmune atrophic gastritis have high serum gastrin levels (Korman *et al*, 1971a) and have thus far only uncovered two situations where this direct pH/serum gastrin relationship does not hold. One of these is the Zollinger-Ellison syndrome where gastrin is high and pH low and gastrin release or secretion is autonomous. The other group is parietal cell antibody-negative gastritis where achlorhydria is present and serum gastrin levels are normal. Recent work has shown that the antrum is involved by gastritis in this disease (unpublished observation).

A similar pH/serum gastrin relationship has also been shown by Trudeau and McGuigan (1971) but Byrnes and Lazarus (1971) have found that gastrin is inversely proportional to pH in a group of subjects comprising duodenal ulcer, gastric ulcer, and normals. This group also reports serum gastrin levels to be grossly elevated in duodenal ulcer (Byrnes *et al*, 1970a) and the reasons for this controversy have already been discussed (Hansky, Korman, and Soveny, 1970; Byrnes, Lazarus, and Young, 1970b; Korman, Soveny, and Hansky, 1971b).

Dragstedt (1969) has postulated increased vagal drive to account for the increased parietal cell mass in duodenal ulcer. Vagal stimulation also causes the release of gastrin from the antrum (Fyrö, 1967;

Korman, Hansky, and Soveny, 1971c) and an increase in gastrin producing G cells might be expected with increased vagal drive in duodenal ulcer. The recent report of G cell hyperplasia in patients with acid hypersecretion (Pearse and Bussolati, 1970) supports the concept of an increased G cell mass in duodenal ulcer. In addition, the absolute rise in gastrin above basal levels following a protein meal was 77 pg/ml in duodenal ulcer and 60 pg/ml in normal subjects (Korman *et al*, 1971b). This difference, although not statistically significant, may indicate the greater release of gastrin from an increased number of G cells.

Although there may be an increase in the number of G cells in duodenal ulcer the significantly lower than normal basal serum gastrin level indicates that these cells still respond to acid inhibition in the normal manner. The increased parietal cell mass results in low antral pH and inhibition of gastrin release in the basal state.

Consideration of the response to protein feeding with prior atropinization indicates an even greater response than with protein alone. It is considered that a combination of decreased acidity and motility allows the stimulus to act for a longer period and in a less acid milieu. However, an additional source of the gastrin may be from an extragastric site in duodenal ulcer. That this is a distinct possibility is suggested by the time of onset of peak gastrin after food. In duodenal ulcer patients, the peak response following atropine is at 75 minutes whereas in normals, irrespective of whether atropine is administered or not, the peak response to food is at 45 minutes after the stimulus. The fact that the response is later in duodenal ulcer suggests that gastrin may be released from a more distal site (duodenum or jejunum) where immunoreactive gastrin has recently been demonstrated by Berson and Yalow (1971a).

Finally, Berson and Yalow (1971b) have stated that there is evidence for some degree of autonomy in gastrin release in duodenal ulcer. They provide evidence that their group measures of gastrin were higher in duodenal ulcer than in normals and consider that Trudeau and McGuigan (1971) support this autonomy. Their explanation is that despite strong acid inhibition, Trudeau and McGuigan still find normal levels in duodenal ulcer whereas the expectation would be for low levels. The present findings of significantly lower basal levels in duodenal ulcer disease is at variance with Berson and Yalow's suggestion of autonomy and indicates that gastrin measured by our immunoassay mirrors physiological acid inhibition precisely.

This work was supported by the National Health and Medical Research Council of Australia.

Please address requests for reprints to Dr J. Hansky, Monash University Department of Medicine, Prince Henry's Hospital, Melbourne, Australia.

References

- Baron, J. H. (1963). An assessment of the augmented histamine test in the diagnosis of peptic ulcer. *Gut*, 4, 243-253.
- Berson, S. A., and Yalow, R. S. (1971a). Nature of immunoreactive gastrin extracted from tissues of gastrointestinal tract. *Gastroenterology*, 60, 215-222.
- Berson, S. A., and Yalow, R. S. (1971b). Gastrin in duodenal ulcer. *New Engl. J. Med.*, 284, 445-446.
- Byrnes, D. J., Young, J. D., Chisholm, D. J., and Lazarus, L. (1970a). Serum gastrin in patients with peptic ulceration. *Brit. med. J.*, 2, 626-629.
- Byrnes, D. J., Lazarus, L., and Young, J. D. (1970b). The many faces of gastrin. *Aust. Ann. Med.*, 19, 380-381.
- Byrnes, D. J., and Lazarus, L. (1971). Serum gastrin and gastric acidity. *Aust. N.Z. J. Med.*, 1, 26-29.
- Card, W. I. (1962). The concept of the parietal cell mass. In *Surgical Physiology of the Gastrointestinal Tract*, edited by A. N. Smith, pp. 81-85. Royal College of Surgeons, Edinburgh.
- Dragstedt, L. R. (1969). Peptic ulcer—an abnormality in gastric secretion. *Amer. J. Surg.*, 117, 143-156.
- Elwin, C. E., and Andersson, S. (1966). Influence of pH on release of gastrin by chemical agents. *Acta physiol. scand.*, Suppl., 277, 44.
- Emås, S., Borg, I., and Fyrö, B. (1971). Antral and duodenal gastrin activity in non-ulcer and ulcer patients. *Scand. J. Gastroent.*, 6, 39-43.
- Fyrö, B. (1967). Reduction of antral and duodenal gastrin activity by electrical vagal stimulation. *Acta physiol. scand.*, 71, 334-340.
- Gregory, R. A., and Tracy, H. J. (1961). The preparation and properties of gastrin. *J. Physiol. (Lond.)*, 156, 523-543.
- Hansky, J., and Cain, M. D. (1969). Radioimmunoassay of gastrin in human serum. *Lancet*, 2, 1388-1390.
- Hansky, J., Korman, M. G., and Soveny, C. (1970). Effect of vagotomy on serum gastrin in patients with duodenal ulceration. *Aust. Ann. Med.*, 19, 379-380.
- Hansky, J., Korman, M. G., Soveny, C., and St John, D. J. B. (1971a). Radioimmunoassay of gastrin: Studies in pernicious anaemia. *Gut*, 12, 97-101.
- Hansky, J., Soveny, C., and Korman, M. G. (1971b). Effect of secretin on serum gastrin as measured by immunoassay. *Gastroenterology*, 61, 62-68.
- Korman, M. G., Strickland, R. G., and Hansky, J. (1971a). Serum gastrin in chronic gastritis. *Brit. med. J.*, 2, 16-18.
- Korman, M. G., Soveny, C., and Hansky, J. (1971b). Effect of food on serum gastrin evaluated by radioimmunoassay. *Gut*, 12, 619-624.
- Korman, M. G., Hansky, J., and Soveny, C. (1971c). Radioimmunoassay of gastrin: The response of serum gastrin to insulin hypoglycaemia. *Scand. J. Gastroent.*, 6, 71-75.
- McGuigan, J. E. (1968). Immunochemical studies with synthetic human gastrin. *Gastroenterology*, 54, 1005-1011.
- McGuigan, J. E., and Trudeau, W. L. (1968). Immunochemical measurement of elevated levels of gastrin in the serum of patients with pancreatic tumors of the Zollinger-Ellison variety. *New Engl. J. Med.*, 278, 1308-1313.
- Pearse, A. G. E., and Bussolati, G. (1970). Immunofluorescence studies of the distribution of gastrin cells in different clinical states. *Gut*, 11, 646-648.
- Snedecor, G. W., and Cochran, W. G. (1967). *Statistical Methods*. 6th ed, pp. 91-119. Iowa State University Press, Ames, Iowa.
- Trudeau, W. L., and McGuigan, J. E. (1970). Serum gastrin levels in patients with peptic ulcer disease. *Gastroenterology*, 59, 6-11.
- Trudeau, W. L., and McGuigan, J. E. (1971). Relations between serum gastrin levels and rates of gastric hydrochloric acid secretion. *New Engl. J. Med.*, 284, 408-412.
- Walsh, J. H., Yalow, R. S., and Berson, S. A. (1971). The effect of atropine on plasma gastrin response to feeding. *Gastroenterology*, 60, 16-21.
- Zollinger, R. M., and Ellison, E. H. (1955). Primary peptic ulcerations of the jejunum associated with islet cell tumours of the pancreas. *Ann. Surg.*, 142, 709-728.