Effect of highly selective vagotomy on pancreatic exocrine function and on cholecystokinin and gastrin release

N I RAMUS, R C N WILLIAMSON*, J M OLIVER, and D JOHNSTON†

From the University Department of Surgery, Bristol Royal Infirmary, Bristol

SUMMARY The effect of highly selective vagotomy on pancreatic exocrine function and the release of gastrin and cholecystokinin was studied in 10 patients with endoscopically-proven duodenal ulceration. Cholecystokinin and gastrin concentrations in serum both increased significantly after highly selective vagotomy. Amylase concentration in the duodenal aspirate increased significantly after vagotomy, but trypsin concentration remained unchanged. The expected reductions in gastric acid secretion were noted. Thus highly selective vagotomy reduces acid secretion effectively in patients with duodenal ulcer without impairing the exocrine function of the pancreas.

Impairment of pancreatic and hepatobiliary function may help to explain the diarrhoea and steatorrhoea that follow truncal vagotomy and pyloroplasty in 25-40% of patients.¹⁻⁸ Reduced pancreatic exocrine secretion after truncal vagotomy has been ascribed variously to parasympathetic denervation,⁹⁻¹⁰ suppressed release of intestinal hormones,¹¹⁻¹³ altered gastric emptying¹³⁻¹⁵ and, most recently, interference with enteropancreatic reflexes.¹³⁻¹⁶ The introduction of highly selective vagotomy for the treatment of duodenal ulceration has greatly reduced the incidence of dumping, diarrhoea, and steatorrhoea,^{5-6 8 17 18} probably because postoperative gastric emptying of solid and semi-solid meals is unaffected,^{15 19-20} and gastric emptying of fluids is less precipitate than after truncal vagotomy and drainage.^{19 21} Highly selective vagotomy might therefore be expected to cause less interference with pancreatic exocrine function than truncal vagotomy. The present study examines this prediction.

Methods

Ten patients with endoscopically-proven duodenal ulceration, who had given informed consent, were studied shortly before and two to three months after highly selective vagotomy; this was performed by a

standard technique.²² A Lundh test meal‡ was chosen to provide an endogenous 'physiological' stimulus to pancreatic secretion. After an overnight fast a Dreiling double-lumen tube was passed into the duodenum under radiographic control, and basal duodenal juice was collected for one hour while the stomach was continuously aspirated. The test meal was then instilled into the stomach *via* the gastric lumen, and duodenal juice was continuously collected over 15 minute periods for the next two hours. Samples of duodenal juice were stored at 5°C for subsequent measurement of the concentration of trypsin²³ and amylase (Phadebas method). The volume and pH of the juice were also recorded. During the three-hour period of study serum samples were obtained for radioimmunoassay of cholecystokinin²⁴ and gastrin.²⁵ Gastric acid secretion was measured separately, before and five to seven days after operation; basal acid output was determined, together with the peak acid output to intramuscular pentagastrin (6 µg/kg:PAO_{Pg}) and intravenous insulin (0.2 IU/kg:PAO_I). For the postoperative test a larger dose of pentagastrin (10 µg/kg) was used. PAO_I was calculated by subtracting basal acid output from the value derived by doubling the two highest consecutive 15-minute outputs after insulin. PAO_{Pg} was calculated by trebling the sum of the two highest consecutive

* Address for correspondence: Professor R C N Williamson, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW.

† Present address: The General Infirmary, Gt George Street, Leeds LS1 3EX.

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‡ Fifteen grams of casilan, 18 g corn oil, 40 g glucose made up to 250 ml with water.

10-minute outputs after pentagastrin. Completeness of vagotomy was assessed using Hollander's criteria.²⁶

Results are expressed as means ($\pm$ SEM). Statistical significance was assessed by Student's *t* test for paired data or the Wilcoxon matched-pairs signed-rank test, as appropriate. Integrated values were calculated as previously described²⁷ to determine the contribution of altered basal levels to the difference observed in stimulated responses.

Results

PANCREATIC EXOCRINE FUNCTION

Trypsin (Fig. 1)

The mean preoperative basal trypsin concentration was 4.9 IU/l. This level increased fourfold during the first hour after the Lundh meal and threefold during the second hour. Operation did not significantly affect either the basal or the stimulated concentration, although the trypsin concentration was reduced during the first hour after the food stimulus ($p=0.1$). Total three-hour output and integrated trypsin values were unchanged postoperatively.

Amylase (Fig. 2)

The Lundh meal failed to produce a significant increase in amylase concentration in the duodenal aspirate either before or after vagotomy. Postoperative amylase concentrations were consistently higher than preoperative values at basal, first, and second hour, but the differences were only significant

Fig. 1 Duodenal trypsin levels in nine fasting duodenal ulcer patients and for two hours after a Lundh test meal, before and after highly selective vagotomy.

Fig. 2 Duodenal amylase levels in seven fasting duodenal ulcer patients and for two hours after a Lundh test meal, before and after highly selective vagotomy. *Significant difference ($p<0.05$)

during the second hour. When the entire three-hour output was considered, however, amylase concentration was found to be significantly greater after than before highly selective vagotomy ($p<0.002$). Integrated amylase values were not significantly different postoperatively, indicating the change to be in basal levels.

HORMONE ASSAYS

Cholecystokinin (Fig. 3 and 4)

Both before and after operation the Lundh meal stimulated the secretion of cholecystokinin: preoperative basal levels (420 pg/ml) were increased threefold 10 minutes after the meal (Fig. 3), while the much greater postoperative basal levels (1987 pg/ml) were further increased to 4282 pg/ml. Integrated cholecystokinin values (Fig. 4) showed that these changes reflected a true increase in release after highly selective vagotomy, from 38×10^3 pg-min/ml to 177×10^3 pg-min/ml.

Gastrin (Fig. 5)

Levels were increased after the test meal in both the pre- and postoperative studies. Before vagotomy mean basal gastrin concentration was 52 pg/ml, reaching a plateau at nearly twice this value 10 minutes after food. After vagotomy basal levels were much higher (210 pg/ml), and stimulated levels remained higher than preoperative values at every time period ($p<0.05$). The integrated gastrin response to the test meal after highly selective vagotomy, however, did not differ significantly from the preoperative values (3550 pg-min/ml).

Fig. 3 Serum cholecystokin levels after a Lundh test meal before and after highly selective vagotomy in nine duodenal ulcer patients. All measurements were significantly higher postoperatively ($p < 0.01$). Crosshatching: standard errors of the mean.

Fig. 5 Serum gastrin levels after a Lundh test meal before and after highly selective vagotomy. All measurements were significantly higher postoperatively ($p < 0.05$). Crosshatching represents standard errors of the mean.

GASTRIC ACID SECRETION (Fig. 6)

Highly selective vagotomy reduced basal acid output by 57%, PAO_{Pg} by 40% and PAO_I by 95%. According to Hollander's criteria no patient had an 'early positive' rise, but two patients had 'late positive' responses.

Fig. 4 Mean integrated cholecystokin levels (0-120 minutes) calculated before and after highly selective vagotomy. *Significant difference ($p < 0.01$).

DUODENAL VOLUME AND pH

After highly selective vagotomy the volume of duodenal juice tended to be lower throughout the test, but differences only reached statistical significance during the second hour, when the volume fell from 138 ml to 68 ml ($p < 0.05$).

Fig. 6 Gastric acid secretion shown before and after highly selective vagotomy at basal (BAO) and after insulin and pentagastrin stimulation (PAO_I and PAO_{Pg}). PAO_I levels have had basal acid output subtracted. *Significant differences ($p < 0.01$).

Duodenal pH was not affected by highly selective vagotomy.

Discussion

The reductions in basal and stimulated gastric acid secretion indicated that most of the vagotomies had been adequate. Although the endogenous stimulus chosen (a standard Lundh meal) was able to produce a marked increase in duodenal trypsin levels, the concentration of trypsin in the duodenal collections was unaltered by highly selective vagotomy. Our findings are consistent with reports showing that truncal, but not highly selective, vagotomy reduces enzyme output from the pancreas after insulin stimulation,^{15 29} and that virtual abolition of gastric acid output by the H₂-receptor antagonist ranitidine does not affect pancreatic enzyme secretion.³⁰

The hypotheses advanced to explain impaired pancreatic exocrine function after truncal vagotomy have implicated gastric emptying, which is particularly affected by concomitant pyloroplasty or gastrojejunostomy.^{14 19} Highly selective vagotomy, by contrast, has been shown to alter emptying minimally and then only after a fluid test meal.^{15 19 21} In the present study the volume of duodenal juice tended to be lower after highly selective vagotomy, though significant differences occurred only during the second hour after the test meal, when trypsin content was unchanged.

Duodenal amylase levels were increased throughout after highly selective vagotomy, but, as there was no amylase response to the Lundh test meal, the reason remains obscure. Increased amylase levels have previously been demonstrated after truncal vagotomy but not after selective vagotomy.³¹ Possible mechanisms for this effect of truncal vagotomy include altered duodenal emptying,³¹ denervation hypersensitivity or loss of vagal inhibition of the pancreas,^{9 11 32} and changes in cholecystokinin release.³³⁻³⁵ None of these explanations, however, seems directly applicable to the present finding that highly selective vagotomy increases duodenal amylase content. It is conceivable, though unlikely, that, in the present study, contamination by salivary amylase may have affected the results, despite attempts to keep the stomach empty throughout the test period.

Although the cholecystokinin assay probably indicates relative rather than absolute values, in the presence of unchanged trypsin output the increases in serum cholecystokinin and gastrin after highly selective vagotomy suggest a reduction in pancreatic sensitivity. Analysis of the integrated hormone response has shown a true increase in cholecy-

stokinin release after highly selective vagotomy. By contrast, raised gastrin levels were only a reflection of the increase in basal levels of gastrin, an established effect of truncal vagotomy.³⁶⁻³⁸ Intragastric titration studies with control of luminal pH have shown that this post-vagotomy hypergastrinaemia cannot be explained entirely by loss of inhibition by endogenous HCl when acid secretion is reduced.³⁹ The increased cholecystokinin release noted in this study might be needed to achieve the same enzyme output from the pancreas, if reduced acid secretion after highly selective vagotomy *diminished* pancreatic sensitivity. Yet Berstad and associates (1976) have demonstrated what they believe to be an *increased* pancreatic sensitivity to secretion after highly selective vagotomy and suggest decreased acid output as the possible aetiological factor.⁴⁰ As gastrin acts as a tropic hormone to the pancreas, at least in the rat,⁴¹⁻⁴³ some indirect increase in exocrine function might be expected to balance the effects of any pancreatic denervation and reduced gastric acidity.

We conclude that highly selective vagotomy produces a satisfactory reduction in acid secretion in duodenal ulcer disease without appreciably altering pancreatic exocrine function.

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References

- 1 Cox AG, Bond MR. Bowel habit after vagotomy and gastrojejunostomy. *Br Med J* 1964; 1: 460-5.
- 2 Logan H. Steatorrhoea and diarrhoea after vagotomy: a comparison of drainage procedures. *Gut* 1964; 5: 188-91.
- 3 Kennedy TL, Connell AM. Selective or truncal vagotomy? *Lancet* 1970; 1: 675.
- 4 Wastell C, Ellis H. Faecal fat excretion and stool colour after vagotomy and pyloroplasty. *Br Med J* 1966; 1: 1194-7.
- 5 Humphrey CS, Johnston D, Walker BE, Pulvertaft CN, Goligher JC. Incidence of dumping after truncal and selective vagotomy with pyloroplasty and highly selective vagotomy without drainage procedure. *Br Med J* 1972; 3: 785-8.
- 6 Johnston D, Humphrey CS, Walker BE, Pulvertaft CN, Goligher JC. Vagotomy without diarrhoea. *Br Med J* 1972; 3: 788-90.
- 7 Parkin GJS, Smith RB, Johnston D. Gall bladder volume and contractility after truncal, selective and highly selective (parietal cell) vagotomy in man. *Ann Surg* 1973; 178: 581-6.
- 8 Edwards JP, Lyndon PJ, Smith RB, Johnston D. Faecal fat excretion after truncal, selective and highly

- selective vagotomy for duodenal ulcer. *Gut* 1974; **15**: 521-5.
- 9 Tinker J, Cox AG. Gallbladder function after vagotomy. *Br J Surg* 1969; **56**: 779-82.
- 10 Wormsley KG. The effect of vagotomy on the human pancreatic response to direct and indirect stimulation. *Scand J Gastroenterol* 1972; **7**: 85-91.
- 11 Thambugala RL, Baron JH. Pancreatic secretion after selective and truncal vagotomy in the dog. *Br J Surg* 1971; **58**: 839-44.
- 12 Malagelada JR, Go VLW, Summerskill WHJ. Altered pancreatic and biliary function after vagotomy and pyloroplasty. *Gastroenterology* 1974; **66**: 22-7.
- 13 MacGregor IL, Parent J, Meyer JH. Gastric emptying of liquid meals and pancreatic and biliary secretion after subtotal gastrectomy or truncal vagotomy and pyloroplasty in man. *Gastroenterology* 1977; **72**: 195-205.
- 14 McKelvey STD. Gastric incontinence and post-vagotomy diarrhoea. *Br J Surg* 1970; **57**: 741-7.
- 15 Lavigne ME, Wiley ZD, Martin P, Way LW, Meyer JH, Sleisenger MH, MacGregor IL. Gastric, pancreatic and biliary secretion and the rate of gastric emptying following parietal cell vagotomy. *Am J Surg* 1979; **138**: 644-51.
- 16 Solomon TE, Grossman MI. Cholecystokinin and secretin release are not affected by vagotomy or atropine. *Gastroenterology* 1977; **72**: A-111/1134.
- 17 De Miguel J. Diarrea tras diversas formas de vagotomía con y sin drenaje complementario. *Rev Esp Enferm Apar Dig* 1972; **38**: 595-600.
- 18 Johnston D, Axon ATR. Highly selective vagotomy for duodenal ulcer: the clinical results after 10 years. *Br J Surg* 1979; **66**: 874.
- 19 Clarke RJ, Alexander-Williams J. The effect of preserving antral innervation and of a pyloroplasty on gastric emptying after vagotomy in man. *Gut* 1973; **14**: 300-7.
- 20 Brandsborg O, Brandsborg M, Løvgreen NA, Mikkelsen K, Møller B, Rokkjaer M, Amdrup E. Influence of parietal cell vagotomy and selective gastric vagotomy on gastric emptying rate and serum gastrin concentration. *Gastroenterology* 1977; **72**: 212-4.
- 21 Binswanger RO, Aeberhard P, Walther M, Vock P. Effect of pyloroplasty on gastric emptying: long term results as obtained with a labelled test meal 14-43 months after operation. *Br J Surg* 1978; **65**: 27-9.
- 22 Johnston D, Wilkinson AR. Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer. *Br J Surg* 1970; **57**: 289-96.
- 23 Wiggins HS. Simple method of estimating trypsin. *Gut* 1967; **8**: 415-6.
- 24 Harvey RF, Oliver JM. Hormonal content and effects on gallbladder of commercial preparations of cholecystokinin-pancreozymin. *Horm Metab Res* 1981; **13**: 446-50.
- 25 Spence RW, Celestin LR, McCormick DA, Owens CJ, Oliver JM. Effect of long term treatment with cimetidine on gastric acid secretion and gastrin response in man. In: W Creuzfeldt, ed. *Cimetidine: Proceedings of International Symposium on Histamine H₂-receptor Antagonists*. Göttingen 1977. Amsterdam: Excerpta Medica, 1978: 116-34.
- 26 Hollander F. The insulin test for the presence of intact nerve fibres after vagal operations for peptic ulcer. *Gastroenterology* 1946; **7**: 607-14.
- 27 Thompson JC, Reeder DD, Bunchman HH, Becker HD, Brandt EN Jr. Effect of secretion on circulating gastrin. *Ann Surg* 1972; **176**: 384-93.
- 28 Greenall MJ, Lyndon PJ, Goligher JC, Johnston D. Long term effect of highly selective vagotomy on basal and maximal acid output in man. *Gastroenterology* 1975; **68**: 1421-5.
- 29 Smith RB, Edwards JP, Johnston D. Effect of vagotomy on exocrine pancreatic and biliary secretion in man. *Am J Surg* 1981; **141**: 40-7.
- 30 Konturek SJ, Obtulowicz W, Kwiecién N, Sito E, Oleksy J, Miszczuk-Jamska B. Effect of ranitidine, a new H₂-antagonist, on gastric and pancreatic secretion in duodenal ulcer patients. *Dig Dis* 1980; **25**: 737-43.
- 31 Kramhöft J, Balslev I, Lindahl F, Backer OG. Vagotomy and the external function of the pancreas. *Scand J Gastroenterol* 1974; **9**: 309-11.
- 32 Davenport HW. *Physiology of the digestive tract. Pancreatic secretion*. Chicago: Year Book Medical Publishers Incorporated, 1966: 136.
- 33 Gamble WS. Impaired pancreatic secretion after vagotomy and pyloroplasty. *J Lab Clin Med* 1970; **76**: 871.
- 34 Moreland HJ, Johnson LR. Effect of vagotomy on pancreatic secretion stimulated by endogenous and exogenous secretin. *Gastroenterology* 1971; **60**: 425-31.
- 35 Grossman MI. Gastrointestinal hormones: some thoughts about clinical applications. *Scand J Gastroenterol* 1972; **7**: 97-104.
- 36 Hansky J, Korman MG. Immunoassay studies in peptic ulcer. In: Sircus W, ed. *Clinics in gastroenterology*. Vol 2. New York and London: Saunders, 1973: 275-91.
- 37 Thompson JC. The effect of vagotomy on circulating gastrin. In: Holle F, Andersson S, eds. *Vagotomy, latest advances*. New York: Springer-Verlag, 1974: 59-64.
- 38 Thompson JC, Fender HR, Watson LC, Villar HV. The effects on gastrin and gastric secretion of five current operations for duodenal ulcer. *Ann Surg* 1976; **183**: 599-607.
- 39 Thompson JC, Lowder WS, Peurifoy JT, Swierczek JS, Rayford PL. Effect of selective proximal vagotomy and truncal vagotomy on gastric acid and serum gastrin responses to a meal in duodenal ulcer patients. *Ann Surg* 1978; **188**: 431-7.
- 40 Berstad A, Roland M, Peterson H, Liavåg I. Altered pancreatic function after proximal gastric vagotomy in man. *Gastroenterology* 1976; **71**: 958-60.
- 41 Mayston PD, Barrowman JA. Influence of chronic administration of pentagastrin on the pancreas in hypophysectomised rats. *Gastroenterology* 1973; **64**: 391-9.
- 42 Debinski AB, Johnson LR. Growth of pancreas and gastrointestinal mucosa in antrectomized and gastrin-treated rats. *Endocrinology* 1979; **105**: 769-73.
- 43 Koizumi K, Okubo M, Inoue S, Masuda H. Trophic effect of tetragastrin on the stomach, duodenum and pancreas in rats. *Tohoku J Exp Med* 1979; **129**: 17-24.