Vagal Impairment of Gastric Secretion in Diabetic Autonomic Neuropathy

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Summary

Gastric acid output in response to insulin-induced hypoglycaemia and pentagastrin was measured in 18 diabetic patients with symptoms of autonomic neuropathy. Two patients had achlorhydria but the rest responded normally to pentagastrin. The acid output evoked by insulin-induced hypoglycaemia was low in 10 of the 16 patients who secreted acid in response to pentagastrin. These changes suggest that vagal impairment is common in diabetics with autonomic symptoms, which might explain the infrequency of duodenal ulcer in diabetics.

Introduction

The incidence of duodenal ulcer in diabetic patients is about a third of that in the non-diabetic population.^{1,2} This reduced incidence is usually ascribed to a decrease in gastric secretion,^{3,4} which in turn has been variously attributed to gastric mucosal atrophy,⁵ reflected in the increased incidence of pernicious anaemia in diabetics,⁶ and diabetic autonomic neuropathy.

Autonomic neuropathy in diabetes is thought to cause anorexia, vomiting,⁷ constipation, and diarrhoea,^{8,9} and the similarity between these symptoms and those occurring after surgical vagotomy¹ supports this view. Furthermore, these alimentary symptoms are often accompanied by impotence, bladder dysfunction, or postural hypotension, which are also thought to result from autonomic disturbance.

We assessed gastric acid secretion in 18 diabetics with various symptoms attributed to autonomic neuropathy using maximal stimulation with pentagastrin as a measure of parietal cell mass and the secretory response to hypoglycaemia as a measure of vagal function.

Patients and Methods

After informed consent had been obtained studies of gastric acid secretion were performed on 18 diabetic outpatients. Diabetic control had been satisfactory in all patients for several months before investigation. The patients were divided into three general clinical groups on the basis of their presenting autonomic symptoms: patients in cases 1-8 suffered from diarrhoea, those in cases 9-11 from recurrent episodes of vomiting, and in cases 12-18 from impotence or bladder dysfunction. There was some overlap of symptoms: patients in cases 1-4 also suffered from vomiting, and all 10 men were impotent; only in cases 12 and 15 were there bladder symptoms. The symptoms were classified as diabetic because they showed many of the described features of autonomic neuropathy and because other aetiological factors had been excluded by investigation (table I).

Laboratory procedure followed closely that described by Baron.¹¹ Studies were performed in the morning after a 12-hour fast and

abstinence from smoking. With the patient in a semi-recumbent position a nasogastric tube was passed into the stomach and its position checked after five minutes by the injection and reaspiration of 20 ml of water. Patients were instructed not to swallow saliva and continuous aspiration of gastric secretions was performed by constant hand suction. Patency of the tube was maintained by the intermittent injection of air. Gastric juice was pooled for 15-minute periods, filtered, and its volume and pH recorded. Titratable acidity was measured by titration with 0.1 M NaOH to pH 7.0, and gastric acid secretion was recorded as a concentration (mmol/l) or converted and expressed conventionally as mmol/h.

TABLE I—Clinical Features of 18 Diabetics with Autonomic Neuropathy

Case No.	Age and Sex	Duration of Diabetes (Years)	Treatment	Retinopathy	Peripheral Neuropathy*	Nephropathy†
1	24 M.	7	Insulin	H., E.	++	—
2	38 M.	15	Insulin	H.	++	++
3	37 F.	15	Insulin	N.V.	+	+
4	59 M.	26	Insulin	—	+	—
5	54 F.	45	Insulin	—	—	—
6	66 F.	5	CLP	—	++	—
7	58 M.	7	CLP	B.C.	+	—
8	21 F.	14	Insulin	H., E.	—	—
9	53 F.	20	Insulin	—	E. M. G.	—
10	56 F.	12	Insulin	H.	++	+
11	73 F.	9	CLP	—	+	+
12	44 M.	1	Insulin	B.C.	+	+
13	50 M.	9	Insulin	—	—	—
14	37 M.	1	CLP	—	—	—
15	51 F.	1	Insulin	H., E.	+	+
16	23 M.	11	Insulin	—	+	—
17	46 M.	16	Insulin	B.C.	+	—
18	45 M.	10	Insulin	—	+	—

* E. M. G. = Neurophysiological changes only. + = loss of ankle jerks with or without vibration sense in feet. ++ = Loss of ankle and knee jerks with or without more extensive secondary loss.

† + = Albuminuria. ++ = Albuminuria and raised blood urea (>40 mg/100 ml). CLP = Chlorpropamide. H. = Haemorrhages. E. = Exudates. N.V. = Neovascularization. B.C. = Background changes.

Insulin Dose and Blood Sugar Measurements.—Neutral insulin (Insulin Novo Actrapid) was given intravenously only after 60 minutes' basal collection of gastric secretion had been completed, and additional intravenous insulin was given 3-120 minutes after the first dose in 11 patients to lower the blood sugar level to below 2.22 mmol/l (40 mg/100 ml). Clinical signs of hypoglycaemia were seen in all patients. An indwelling venous cannula was inserted to facilitate frequent sampling for venous blood sugar concentration and provide a route for 50% dextrose solutions should they be required. Blood sugar was measured by the glucose oxidase method, but in addition rapid estimations were provided by a reflectance meter technique (Dextrostix, Ames). Blood sugar was measured after completion of the basal collection and thereafter every 15 minutes until the end of the study (at which time normoglycaemia was restored, if not already present, by intravenous or oral administration of dextrose solutions).

Pentagastrin Test.—Immediately after completion of the insulin test pentagastrin 6 µg/kg body weight was injected subcutaneously and gastric secretion aspirated for a further 60 minutes.

Results

A minimum blood sugar of <1.94 mmol/l (35 mg/100 ml) was obtained in all but two patients (who experienced severe neuroglycopenic symptoms at a blood sugar of 2.50 mmol/l (45 mg/100 ml). The length of the post-hypoglycaemia collection tended to relate inversely to the time taken to obtain adequate hypoglycaemia, and in all but one case 15-minute collections were continued for at least 75 minutes (table II).

After the insulin injections there was a mean linear fall (±S.E. of

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TABLE II—Gastric Acid Secretion After Insulin and Pentagastrin

Case No.	Minimum Blood Sugar (mmol/l)	Duration of Post-hypoglycaemic Collection (min)	Basal Acid (mmol/l)	Maximum Acid After Insulin (mEq/l) (mmol/l)	Maximum Difference in Acid after Insulin (mmol/l)	P.A.O. ₁ (mmol/h)	P.A.O. _{Pg} (mmol/h)	P.A.O. ₁ /P.A.O. _{Pg} (%)
1	1.78	60	61.5	60.5	-1*	2.42	29.84	8.11
2	1.28	75	74.5	59.0	-15.5*	1.04	21.86	4.76
3	0.94	90	59.5	52.0	-7.5*	3.12	22.12	14.10
4	1.11	90	0	0	0	0	0	
5	0.78	90	45.7	58.6	-12.9*	1.28	28.72	4.46
6	2.50	75	8.2	24.0	15.8*	1.46	14.32	12.40
7	1.67	120	0	32.8	32.8	1.62	2.76	58.70
8	1.44	90	38.1	128.2	90.1	28.5	29.24	97.47
9	0.67	75	83.5	91.5	8.0*	4.34	20.34	21.34
10	1.78	90	41.4	69.0	27.6	5.10	20.46	24.93
11	1.67	120	48.3	99.4	51.1	12.82	26.10	49.12
12	1.22	90	0	3.5	3.5	0	0	
13	1.33	75	20.8	106.9	86.1	20.04	37.58	53.33
14	1.00	120	50.0	101.5	51.5	13.64	23.42	58.24
15	1.50	120	97.0	119.0	22.0	14.22	20.66	68.83
16	1.28	105	55.0	32.0	-23.0*	1.44	22.28	6.46
17	2.50	75	68.2	60.6	-7.6*	4.84	54.06	8.95
18	1.67	105	61.4	45.7	-15.7*	2.54	33.30	7.63

* Abnormal values according to Hollander's criteria,¹² indicating impaired vagal function.
Conversion: SI to Traditional Units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

mean) in blood sugar of 0.12 ± 0.011 mmol l⁻¹ min⁻¹ (2.17 ± 0.19 mg/100 ml/min). In the earlier tests an initial insulin dose of 0.4 U/kg body weight was given but this invariably required supplementation before adequate hypoglycaemia was achieved. In later tests a dose of soluble insulin equal to the patients' usual total daily insulin requirement was found to be more effective in producing the desired level of hypoglycaemia.

Hollander¹² considered vagal function to be intact if there was an increase of more than 20 mmol/l in titratable acidity in two consecutive 15-minute periods after insulin-induced hypoglycaemia (blood sugar <2.22 mmol/l (40 mg/100 ml) compared with the basal concentration. If the basal samples contained no free acid then vagal function was regarded as being intact if the post-insulin concentration exceeded 10 mmol/l. These criteria for intact vagal function were not fulfilled in five patients with diarrhoea, one with vomiting, and three with impotence (table II). Two other patients (cases 4 and 12) had pentagastrin-fast achlorhydria and, therefore, vagal function was not susceptible to testing by insulin-induced hypoglycaemia. The rate of fall of blood sugar was 0.13 ± 0.020 mmol l⁻¹ min⁻¹ (2.34 ± 0.36 mg/100 ml/min) and the absolute fall 11.1 ± 1.11 mmol/l (199 ± 20 mg/100 ml) in those negative on insulin testing (impaired vagal function) and 0.11 ± 0.009 mmol l⁻¹ min⁻¹ (1.92 ± 0.17 mg/100 ml/min) and 7.88 ± 1.44 mmol/l (142 ± 26 mg/100 ml) respectively in those positive on insulin testing (intact vagal function); these differences were not significant. In those with negative responses the basal hydrogen ion concentration was higher, 57.5 ± 7.1 mmol/l, than those with positive responses, 42.2 ± 11.2 mmol/l, but this difference was not significant. The maximum hydrogen ion concentration after hypoglycaemia in the group with impaired vagal function was lower, 53.8 ± 6.5 mmol/l, than that in those with intact function, 93.8 ± 12.4 mmol/l ($P < 0.01$).

Peak acid output (P.A.O.) after pentagastrin was normal in all but three patients, two of whom had achlorhydria (table II). Mean P.A.O. was slightly higher in the group with negative insulin test results (27.4 mmol/h) than in those with intact vagal function (22.8 mmol/h). This difference was not significant and both figures were close to the reported mean normal value of 25.25 mmol/h.¹³

P.A.O. after insulin expressed as a percentage of the P.A.O. after pentagastrin (P.A.O.₁/P.A.O._{Pg} %) reflects the proportion of the parietal cell mass capable of being maximally stimulated by the vagus and can thus be used as a quantitative index of vagal intactness. The range for intact vagal function is 45–165%.¹⁴ Ten patients had values of less than 40%—that is, values similar to those found after surgical vagotomy—achlorhydria was found in two patients, and of the remaining six only one was clearly normal, five falling in the lower part of the normal range with values of 49–68% (table II). The mean values for diabetic patients with diarrhoea did not differ significantly from those with impotence or bladder dysfunction.

Discussion

Though we performed no gastric mucosal biopsies the normality of the gastric secretory response to pentagastrin makes it unlikely that gastric mucosal atrophy is common in diabetes. The serum B₁₂ level was normal in all patients, and only two of the 18 patients had achlorhydria after pentagastrin. These findings

agree with those of others^{8, 15} who used histamine as the secretory stimulus, and it seems unlikely that the parietal cell mass is reduced in most diabetics.

The use of insulin in assessing whether gastric vagal innervation is intact presents problems in the diabetic patient; more insulin is required to induce hypoglycaemia than in non-diabetic patients. Since all our patients who needed insulin were being treated with beef insulins we used a pork insulin in tests of vagal function in the hope that its lower antigenicity¹⁶ would reduce variations in insulin requirements and help to standardize the dose in relation to body weight. This did not happen, but we found that an initial dose of soluble insulin equal to the total daily requirement usually produced adequate hypoglycaemia. Those patients on oral hypoglycaemic agents were given an initial insulin dose of 0.4 U/kg, which often, however, required augmentation.

The rate of fall of the blood sugar level was similar in all patients and hence the time required to induce hypoglycaemia was longer in those patients with high initial blood sugar levels. Unfortunately the problem of high initial blood sugar levels cannot be overcome by performing the test on an inpatient basis giving the regular dose of insulin on waking.¹⁷ The longer time required to induce hypoglycaemia in diabetics compared with normal people may lead to premature discontinuation of the test before the secretory response has occurred. This did not occur in our patients, however, because the collection was usually continued for at least 75 minutes after hypoglycaemia, and during such a period the secretory response is demonstrable in 95% of unoperated duodenal ulcer patients.¹⁸

Our findings indicate that many diabetics with symptoms usually attributed to autonomic neuropathy show evidence of impaired vagal function. On Hollander's¹² criteria nine out of 16 diabetics who were suitable for testing showed such impairment. By the more preferable P.A.O.₁: P.A.O._{Pg} 10 of the 16 were clearly abnormal and in five others the ratio lay low in the normal range. This incidence is higher than that reported by Dotevall *et al.*,¹⁷ who found abnormality in only two out of 11 diabetics—most of whom had peripheral neuropathy and retinopathy though little data were given about gastrointestinal and genitourinary symptoms. Langer¹ found that the P.A.O.₁: P.A.O._{Pg} was less than 40% in three out of 10 diabetics without recorded autonomic symptoms. The fact that we selected for study only those diabetics who showed autonomic symptoms might account for our finding a higher incidence of gastric vagal impairment.

The role of impaired vagal function in the genesis of alimentary symptoms in diabetes is uncertain. We did not study diabetics without autonomic symptoms as controls, but certainly abnormality in insulin-induced gastric secretion was no commoner in those with diarrhoea or vomiting than in those with genitourinary symptoms. Oesophageal motility studies in diabetics provide further evidence of vagal impairment,¹⁹ and

since in the individual patient the degree of abnormality of oesophageal motility does not correlate closely with that of insulin-induced gastric secretion vagal impairment may predominantly affect different parts of the gut in different patients and may indeed be as highly selective as current surgical vagotomy. Vagal impairment complicating diabetics may, by the resulting reduction in gastric acid secretion, account for the low incidence of duodenal ulcer in this disease, and our findings indicate that this is a more likely mechanism than reduction of parietal cell mass as a consequence of gastric mucosal atrophy.

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Localized Avascular Necrosis of Lesser Curve of Stomach Complicating Highly Selective Vagotomy

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Summary

The fourth case of localized avascular necrosis of the lesser curve of the stomach after highly selective vagotomy is reported. The pathogenesis was probably related to the relative poverty of the submucosal blood supply along the lesser curve. This complication may be prevented by peritonealizing the lesser curve before closing the abdominal wall.

Introduction

Interest in highly selective vagotomy without a drainage procedure (H.S.V.) in the treatment of duodenal ulcer is increasing. The operation effectively reduces the acid output and early and late complications are less frequent than after other operations for duodenal ulcer.¹⁻¹² Among 350 patients who were followed for up to five years after H.S.V. in Leeds and Copenhagen there were no cases of proved recurrent duodenal ulceration and only two cases of gastric ulcer.¹¹

Only three deaths after H.S.V. have been reported, two of them after operation for duodenal ulcer^{13 14} and one after operation for gastric ulcer.¹¹ We report here the third death after H.S.V. for duodenal ulcer, which bears a striking resemblance to those reported by Newcombe¹³ and Hall *et al.*¹⁴

Case Report

This 36-year-old man had a three-year history of recurrent duodenal ulceration. On 12 February 1974 H.S.V. was performed. The duodenal cap was scarred but there was no stenosis. No difficulty was encountered during the operation. Diathermy was not used, all vessels and nerves being ligated with 00-silk. The raw surface of the lesser curve was not peritonealized. The patient was participating in a post-operative metabolic study, for which a subclavian catheter for intravenous alimentation and a nasogastric tube had been positioned.

Two days after operation the patient had pains in the epigastrium and left hypochondrium and became dyspnoeic. Chest x-ray examination showed a large bilateral hydrothorax. Thoracocentesis yielded 1400 ml of milky fluid from the right pleura and 400 ml from the left pleura. The fluid was a diluted solution of Intralipid, which the patient had received through the left subclavian vein. The subclavian catheter was removed.

FIG. 1—Microscopic appearance of gastric perforation showing necrotic border (arrowed) and thrombosed vessel. (H. and E. $\times 36$.)

For the next three days the patient remained comparatively well. He passed flatus on the third day after operation, but the abdomen

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