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Somatostatin and the dumping syndrome

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Abstract

Infusion of somatostatin reduced the symptoms of the early dumping syndrome after oral glucose was given and also reduced the associated tachycardia and rise in packed cell volume. It inhibited the secretion of enteroglucagon, neurotensin, and vasoactive intestinal polypeptide, which are raised in patients with the dumping syndrome and may have an aetiological role. It also prevented the reactive hypoglycaemia of late dumping by inhibiting the release of gastric inhibitory polypeptide and insulin.

Somatostatin, possibly through its inhibitory effects on hormonal secretion, may have a role in the management of patients with the early and late dumping syndrome.

Introduction

The dumping syndrome is a complication of gastric surgery and has two phases. Early dumping occurs within 30 minutes after a meal and is thought to be due to the rapid transit of hyperosmolar food into the upper small bowel; this causes secretion of water and electrolytes into the small intestine, haemoconcentration, and thus the characteristic symptoms of sweating, palpitations, faintness, dizziness, abdominal distension, and diarrhoea. In early dumping the plasma concentrations of the gut regulatory peptides, enteroglucagon,¹ neurotensin,² and vasoactive intestinal polypeptide,³ are considerably raised, and it has been suggested that the vasomotor peptides neurotensin and vasoactive intestinal polypeptide may contribute to the

pathogenesis of the symptoms. Late dumping is due to hypoglycaemia several hours after a meal and is attributed to hyperinsulinaemia secondary to the rapid initial rise of blood glucose concentration.

Somatostatin is a peptide made up of 14 amino acids that is found in high concentrations in the pancreas and gut. It inhibits the secretion of numerous hormones in the gut and pancreas, including enteroglucagon, neurotensin, vasoactive intestinal polypeptide, and insulin,^{4,5} and also small intestinal secretion of water and electrolytes in animals⁶ and patients with pancreatic cholera.⁷ These actions suggested that it might be useful in managing the early and late dumping syndrome, and we carried out a study to test this.

Patients and methods

We studied six men with a mean (SEM) age of 50 (5.5). Surgical procedures were two total gastrectomies, two Polya's operations, one gastrojejunostomy and vagotomy, and one vagotomy and pyloroplasty followed by antrectomy and gastrojejunostomy. The last operation had been performed a mean of 11 (3) years previously. During normal life all six patients regularly experienced symptoms of the early dumping syndrome such as faintness, palpitations, sweating, weakness, and somnolence, and one also had the symptoms of reactive hypoglycaemia.

The patients were admitted to hospital and fasted from midnight. The next morning a venous cannula was put into a vein of each arm and basal blood samples were taken at -30, -15, and 0 minutes. At 0 minutes an infusion of isotonic sodium chloride with 0.3 mmol (20 g) human albumin/l was started in the other arm on the control day and somatostatin (Serono Laboratories, UK) 70 pmol (110 ng)/kg/min was added on the treatment day. The control day always preceded the treatment day; the researcher knew what the patient was receiving, but this information was withheld from the patient. After 30 minutes of infusion oral glucose 50 g in 200 ml water was given and the patients assessed for a further three hours. In the three patients who did not develop symptoms of early dumping with 50 g glucose the test was repeated with 100 g glucose in 400 ml water, and dumping was then provoked. The pulse rate was monitored regularly and blood samples collected throughout.

Packed cell volume and serum glucose concentration were monitored by standard techniques. Blood for hormonal radioimmunoassay was collected into heparinised tubes containing 200 µl aprotinin/10 ml blood. The tubes were centrifuged and the plasma decanted within

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one hour after venesection and stored at -20°C until the time of radioimmunoassay.⁸ The research protocol was approved on ethical grounds by the hospital research committee, and the patients gave informed consent. Results are expressed as means (SEM). Student's *t* test for paired data was used, and *p* < 0.05 was taken to be significant.

Results

All of the patients developed subjective symptoms of the early dumping syndrome after receiving oral glucose. Symptoms were primarily described as weakness and somnolence in three patients, lightheadedness in two, and nausea in one. These symptoms all started about 15 minutes after the oral glucose was given and lasted 30-60 minutes. Early dumping was associated with tachycardia (fig 1), a rise in the packed cell volume (fig 2), and a rapid rise in serum glucose concentration (fig 3). When somatostatin was infused the three patients who had suffered lightheadedness and nausea were asymptomatic. In the three patients with weakness and somnolence the symptoms of two improved and of one were unchanged. Somatostatin blocked the rise in pulse rate and significantly reduced the initial rise in the packed cell volume and serum glucose concentration. In addition, it totally suppressed the rises in concentrations of entero-glucagon, neurotensin, and vasoactive intestinal polypeptide that are associated with dumping (table).

FIG 1—Mean (SEM) pulse rate after administration of oral glucose with (■—■) and without (●—●) somatostatin. Infusion was started at time 0 and oral glucose given at 30 minutes. **p* < 0.05.

Effect of somatostatin on plasma hormone concentrations (pmol/l) in the dumping syndrome. (Values are means (SEM))

	Time (mins) from start of infusion											
	- 30	0	15	30	45	60	75	90	120	150	180	210
Entero-glucagon:												
Control	79 (17)	72 (16)	73 (14)	74 (13)	265 (51)*	372 (55)*	348 (69)*	270 (64)*	198 (34)*	159 (40)*	120 (24)	115 (23)
Somatostatin	71 (12)	61 (10)	43 (5)	54 (11)	46 (11)	44 (14)	47 (13)	51 (13)	47 (13)	51 (14)	73 (23)	67 (17)
Neurotensin:												
Control	17 (3)	16 (2)	15 (3)	16 (3)	81 (15)*	64 (16)*	39 (8)*	36 (12)	21 (4)	15 (3)	15 (2)	15 (2)
Somatostatin	18 (4)	17 (3)	11 (1)	10 (1)	10 (1)	10 (3)	13 (2)	12 (3)	12 (1)	10 (1)	11 (1)	12 (1)
Vasoactive intestinal polypeptide:												
Control	3 (1)	3 (1)	5 (1)	6 (1)	6 (1)*	5 (1)	4 (1)	5 (2)	3 (1)	3 (1)	3 (1)	3 (1)
Somatostatin	4 (1)	3 (1)	4 (1)	3 (1)	4 (1)	3 (1)	3 (1)	2 (1)	3 (1)	4 (2)	4 (1)	4 (1)
Gastric inhibitory polypeptide:												
Control	15 (2)	15 (2)	14 (2)	13 (2)	39 (8)*	51 (4)*	43 (6)*	33 (4)*	25 (3)*	24 (4)*	16 (2)*	15 (4)*
Somatostatin	12 (1)	13 (2)	12 (3)	10 (2)	10 (1)	11 (2)	9 (2)	9 (2)	9 (2)	7 (2)	8 (2)	7 (2)
Insulin:												
Control	30 (7)	28 (8)	25 (8)	29 (13)	241 (46)*	529 (151)*	425 (113)*	415 (125)*	339 (246)*	40 (11)	29 (10)	43 (26)
Somatostatin	29 (7)	29 (10)	10 (2)	5 (1)	5 (1)	7 (2)	13 (4)	13 (6)	37 (25)	33 (21)	34 (14)	89 (51)

**p* < 0.05.

FIG 2—Mean (SEM) packed cell volume after administration of oral glucose with (■—■) and without (●—●) somatostatin. Infusion was started at time 0 and oral glucose given at 30 minutes. **p* < 0.05.

FIG 3—Mean (SEM) serum glucose concentration after administration of oral glucose with (■—■) and without (●—●) somatostatin. Infusion was started at time 0 and oral glucose given at 30 minutes. **p* < 0.05.
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

On the control day five of the six patients developed a mean nadir in blood glucose concentration of 2.7 (0.2) mmol/l (48.7 (3.6) mg 100 ml). This asymptomatic hypoglycaemia was corrected by an infusion of somatostatin (fig 3), and the effect was associated with a significant decrease in the secretion of insulin and gastric inhibitory polypeptide (table).

Discussion

This study shows that somatostatin can prevent the symptoms of the early dumping syndrome. It also blocks the accompanying tachycardia, haemoconcentration, and rapid rise in serum glucose concentration. In normal subjects this dose of somatostatin accelerates gastric emptying of glucose, so a slowing of gastric emptying is unlikely to be its mode of action.⁹ Somatostatin may act partly by preventing the secretion of water and electrolytes into the intestine^{6,7} and partly, as this study shows, by reducing the secretion of regulatory peptides, which are known to be secreted in excess and so may play a part in the pathophysiology of the dumping syndrome. Enteroglucagon and neurotensin are hormones localised to the terminal ileum and are released probably because large amounts of undigested nutrients are reaching this part of the intestine. Enteroglucagon is thought to have a trophic effect on intestinal villi, and in animals infusion reduces the secretion of gastric acid.¹⁰ Infusion of neurotensin delays gastric emptying and also has a vasodilative and hypotensive effect.¹¹ Vasoactive intestinal polypeptide has noticeable hypotensive effects, and the reduction in concentrations of neurotensin and vasoactive intestinal polypeptide after oral glucose has been given may explain some of the beneficial effects of somatostatin in preventing the symptoms of the early dumping syndrome.

Somatostatin prevents the reactive hypoglycaemia that occurs in patients with the dumping syndrome after oral glucose has been given. Gastric inhibitory polypeptide is released when glucose is given orally and is thought to contribute to the effect whereby much larger amounts of insulin are secreted when glucose is given orally rather than intravenously.¹² In this study a great reduction in early secretion of gastric inhibitory polypeptide and insulin was seen after oral glucose was given during somatostatin infusion, and this probably explains the alleviation of subsequent hypoglycaemia.

Somatostatin has a role in managing numerous diseases such as bleeding peptic ulcers,¹³ the carcinoid syndrome,¹⁴ pancreatic endocrine tumours,⁵ nesidioblastosis,¹⁵ and diabetes mellitus.¹⁶ Although it has multiple effects on physiological function, side effects are unusual, and none were seen in this study. Long acting analogues have been developed that are effective when given subcutaneously twice daily.^{5,14,17} Analogues of somatostatin have also been developed that in animals specifically inhibit secretion in the gut and have less generalised effects.¹⁸ If

dumping is found to be due more to intestinal secretion than to the vasomotor effects of hormones analogues specific to the gut might have a particular role in the early dumping syndrome.

Dumping is fairly rare after gastric surgery but can be a disabling and unpredictable problem. Treatment is unsatisfactory. Small, frequent meals are usually encouraged, but, although these should abolish late dumping, early dumping often persists. Ingestion of isomolar meals is impracticable, but particular precipitating foods can be avoided. Use of high fibre foods such as guar and pectin and of glycoside hydrolase inhibitors, so that intestinal osmotic activity is reduced, may be beneficial,¹⁹ but the foods are unpalatable. Somatostatin, and possibly its analogues, thus offer an attractive new approach to treatment.

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100 YEARS AGO

Considering how few facilities there are in London for open-air bathing, especially since our once noble river has become, below lock, little better than a sewage-duct, it is a pity that any obstacles beyond reasonable restrictions should be laid in the way of the utilisation for this purpose of the lakes and ponds in our parks; and it is disappointing to learn that the Commissioners of Works, in response to a request of Lord Brabazon that bathing might be permitted in what is known as the Ladies' Pond, Battersea Park, have stated that they are not prepared to accede to the suggestion. This appears the more unreasonable as the lakes in Victoria and Hyde Parks have long been used for bathing, at certain hours, without complaints from the frequenters of the parks or the residents in their neighbourhoods. At this season of the year, most persons are compelled to take their morning dip at home, or within the shelter of the covered swimming-bath, though it is said

there are a hardy and heroic few who trouble the waters of the Serpentine throughout the winter; but in the summer-time, open-air bathing is a luxury to all who can enjoy it, and a necessity to the health of many thousands whose domestic means of ablution are limited to the circumference of a wash-hand basin. Is there any logical reason, we would ask, why what is decent and commendable at Brighton or at Trouville should be immoral and objectionable in London? and why, with suitable dresses and dressing-sheds, bathing should not be permitted in our parks, even to persons of both sexes? We can hardly hope that a plunge in the Serpentine will ever become as much a *sine qua non* of fashionable existence in dusty June as a ride or saunter in the Row; but we would plead for those who can seldom visit, and are often unwelcomed at, seaside watering-places, and whose means of healthful and innocent recreation are sadly limited. (*British Medical Journal* 1885;i:449.)