SHORT COMMUNICATION

Effect of a long-acting octapeptide analogue of somatostatin on growth hormone and pancreatic and gastrointestinal hormones in man


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Summary

1. The biochemical specificity and duration of action of a single 5 mg subcutaneous dose of des-AA^{1,2,4,5,12,13}-D-Trp^8-somatostatin were evaluated in eight patients with symptomatic pancreatic endocrine tumours.

2. There was a reduction by more than 50% for at least 10 h in plasma concentrations of growth hormone, glucagon, gastrin and motilin and for 4-5 h in plasma insulin, pancreatic polypeptide, gastric inhibitory polypeptide and enteroglucagon.

3. This study shows that this octapeptide analogue of somatostatin, like somatostatin itself, lacks specificity in the hormones it suppresses. However, its prolonged duration of action against several hormones when given subcutaneously suggests that it may be of therapeutic use in a number of disease states where excessive plasma concentrations of one or more of these hormones occur.

Key words: gastrointestinal hormones, growth hormone, pancreatic hormones, somatostatin.

Introduction

Somatostatin is a tetradecapeptide which has been demonstrated both in neural tissue, particularly the hypothalamus, and endocrine cells, for example the pancreatic D cell. Its action in reducing the secretion of numerous hormones including growth hormone [1], insulin [2], pancreatic glucagon [3] and gastrin [4] suggested its use as a treatment in endocrine disease characterized by excess production of one or more of these hormones. Favourable therapeutic responses have been reported in patients with diabetes mellitus, nesidioblastosis due to hyperinsulinism [6] and carcinoid flushing [7].

However, the clinical use of somatostatin is limited by its very short duration of action (plasma half-life about 2–3 min) and by its lack of hormone specificity. In an attempt to overcome these problems a large number of somatostatin analogues has been synthesized recently, several of which have been reported with either prolonged activity or hormone specificity in experimental animals [8–10]. Excision of six of the constituent 14 amino acids has led to the development of a hydrophobic molecule which maintains the effects of the parent compound. This analogue (des-AA^{1,2,4,5,12,13}-D-Trp^8-somatostatin) was administered by subcutaneous injection to patients with symptomatic pancreatic endocrine tumours and was found to have a prolonged duration of action of up to 24 h on tumour-produced plasma hormones [11]. The aim of the present study was to assess the selectivity and duration of action of this peptide against a spectrum of non-tumour-derived hormones.

Patients and methods

des-AA^{1,2,4,5,12,13}-D-Trp^8-Somatostatin (hereafter referred to as the octapeptide analogue) was
synthesized by total solid-phase synthesis and was administered as a single dose of 5 mg [dissolved in 1 ml of 10% (w/v) human albumin] by subcutaneous injection to eight overnight fasted patients with symptomatic pancreatic endocrine tumours. There were three patients with insulinomas, three with gastrinomas and one each with a vasoactive intestinal polypeptide-secreting tumour (vipoma) and a glucagonoma.

The patients fasted for the 3 h after the injection, ate lunch at 12.00 hours and dinner at 18.00 hours, and were ambulant during the investigation. The analogue was injected at 09.00 hours and venous blood was taken at −1, 0, 1, 2, 3, 4, 5, 8, 12 and 24 h for measurement of plasma glucose by the glucose oxidase technique [12] and growth hormone [13], glucagon [14], insulin [15], pancreatic polypeptide [16], gastrin [17], motilin [18], gastric inhibitory polypeptide [19] and enteroglucagon [20] by radioimmunoassay.

Blood for glucose analysis was collected into fluoride oxalate and for hormone analysis into heparinized tubes containing Trasylol (400 kallikrein inactivating units/1 ml of blood). Samples for hormone measurement were centrifuged immediately and the plasma separated and stored at −20°C until radioimmunoassay. In view of the variation in plasma concentrations of some of the hormones, results are expressed as means ± SEM of the percentage of the basal hormone concentrations (the mean of the −1 and 0 h samples).

Ethical permission was obtained for the study from the Research Ethics Committee of the Royal Postgraduate Medical School. The nature of the study was carefully explained to each patient and written consent obtained.

Results

Percentage changes in the eight hormones over the 24 h period after subcutaneous octapeptide somatostatin are shown in Fig. 1. Mean plasma concentrations were respectively suppressed by more than 50% for 11 h for growth hormone, 10 h for glucagon, gastrin and motilin, 5 h for insulin and pancreatic polypeptide and for 4 h for gastric inhibitory polypeptide and enteroglucagon. The

![Fig. 1. Effect of subcutaneous des-AAA1,2,4,5,12,13,D-Trp8 somatostatin on plasma concentrations of (a) growth hormone (HGH), glucagon, insulin and pancreatic polypeptide (PP) and (b) gastrin, motilin, gastric inhibitory polypeptide (GIP) and enteroglucagon. Results are expressed as means ± SEM.](image-url)
percentage fall in plasma insulin and gastrin was similar whether the hormone originated from tumour or non-tumour cells. Plasma glucose showed no consistent changes over this period of time, but rose in all cases after meals.

No subject noted any adverse clinical effects from this somatostatin analogue and haemoglobin, leucocyte count, platelet count, plasma urea, electrolytes and serum creatinine and liver function tests were similar before and 24 h after the peptide was administered. On three occasions in two patients 10 mg doses of the analogue have also been given subcutaneously without any adverse effects.

Discussion

Natural tetradecapeptide somatostatin when given subcutaneously has a very short duration of action and coupling to protamine zinc only prolongs the duration of action for about 30 min [21]. By contrast, the octapeptide analogue reduced plasma levels of several hormones by more than 50% for up to 11 h in the present study. Previous studies have shown that plasma concentrations of hormones return to normal in under 60 min when an intravenous infusion of this somatostatin analogue is discontinued suggesting its functional half-life to be as rapid as that of the parent peptide [22]. Thus its prolonged action would appear to be due to slower release from the site of injection (perhaps the result of its very hydrophobic nature) rather than reduced clearance from either plasma or receptor sites.

The two main limitations of somatostatin as a therapeutic agent are its short duration of action and its lack of hormonal specificity. Octapeptide somatostatin would appear to have overcome the first of these problems, but retained the capacity of tetradecapeptide somatostatin to inhibit the release of a broad spectrum of hormones. Although the suppression of several hormones for prolonged periods in patients is theoretically undesirable the consequences of such a manoeuvre are far from clear. None of our patients experienced any untoward symptoms at the dose of octapeptide somatostatin used in the present study and intravenous infusion of linear somatostatin for 3 days in previous reports similarly had no apparent adverse effects [5]. In patients with pancreatic tumours secreting somatostatin plasma levels of somatostatin may be raised to over 500 pmol/l for long periods and although hyperglycaemia and steatorrhoea are usual features, symptoms are not incapacitating and may be fully reversible after treatment [23].

Thus, although hormone specificity would be a desirable property of long-acting somatostatin analogues, it may not be essential when only relatively short-term therapy is envisaged.

No subjective, haematological or biochemical side-effects were seen with these 5 mg injections of the octapeptide analogue. In short-term infusions of tetradecapeptide somatostatin the plasma glucose concentration may fall during fasting but, even though the patients in this study fasted for the first 3 h of the experiment, no consistent change in blood glucose concentrations was observed. Thus this dose was free of complications and in preliminary studies we have also found no side-effects with 10 mg subcutaneous injections.

The ability of the octapeptide analogue to effect prolonged suppression of both growth hormone and glucagon suggests that it might be useful in patients with acromegaly and hyperglucagonaemia. Other groups of patients who might benefit from treatment with this analogue include those with nodulated oesophagus, pancreatic endocrine tumours, the carcinoid syndrome, diarrhoea of various types and bleeding peptic ulcers. Clearly further studies of the therapeutic potential of this peptide are indicated.

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References


