Clinical Evaluation of Somatostatin as a Potential Adjunct to Insulin in the Management of Diabetes Mellitus

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Summary. To determine whether somatostatin, an inhibitor of glucagon and growth hormone secretion, might be useful as an adjunct to insulin in the management of diabetic hyperglycaemia, seven insulin-requiring diabetic men were given somatostatin (100 µg/h, IV) continuously for 3 days after their diabetes had been treated intensively by diet and insulin on a metabolic ward. During infusion of somatostatin and despite reduction in average insulin dose exceeding 50%, there was improvement in diabetic control as assessed by postprandial hyperglycaemia, 24-h glycosuria and the average daily serum glucose level and its fluctuation; when somatostatin was discontinued, but insulin doses held constant, diabetic control rapidly worsened. No adverse effects were observed. These results indicate that somatostatin plus insulin can be a more effective regimen than insulin alone in controlling diabetic hyperglycaemia. A longer acting and more selective somatostatin preparation may prove useful as an adjunct to insulin in the management of diabetes.

Key words: Somatostatin, glucagon, insulin, growth hormone, treatment of diabetes.

Impaired insulin secretion or action is widely acknowledged to be the prime factor responsible for carbohydrate intolerance in both juvenile-onset and adult-onset varieties of diabetes mellitus [1, 2]. Conventional insulin therapy, however, has not proved uniformly successful in normalizing blood glucose [3, 5] or in preventing long-term complications [6, 7]. Consequently, improved methods for insulin delivery, such as an artificial pancreas and transplantation of pancreatic tissue are currently being

sought. Since factors other than insulin lack, such as glucagon [8, 9] and growth hormone excess [9, 11], may also contribute to the severity of diabetic hyperglycaemia, the removal or reduction of such insulin antagonists might improve metabolic control in diabetes.

This view is supported by recent studies employing somatostatin [12, 13] which, in addition to other actions [12, 14–16], inhibits the secretion of glucagon [17] and growth hormone [13]. In short-term experiments infusion of this peptide reduced both fasting [18–21] and postprandial hyperglycaemia [22–24] in insulin-requiring diabetic patients and rendered exogenous insulin more effective [22, 23]. This suggests that such an agent might act as an adjunct to insulin in the treatment of diabetes mellitus. Therefore, the present investigation was undertaken to determine whether combined use of somatostatin and insulin would be better than the optimal use of insulin alone.

Materials and Methods

Subjects

Informed consent was obtained from seven men with diabetes mellitus requiring insulin therapy. All were in good health and took no medications except insulin; their clinical characteristics are shown in Table 1. Three had ketosis-prone diabetes as evidenced by recent episodes of ketoacidosis; the remaining patients (two of whom were slightly obese) had ketosis-resistant adult-onset diabetes.

Experimental Protocol

Patients were admitted to a metabolic ward and placed on a diet designed to maintain their weight

Table 1. Clinical characteristics of diabetic subjects

Sub- ject	Age			Duration	
	(Yr)	% IBW ^a	Ketoacidosis	Diabetes	Insulin therapy
1	21	93	+	6 wks	6 wks
2	22	97	+	6 wks	6 wks
3	25	98	+	7 yrs	7 yrs
4	46	104	—	6 yrs	3 yrs
5	59	139	—	15 yrs	2 wks
6	69	110	—	4 yrs	1 wk
7	53	125	—	13 wks	13 wks

^a Metropolitan Life Insurance Co. tables

and facilitate optimal diabetic control. The diet contained 2032 Kcal/day as 50% carbohydrate (C), 30% fat (F), and 20% protein (P) distributed over 5 meals taken at 0800, 1100, 1300, 1800, and 2200 h as follows: breakfast (26 g P, 21 g F, 58 g C — 518 Kcal), midmorning snack (1 g P, 2 g F, 28 g C — 131 Kcal), lunch (23 g P, 19 g F, 64 g C — 518 Kcal), dinner (38 g P, 20 g F, 79 g C — 652 Kcal), and evening snack (13 g P, 7 g F, 26 g C — 213 calories). These diets were maintained constant throughout the study. Additionally patients were placed on divided doses of insulin consisting of mixtures of Soluble and NPH insulin (Eli Lilly Monocomponent®) given subcutaneously $\frac{1}{2}$ h before breakfast and dinner. Insulin regimes were individualized over a 5- to 7-day equilibration period so that serum glucose values obtained prior to each meal were maintained at a level considered the lowest possible without inducing symptomatic hypoglycaemia. The regime for each subject is shown in Table 2. In several instances patients experienced transient mild symptoms of hypoglycaemia, but these passed without necessitating intervention.

Upon completion of the equilibration period the patients were studied for 7 consecutive days: blood was sampled at hourly intervals from 0700 to 2200 h and thence at 2400, 0400, and 0700 h through an indwelling 18-gauge angiocath® inserted into a forearm vein and kept patent by a slow infusion of 0.9% NaCl solution. To conserve blood, serum glucose levels alone were determined on days 1 and 7; whereas on days 2 through 6 serum glucose, free insulin, growth hormone, and plasma glucagon levels were also determined. During the first 2 days (control period 1) the previously "optimized" insulin regimen was maintained. On the morning of the third experimental day between 0700 and 0730 h an infusion of synthetic linear somatostatin (100 µg/h) (kindly supplied by Doctors Roger Guillemin and Jean River of the Salk Institute, San Diego, California, and under IND 10416 from the U. S. Food and

Drug Administration) was started in a forearm vein of the arm contralateral to the one used for blood sampling. The somatostatin was dissolved in 0.9% NaCl, sterilized by passage through a millipore® filter (0.22 µ) and infused as previously described [25] except for the different infusion rate (100 µg/h vs. 500 µg/h). Each day of the 3-day somatostatin infusion, while patients were maintained on a constant diet, insulin doses were reduced stepwise to avoid anticipated hypoglycaemia [22] (see Table 2 for insulin given each day) so that by the third day of the somatostatin infusion patients were receiving less than 50% of the insulin they had received during the first control period. This dose of insulin was then maintained for an additional 2 days (control period 2) after stopping the somatostatin infusions between 0700 and 0730 h on the morning of the sixth experimental day.

Analytical Determination

Serum glucose was determined enzymatically (glucose oxidase) using a Yellow Springs® glucose analyzer. Plasma glucagon and serum growth hormone were measured by radioimmunoassay as previously described [26]. Because insulin antibodies in the sera of some patients would interfere with the insulin immunoassay, these antibodies and any insulin bound to antibody were removed from sera prior to the immunoassay of insulin using the polyethylene glycol extraction method of Nakagawa et al. [27] and then insulin levels were determined in triplicate as free insulin in a solid phase assay system. Recovery of insulin added to normal serum averaged $93 \pm 1\%$ using this technique. Briefly, 0.5 ml serum was added to 0.5 ml chilled 25% (w/w) polyethylene glycol (average molecular weight 6000–7500, Matheson, Coleman & Bell). The mixture was immediately agitated with a vortex mixer for 1 min and then centrifuged (1600 g) for 45 min at 4° C. Supernatant, 0.1 ml, and similarly extracted human insulin standards (Burroughs Wellcome), made up in 0.4 mol/l glycine buffer pH 8 containing 1 g/100 ml human serum albumin, were added to polystyrene tubes (# 2052 Falcon) previously coated with insulin antibody (Miles Laboratories). In the coating procedure 1 ml insulin antibody, diluted to 1:1000 in 0.4 mol/l glycine buffer pH 8 containing no albumin, was pipetted in assay tubes, allowed to stand 2 h at room temperature and then aspirated. Coated tubes were washed twice with 1.3 ml human serum albumin, 1 g/100 ml, in 9 g/l NaCl, inverted and allowed to dry overnight at 4° C. Tubes were used within 1 wk of coating and the coating solution was reused only once. To the

Fig. 1. Effect of 3-day somatostatin infusion on glucose, free insulin, glucagon and growth hormone levels in three juvenile-onset type diabetic subjects

above assay mixture, 0.5 ml ^{125}I insulin (70–140 $\mu\text{Ci}/\mu\text{g}$, Union Carbide) was added. After gentle mixing tubes were incubated overnight at 4° C and subsequently aspirated, washed twice with distilled water, and counted. The sensitivity of this system is 5 $\mu\text{U}/\text{ml}$ with an interassay variation less than 15%.

Daily glucose, creatinine, and amylase content in 24 hour urine specimens and daily serum total bilirubin, cholesterol, triglyceride, uric acid, alkaline phosphatase, glutamic oxaloacetic transaminase, lactic dehydrogenase, and serum electrolyte (sodium, potassium, chloride, and bicarbonate) levels were determined by Technicon Auto Analyzer®. Daily RBC, WBC, and platelet counts were determined using a Coulter Counter®. Template bleeding times on the day prior to, the last day of, and the day after the somatostatin infusions, were determined as previously described [28].

Calculations and Statistical Analyses

An “average diurnal glucose level” for each patient was calculated by dividing the sum of all glucose determinations for a given 24-h period by the number of determinations ($n = 18$). As an indicator of fluctuation in glucose levels throughout the day (and hence stability of diabetic control) standard deviations of the “average diurnal glucose level” were calculated from glucose determinations made throughout the experimental days in each patient using computer programme STI-01 (Texas Instruments). Statistical significance was evaluated using paired two-tailed Student *t* tests after checking

Fig. 2. Effect of 3-day somatostatin infusion on glucose, free insulin, glucagon and growth hormone levels in four adult-onset type insulin-requiring diabetic subjects

for parametric distribution, unless stated otherwise. All data are presented as mean $\pm$ SEM.

Results

Mean serum glucose, free insulin, growth hormone and plasma glucagon levels during the 7 consecutive days of the study are shown separately for the three juvenile-onset type diabetic subjects and the four adult-onset type diabetic subjects in Figures 1 and 2 respectively. Insulin doses, average diurnal serum glucose levels and its variability (standard deviation) and 24-hour glucosuria for each subject during each day of the study are given in Table 2. The same amount of insulin was administered to a given patient on the first 2 days. This averaged 79 ± 9 U per day given as a mixture of soluble and NPH insulin $\frac{1}{2}$ h before breakfast and dinner for the seven subjects. Insulin doses were similar in six of the subjects (67–86 U/day), but one adult-onset type diabetic received 125 U/day, which resulted in a greater average insulin dose for this group. Diabetic control, as assessed by serum glucose levels, average diurnal glucose level and its variability, and 24 hour glucosuria was similar on each of the initial two control days for each group of subjects, indicating that a stable baseline had been achieved for subsequent studies. Slightly better control was achieved in the juvenile-onset type diabetic subjects, although both groups had excessive postprandial hyperglycaemia, elevated average diurnal serum glucose levels, and abnormally wide fluctuations in serum glucose levels throughout the day.

Table 2. Individual and mean insulin doses, average diurnal serum glucose level and its standard deviation, and 24-h glucosuria

Day	1	2	3	4	5	6	7
<i>Insulin doses (U)</i>							
Subject	Soluble AM PM	NPH AM PM	Soluble AM PM	NPH AM PM	Soluble AM PM	NPH AM PM	Soluble AM PM
1	15 11	30 11	8 7	18 7	7 6	16 6	7 6
2	12 10	36 10	7 7	14 7	7 6	12 6	5 5
3	13 10	39 13	8 5	16 8	8 5	16 8	8 8
4	14 15	42 15	8 8	16 8	8 8	16 8	8 8
5	23 26	50 26	16 12	32 12	10 10	20 10	20 10
6	10 10	22 14	5 6	10 5	5 6	10 5	5 6
7	15 12	36 16	12 10	30 12	10 10	28 10	8 8
Mean	15 13	36 15	9 8	19 8	7 7	17 8	7 7
<i>Average diurnal serum glucose and its standard deviation (SD) — mg/100 ml</i>							
1	111 (49)	111 (47)	95 (32)	92 (27)	101 (27)	156 (43)	164 (41)
2	115 (33)	114 (35)	93 (23)	104 (20)	104 (26)	171 (36)	176 (37)
3	127 (58)	125 (57)	100 (23)	101 (23)	105 (23)	238 (68)	229 (63)
4	140 (65)	141 (61)	135 (54)	139 (58)	133 (41)	155 (65)	162 (61)
5	149 (49)	147 (48)	134 (40)	132 (37)	121 (25)	159 (46)	167 (47)
6	171 (55)	169 (54)	200 (49)	165 (40)	147 (38)	182 (55)	185 (51)
7	107 (26)	106 (27)	111 (21)	100 (18)	92 (14)	121 (28)	128 (29)
Mean	131 (48)	130 (47)	124 (35)	119 (32)	115 (28)	169 (49)	173 (47)
± SEM	9 5	9 5	14 5	10 5	7 4	14 6	14 5
<i>24-h glucosuria (g)</i>							
1	0	0	0	0	0	6.2	6.8
2	0	0	0	0	0	10.2	10.5
3	1.5	1.6	0	0	0	57.4	58.4
4	4.2	3.9	2.8	3.9	2.8	6.7	6.8
5	4.9	3.9	3.0	3.3	1.7	7.1	8.6
6	8.9	8.6	12.1	8.4	5.5	11.2	11.6
7	0	0	0	0	0	1.7	1.4
Mean	2.8	2.6	2.6	2.2	1.4	14.3	14.9
± SEM	1.2	1.2	1.6	1.2	0.8	7.2	7.4

Fig. 3. Comparison of glucose, free insulin, glucagon and growth hormone levels during administration of identical quantities of insulin with (last day of somatostatin infusion) and without somatostatin (first day off somatostatin). Insulin alone 38U (□ □) when not significantly different, and (■ ■) when significantly different ($p < 0.05$) from insulin 38U plus somatostatin (o-o)

During infusion of somatostatin continuously for the next 3 days, insulin doses were reduced a similar degree in each group of subjects, averaging for the seven patients 47 ± 8 , 42 ± 5 , and 38 ± 3 U/day on the first, second and third days of the somatostatin infusion respectively. In both groups diabetic control did not worsen despite this overall 50% reduction in insulin dosage. The juvenile-onset type diabetics had an immediate diminution in hyperglycaemia, which persisted throughout the infusion of somatostatin; diabetic control in the adult-onset group also improved, but this was not clearly evident until the third day of the somatostatin infusion. In both types of diabetic subjects diabetic control deteriorated immediately after stopping the somatostatin infusion, although insulin doses were unchanged; in all subjects average diurnal serum glucose levels and its variability and 24 hour glucosuria increased (Table 2). Although the adult-onset diabetic subjects' control deteriorated less than that in the juvenile-onset group, similar degrees of deterioration were observed on the first and second days after discontinuation of the somatostatin in each group, indicating the reproducibility and persistence of the effect.

Fig. 4. Comparison of glucose, free insulin, glucagon and growth hormone levels during administration of somatostatin plus insulin (last day of somatostatin infusion) vs. twice as much insulin alone (day immediately preceding start of somatostatin infusion). Insulin alone 79U (□ □) and (■ ■) when significantly different ($p < 0.05$) from insulin 38U plus somatostatin (o-o)

Comparison of Glucose, Free Insulin, Glucagon and Growth Hormone Levels During Administration of Identical Quantities of Insulin with and without Somatostatin (Fig. 3)

Since both juvenile and adult-onset type of diabetic subjects responded similarly during the study, their data were pooled for statistical evaluation. Figure 3 compares the mean ($\pm$ SEM) serum glucose, free insulin, growth hormone and plasma glucagon levels for the seven subjects observed on days 5 and 6 of the study during administration of identical quantities of insulin, with and without somatostatin, respectively. At almost all sampling times serum glucose and glucagon levels were significantly lower during infusion of somatostatin. The average diurnal glucose level with somatostatin (114 ± 9 mg/100 ml) was significantly lower than that found without it (168 ± 14 mg/100 ml, $p < 0.01$). Moreover, there was less variability in glucose levels throughout the day during infusion of somatostatin, as indicated by the standard deviations of glucose determinations obtained throughout the day in each patient (Table 2, $p < 0.01$).

Circulating free insulin levels were virtually identical on both days, although occasionally higher values were found without somatostatin. Transient rises in both glucagon and growth hormone levels were observed during infusion of somatostatin, reflecting incomplete suppression of the release of these hormones using an infusion of 100 µg/litre somatostatin. Indeed growth hormone levels were significantly lower than control values at only a few sampling times during infusion of somatostatin.

Comparison of Glucose, Free Insulin, Glucagon, and Growth Hormone Levels during Administration of Somatostatin Plus Insulin with Those Observed during Administration of Twice as Much Insulin Alone (Fig. 4)

Figure 4 compares glucose, free insulin, glucagon and growth hormone levels in the seven diabetic subjects on days 2 and 5 of the study when, respectively, subjects received an average of 79 U insulin/day alone and 38 U insulin/day with somatostatin. As anticipated, serum free insulin levels, especially postprandial values, were much higher when patients received the higher dose of insulin without somatostatin. Despite this, serum glucose rose to significantly higher levels after breakfast, lunch and dinner than when patients received half as much insulin plus somatostatin. This resulted in significantly higher average diurnal glucose levels (131 ± 9 vs. 114 ± 9 , $p < 0.01$), although serum glucose levels prior to the evening snack and during the early morning hours were significantly lower when patients received the higher dose of insulin without somatostatin. Accordingly, fluctuation in glucose levels throughout the day (standard deviation of average diurnal glucose levels (46 ± 5 vs. 28 ± 4 mg/100 ml, $p < 0.01$) was less during administration of somatostatin and less insulin. Plasma glucagon levels were significantly lower during infusion of somatostatin at most sampling times, while growth hormone levels were only occasionally lower than those found during administration of the higher dose of insulin without somatostatin.

Adverse Effects

No symptoms or signs of untoward effects were observed during the course of these studies. The patients' appetites and weight remained stable; no nausea, vomiting, abdominal pain, or diarrhoea occurred. No change in urinary amylase and creatinine excretion, serum electrolytes, creatinine, uric acid, cholesterol, triglyceride, glutamic oxaloacetic transaminase, lactic dehydrogenase, or total bilirubin

levels was observed. Red blood cell count decreased significantly, but this was within the range anticipated from the volume of blood sampled during the course of the study (≈ 200 cc/day). No change in white blood cell count, platelet count, or template bleeding time was observed (Full data available from the authors).

Discussion

In short-term studies somatostatin reduces both fasting [18–21] and postprandial hyperglycaemia [22–24] in insulin-dependent diabetic patients. The present investigation was undertaken to determine whether during a more prolonged period of observation addition of somatostatin would offer any advantage over the optimal use of diet and insulin alone. It is to be emphasized, therefore, that prior to administering somatostatin diabetic hyperglycaemia was managed intensively on a metabolic ward with diet manipulation and use of twice-a-day mixtures of soluble and NPH insulin titrated in each patient so as to diminish serum glucose levels just short of hypoglycaemia. The degree of control achieved on this intensive regimen (as assessed by serum glucose levels, average diurnal glucose level, fluctuation of glucose levels and 24 hour glycosuria) would be considered 'good' to 'excellent' by most standards [5, 29–31], but was clearly not normal. In most instances greater amounts of insulin than those chosen as optimal had been used during the preliminary equilibration period; this did result in lower postprandial serum glucose levels, but not without inducing subsequent hypoglycaemia. Thus, in the patients studied who were not considered "brittle" or insulin resistant, the degree of control achieved was probably the best obtainable under the circumstances.

During the infusion of somatostatin over the next three days, while insulin doses were reduced stepwise in excess of 50%, diabetic control improved as indicated by significantly lower postprandial serum glucose values, lower average diurnal glucose levels, and less fluctuation in serum glucose throughout the day. These results appeared to be directly related to the infusion of somatostatin, since diabetic regulation rapidly deteriorated and was worse on both days during the second control period after discontinuation of the somatostatin infusion while the insulin doses were held constant. Thus somatostatin plus insulin can be a more effective therapeutic regimen than insulin alone, even when twice as much insulin is administered alone under presumably optimal conditions.

The maximum therapeutic benefit from somatostatin was probably not achieved in these studies. First of all, no attempt was made to determine the optimal combination of insulin and somatostatin. Rather a suboptimal dose of insulin plus somatostatin was compared to an optimal insulin regimen. Secondly, the dose of somatostatin used in accordance with current Food and Drug Administration limitations was clearly not maximally effective since glucagon and growth hormone levels were not suppressed to the degree found with higher doses of somatostatin [22, 28]. Thirdly, the diabetic patients studied were stable and relatively easy to control; presumably greater advantage may accrue to "brittle" diabetic patients.

The effects on blood glucose levels observed during administration of somatostatin have been attributed generally to its suppression of glucagon and growth hormone secretion [9, 19, 21, 22, 25, 32–34] since it has no intrinsic effects on glucose production [34, 35] or utilization [35]. The results of the present study would support this, since circulating glucagon and growth hormone levels were diminished during infusion of somatostatin and the former generally paralleled changes in diabetic control. However, because of the effects of this peptide on the secretion of other hormones [12, 14, 16] and its effects on gastrointestinal function [15], particularly diminution of splanchnic blood flow [24], delayed gastric emptying [15], inhibition of pancreatic exocrine [36, 37] and gastric acid secretion [38, 39] and delayed xylose absorption [24], mechanisms other than or in addition to suppression of glucagon or growth hormone secretion could have been involved. No gastrointestinal symptoms were observed during the course of the study, and patient weights remained constant suggesting that malabsorption or severe perturbation of gastrointestinal function probably did not occur. Indeed, of the many variables monitored for possible adverse effects, including platelet count and template bleeding time [41], only red blood cell count was altered; and this could readily be explained from the amount of blood sampled.

Because of its short half-life (≈ 2 minutes) [40] and potentially undesirable effects (e. g. inhibition of thyrotropin secretion) [13, 15–17], it seems unlikely that somatostatin itself, as presently available, can be administered therapeutically on a long-term basis. However, the present demonstration that such an agent plus insulin can be superior to insulin alone in the treatment of diabetes mellitus will stimulate the development of a longer acting and more specific preparation.

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