Effects of Somatostatin Added to Insulin in a Glucose-Controlled Insulin Infusion System

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Summary. Five insulin treated diabetics were studied on three consecutive days. Overnight variable intravenous insulin infusions were used before each study to maintain normoglycaemia and to calculate the optimal basal insulin infusion rate (1.1 ± 0.1 U/h) which was then kept constant throughout the study day. A standard 400 kCal breakfast with 25 g xylose was given at 0800 h. When the blood glucose rose above 4.1 mmol/l, an external artificial pancreas was used to infuse either extra insulin (day INS) or somatostatin for either 3 h (day som) or the entire 8 h experimental period (day SOM). Peak post-prandial blood glucose values were similar on all three days. The blood glucose rebounded after the cessation of the somatostatin infusion on day som. Post-prandial blood xylose peaks were lowered by somatostatin on both days but rebounded after the cessation of the somatostatin infusion on day som. The area under the plasma and urinary xylose curves was lowered by somatostatin only on day SOM. Growth hormone and glucagon levels were not statistically different on all 3 days. Thus somatostatin, when added to an optimal insulin infusion, minimised the insulin requirements by slowing intestinal absorption, but led to rebound hyperglycaemia if not feedback controlled.

Key words: Somatostatin, insulin infusion, artificial pancreas, xylose, carbohydrate absorption, glucagon, growth hormone

Continuous insulin delivery systems using feedback (artificial pancreas) or preprogrammed (open-loop) control devices are currently the most effective methods of restoring a normal glycaemic profile in

diabetic subjects [1]. Excessive insulin administration is an unavoidable problem with all such peripheral infusion [2, 3], particularly post-prandially [4]. Somatostatin infusion has been reported to lower the subcutaneous insulin requirements in insulin dependent diabetics [5, 6]. Thus, the present study was carried out to establish whether somatostatin when added post-prandially to a basal IV insulin infusion might obviate the need for high post-prandial doses of insulin. The opportunity was also taken to study the effects of this bi-hormonal infusion on circulating growth hormone and glucagon and the absorption of xylose.

Subjects and Methods

Subjects

Informed consent was obtained from five insulin treated stable uncomplicated diabetics, whose clinical characteristics are shown in Table 1. No residual insulin secretion was detected in any of the patients by using urinary C-peptide determinations. No patient was taking any drug other than insulin, or suffered from any disease other than diabetes at the time of the study.

Table 1. Clinical characteristics of subjects studied

Patients	Age (years)	Ideal body weight (%)	Duration of diabetes (years)	SC insulin doses (U/day)
1	35	88	29	48
2	59	105	15	34
3	65	113	5	38
4	31	105	14	49
5	61	110	19	54
Mean	50	104	16	45
SEM	7	4	4	4

Table 2. Insulin and somatostatin doses during the three periods of the study. The basal insulin infusion rate was the same on each day

		Day INS	Day som		Day SOM	
	Basal insulin rate (U/h)	Superimposed insulin (U)	Somatostatin dose (µg)	Somatostatin rate (µg/h)	Somatostatin dose (µg)	Somatostatin rate (µg/h)
1	0.8	15	600	327	900	300
2	1.2	27	800	300	2000	444
3	1.0	15	500	300	600	240
4	1.3	9	250	500	600	185
5	0.7	24	600	360	1600	267
Mean	1.0	18	550	357	1140	287
SEM	0.1	3	89	37	282	44

Day INS = basal insulin plus glucose-controlled insulin infusion available for 8 h

Day som = basal insulin plus glucose-controlled somatostatin infusion available for 3 h

Day SOM = basal insulin plus glucose-controlled somatostatin infusion available for 8 h

Fig. 1. Mean $\pm$ SEM blood glucose and plasma xylose on day INS (—), day som (-----) or day SOM (- · -). *Blood glucose:* INS results were significantly different ($p < 0.05$) from SOM results between 2 and 3 h, and from som results between 3 and 8 h. SOM and som results differed significantly ($p < 0.05$) between 4 and 7 h. *Plasma xylose:* INS results differed significantly ($p < 0.05$) from SOM results at 3 and 4 h, and from som results at 5 h. SOM and som results differed significantly at 5 h

Experimental Protocol

Subjects were studied at bed-rest on three consecutive randomly-ordered days from 0800 h to 1600 h.

On the night preceding each period of study, insulin was infused IV by a variable rate pump in order to begin each experiment at normoglycaemic levels. In addition, the mean individual basal infusion rate was calculated from the first night of infusion and then held constant throughout the three 8 h studies.

A standard breakfast, containing 400 kCal (40% carbohydrate, 20% protein and 40% fat) was given at 0800 h together with 25 g xylose (Prolabo, France) dissolved in 200 ml water. No additional meal or drink was given before 1600 h. When blood

glucose rose above 4.1 mmol/l, an infusion given by an external artificial pancreas [7] was superimposed on the basal constant insulin rate until the blood glucose returned to 6.0 mmol/l or less. On day INS the reservoir of the artificial pancreas was filled with insulin (Actrapid, Novo) diluted in 0.154 mmol/l saline to a final concentration of 3 U/ml. According to the algorithm used [8] the maximum infusion rate was 15 U/h. On day som insulin was replaced in the reservoir by cyclic somatostatin (Clin-Midy, France) diluted in 0.154 mmol/l saline to a final concentration of 100 µg/h. After 3 h, the feedback somatostatin infusion was stopped whatever the blood glucose level in order to mimic the conditions of a pre-programmed infusion system. On day SOM, somatostatin was infused as on day som but the somatostatin primed artificial pancreas was left in the closed-loop mode for the whole 8-h period.

Table 3. Area under plasma xylose curves, and urinary xylose elimination

	Day INS	Day som	Day SOM
Plasma xylose areas under the curves (arbitrary units)	167±12	186±12	126±16
		**	**
Urinary xylose elimination (mmol)			
0-4 h	16±2	14±3	13±2
4-8 h	16±2	19±2	13±2
Total	32±2	33±3	26±5
		*	*

See Table 2 for abbreviations. *: $p < 0.05$ **: $p < 0.01$

Analytical Methods

Blood was taken from the ante-cubital vein of the non-infused arm. Heparinized blood was drawn continuously (1.3 ml/h) for continuous blood glucose determination using a Technicon auto-analyzer incorporated into our artificial pancreas [7]. In addition, 10 ml blood were taken hourly and immediately centrifuged. Urine was collected every 4 h. D-Xylose was measured in plasma and urine by a colorimetric method [9]. Absence of interference with glucose was first verified. Immunoreactive plasma glucagon was measured using the Unger antibody 30 K [10]. Plasma growth hormone was measured by a double antibody technique [11].

Statistical Methods

The results were expressed as mean ± SEM. Differences between the mean results of the three periods were analyzed for statistical significance by Student's paired t test.

Fig. 2. Mean ± SEM plasma glucagon and growth hormone on day INS (—) day som (-----) or day SOM (- · -)

Results

Insulin and Somatostatin Doses (Table 2)

The mean basal insulin infusion rate was 1.0 ± 0.1 U/h. An additional 18 ± 3 U were infused postprandially on day INS by the artificial pancreas. Hence a total of 26 U was infused on day INS compared with 8 U on days som or SOM.

The doses of somatostatin infused on days som and SOM were 550 ± 89 and 1140 ± 282 μ g respectively at a rate of 357 ± 37 and 287 ± 44 μ g/h.

Blood Glucose Control (Fig. 1)

Post-prandial glycaemic excursions were similar with the three methods. Maximum blood glucose values were 7.7 ± 0.6 mmol/l at 69 ± 7 min on day INS, 7.3 ± 0.3 mmol/l at 58 ± 14 min on day som and 7.7 ± 0.6 mmol/l at 84 ± 6 min on day SOM. Blood glucose returned rapidly to the initial values on day INS but exhibited a large rebound on day som beginning immediately after the cessation of somatostatin infusion. Values on day SOM were intermediate, showing no rebound but a slower return to initial values which were not reached before 6 h.

Xylose

Plasma xylose results are shown on the lower part of Fig. 1. The postprandial xylose peaks were lower during somatostatin infusion, being 1.5 ± 0.3 mmol/l on day som and 1.3 ± 0.2 mmol/l on day SOM versus 2.1 ± 0.3 mmol/l on day INS ($p < 0.05$ between INS and SOM). A rebound was noted on day som only. After stopping the somatostatin infusion plasma xylose values reached 2.5 ± 0.2 mmol/l at 264 ± 14 min versus 1.6 ± 0.2 ($p < 0.05$) and 1.1 ± 0.2 ($p < 0.01$) on days som, INS and SOM respectively. The areas under the plasma xylose and total xylosurias curves were similar on days INS and som, but 25% lower on day SOM ($p < 0.01$) (Table 3).

Growth Hormone and Glucagon (Fig. 2)

Fasting plasma growth hormone values were in the normal range (3–6 ng/ml). Post-prandial values decreased similarly on the 3 days and showed a late rebound on day INS only. Plasma glucagon was initially in the upper normal range (40–100 pg/ml) and did not exhibit any clear inhibition or rebound during the three studies.

Discussion

This study shows that in the presence of a basal infusion of insulin, the post-prandial rise in blood glucose seen in insulin-dependent diabetics may be as effectively controlled by a timed infusion of somatostatin as by insulin. Somatostatin infused at 300 μ g/h was equivalent to an insulin dose of 18 units. Thus, a bi-hormonal system where mealtime infusions of somatostatin are superimposed on a continuous basal insulin infusion may reduce the hyperinsulinism which invariably occurs when doses of insulin are given prandially [2], and consequently decrease the potential risks of high insulin levels [12]. On the other hand, the absence of any post-prandial increase of insulin values may result in abnormalities of amino-acid and lipid metabolism. In our experimental model, the antidiabetic effect of somatostatin seems to result from a decrease in carbohydrate absorption [13–15], rather than a direct hormonal effect on blood glucose. The paradoxical findings of an unchanged growth hormone and glucagon [16–17] may simply be due to their prior normalisation by the overnight insulin infusion [18–20] although transitory hormonal change cannot be excluded between the samples.

Christensen et al., studying patients in the fasting state, found similar glycaemic rebound to ourselves on stopping somatostatin infusion but also noted a parallel rebound of growth hormone and glucagon [17]. This apparently conflicting result may have been due to the lower infusion of insulin.

In conclusion therefore somatostatin could serve to replace post-prandial doses of insulin in an insulin dependent blood glucose regulating system and thus reduce the quantities of insulin infused. Somatostatin acts primarily by reducing or delaying carbohydrate absorption. Whilst this is less than the reduction seen in states of malabsorption, the potential long term consequences will require consideration and could limit the potential use of somatostatin.

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