Improvement of Glucose Homeostasis in Insulin-dependent Diabetics Using a Miniature Insulin Infusion Pump with a Fixed Profile

K. Kølendorf¹, J. Bojsen², and B. Lørup¹

¹Steno Memorial Hospital, Gentofte and ²The Finsen Laboratory, The Finsen Institute, Copenhagen, Denmark

Summary. Glucose homeostasis was studied in nine longstanding insulin-dependent diabetic patients using a portable pump for intravenous insulin infusion. The 24 h infusion dose was calculated from the conventional SC insulin treatment. The range of basal infusion rates was 2.5 to 15 mU/min and peak delivery rates were raised up to 16-fold from start of main meals for 30–60 minutes. Mean blood glucose improved from 12.0 ± 2.4 to 6.4 ± 1.0 mmol/l (SD) during infusion ($p < 0.01$). Glucose excretion decreased from 23 g/24 h (range 1–42) to 4 g/24 h (range 0–14) ($p < 0.01$). Mean amplitude of glycaemic excursions was significantly improved during infusion (from 8.9 ± 4.8 to 4.7 ± 0.9 mmol/l; $p < 0.01$). No severe hypoglycaemic episodes or other adverse reactions were seen.

Key words: Portable insulin infusion pump, preprogrammed IV insulin infusion, control of blood glucose, insulin-dependent diabetics.

Strict control of blood sugar is accompanied by a reduction in microvascular complications [5, 10, 11, 23]. Long term normoglycaemia is rarely achieved, however, with conventional subcutaneous insulin treatment. In order to mimic the physiological insulin secretion pattern by delivering small amounts of the hormone intravenously, two types of devices have been used: A glucose-controlled insulin and glucose delivery apparatus (the “artificial endocrine pancreas”) [1, 12, 15], and a simpler system consisting of a pump, which can deliver insulin at different rates, but without glucose sensing and servo-control mechanism [2–4, 7–9, 13, 20]. Continuous subcutaneous insulin infusion with a portable pump has

also been shown to be able to improve blood glucose control [16–18, 21, 22].

The aim of the present study was to show if preprogrammed intravenous insulin infusion with a 16-rate portable pump could result in normalisation of the 24 h blood glucose profile in longstanding and insulin-dependent diabetic patients.

Patients and Methods

Patients

Nine patients with juvenile-onset insulin-dependent diabetes mellitus (4 males and 5 females) were studied after informed consent had been obtained. Clinical details are shown in Table 1. None of the diabetics suffered from any other illness at the time of the study or was taking any medication other than insulin. Mean age of the patients was 39 years with an average duration of diabetes of 16 years. All had grossly normal renal function (no proteinuria and normal serum creatinine values). Three patients had neuropathy, and seven had background retinopathy.

Endogenous insulin production was estimated by determining human plasma C-peptide in the fasting state (three times) and 2, 4, 6, 8, 10, 15 and 20 min after intravenous injection of 1.0 mg glucagon [6]. No C-peptide could be detected in any patient. All patients had been treated with highly purified porcine NPH insulin (Insulin Leo Retard RI®) twice daily for several years. Seven patients mixed NPH with short acting insulin (Insulin Leo Neutral RI®) in the morning. The insulin requirement varied between 0.17 and 1.24 U/kg body weight.

Insulin-delivery System

Insulin was administered by a portable, battery-driven infusion pump. The impulse-controlled infusion system consists of a 250 g programmable electronic unit ($16 \times 9 \times 2$ cm) carried in a belt round the waist and an electromechanical syringe infuser (250 g) (Fig. 1) containing a 10 ml plastic syringe ($18 \times 10 \times 2$ cm) carried in a pocket on the upper arm. The units are interconnected by a thin flexible cable. The system can be manually preprogrammed by pinconnectors in a miniature X-Y matrix board as a fixed 24 h

Table 1. Individual data of 9 juvenile-onset insulin-dependent diabetics

Case no.	Sex	Age (years)	Duration of diabetes (years)	Weight (kg)	Weight (percent ideal) ^a	Retinopathy	Insulin dose (U/24 h)
1	M	35	10	81.0	102	—	32
2	M	54	19	81.0	119	+	52
3	M	34	14	74.5	97	+	36
4	F	34	23	58.6	91	+	10
5	F	41	19	52.2	88	+	32
6	F	25	21	61.6	99	+	52
7	M	54	19	84.0	123	+	62
8	F	38	5	50.2	78	—	62
9	F	34	13	56.0	91	+	28
mean	4M	39	16	66.6	99	7/9	41
± SD	5F	10	6	13.5	14		18

^a The percent ideal body weight was calculated from the Tables of Natvig [14]. The IV infused insulin dose was identical to that of the last day of conventional SC insulin treatment

Fig. 1. The electromechanical syringe pump with a 10 ml plastic syringe

profile. Sixteen rates can be programmed as a function of 48 half-hour intervals. The infusate volume is 48 to 768 μ l/h. The portable pump has been described in detail elsewhere [2].

Insulin Leo Neutral RI[®] was dissolved in isotonic phosphate/sodium chloride solution (0.154 mol/l) with human albumin 10 mg/ml, pH 7.4.

Experimental Design

The patients received a diet of 7459 ± 428 kJoule including about 150 g carbohydrate per day, divided into three main meals (at 0800 h, 1200 h and 1800 h) and two snacks (at 1400 h and 2100 h). Twenty per cent of the carbohydrate was given at 0800 h, 25% at 1200 h and 1800 h, and 15% at 1400 h and 2100 h. Patients were fully mobile throughout the study, performing exercise three times daily for half an hour on a bicycle ergometer at 1030 h, 1500 h and 1830 h. Diet and exercise were standardized on all days.

Attempts were made to get the best possible control on twice daily SC insulin during hospitalization. After about five days NPH-insulin treatment was stopped and short acting insulin given 4 times daily subcutaneously for 36 h in order to achieve a more physiological plasma insulin concentration during the 3 chief meals. Of the total daily insulin requirement, about 30% was given at 0700 h, about 25% at 1200 h, about 30% at 1800 h and about 15% at 2400 h.

The IV insulin infusion was started between 1500 h and 1900 h through an indwelling teflon catheter in the forearm, and an over-

night infusion period until 0800 h was carried out, so that the run-in period would bring blood glucose into approximately the normal range. Seven diabetics were studied for 48 h and two for 36 h after the run-in period. To achieve better control however, the fixed programme was changed after 24 h in some patients.

The 24 h infusion dose for each patient was calculated from that patient's total daily insulin dosage on the last day of conventional SC insulin therapy. Insulin infusion with the portable infusion pump was preprogrammed according to the following guidelines: Between 0800 h and 1000 h 22% of the total daily insulin dose was infused, between 1000 h and 1200 h 8%, between 1200 h and 1400 h 15%, between 1400 and 1600 h 8%, between 1600 h and 1800 h 5%, between 1800 h and 2000 h 18%, between 2000 h and 2230 h 9% and between 2230 h and 0800 h 15%. The range of basal infusion rates were 2.5 to 15.0 mU/min and was given from 2230 h to 0600 h, from 1000 h to 1200 h, from 1530 h to 1600 h, from 1730 h to 1800 h, and from 1930 h to 2000 h. The peak levels were raised up to sixteen fold and given for 30–60 min from the start of each main meal.

Capillary blood was drawn from earlobes every hour during the day and every 2 hours at night during NPH insulin treatment and 31 times daily during SC short acting insulin and IV infusion. Whole blood glucose was measured by the glucose oxidase method (Kabi[®]), as was glucose excretion in 24 h urine samples. 24 h calculations were made for mean blood glucose (MBG). The mean amplitude of glycaemic excursions (MAGE) served as a measure of instability of the diabetes regulation [19]. Hypoglycaemic reactions were recorded when the patient had appropriate symptoms and blood glucose levels were lower than 2.5 mmol/l. MBG and MAGE in nondiabetics were calculated from 31 capillary blood glucose measurements in 15 persons 20–50 years of age (mean 29 ± 12).

For statistical evaluation the Wilcoxon's Matched-pair sign test (two-tailed) was used. The results are given as mean $\pm$ SD.

Results

All patients felt well. In two cases phlebitis appeared and infusion had to be stopped approximately 36 h after the run-in period. Table 2 compares the MGB and glucose excretion on the control and infusion

Table 2. Individual capillary mean blood glucose (mean $\pm$ SD) and glucose excretion on control days (NPH and short acting insulin, respectively) and on IV infusion day, and minimal and maximal blood glucose values during IV infusion. Capillary blood was taken every 1 to 2 h for glucose measurement during NPH insulin and 31 times daily during SC short acting insulin and IV infusion

Case no.	Mean blood glucose (mmol/l)			Glucosuria (g/24 h)			Range of blood glucose during IV infusion mmol/l
	NPH	Short-acting SC	Short-acting IV	NPH	Short-acting SC	Short-acting IV	
1	16.2 $\pm$ 2.7	11.3 $\pm$ 2.1	7.1 $\pm$ 1.4	37	5	4	4.4 to 11.9
2	15.4 $\pm$ 0.5	9.2 $\pm$ 3.3	6.2 $\pm$ 1.5	42	3	0	4.1 to 9.8
3	10.7 $\pm$ 4.9	8.9 $\pm$ 2.3	5.8 $\pm$ 1.9	30	10	3	2.0 to 9.9
4	12.8 $\pm$ 2.2	7.6 $\pm$ 2.8	6.5 $\pm$ 2.8	26	0	0	2.5 to 11.3
5	10.0 $\pm$ 7.0	9.4 $\pm$ 4.8	6.4 $\pm$ 2.7	11	15	14	2.3 to 12.2
6	9.5 $\pm$ 2.0	9.1 $\pm$ 2.0	6.3 $\pm$ 2.2	12	2	4	3.1 to 10.9
7	11.1 $\pm$ 3.0	10.9 $\pm$ 2.2	5.7 $\pm$ 2.2	18	15	0	2.8 to 10.5
8	10.6 $\pm$ 2.8	9.6 $\pm$ 3.4	8.4 $\pm$ 2.2	32	39	12	4.0 to 11.6
9	11.4 $\pm$ 3.6	6.8 $\pm$ 6.0	5.0 $\pm$ 2.7	1	8	0	1.7 to 11.4
Mean $\pm$ SD	12.0 $\pm$ 2.4	9.2 $\pm$ 1.4	6.4 $\pm$ 1.0	23 $\pm$ 14	11 $\pm$ 12	4 $\pm$ 5	3.0 to 11.1 1.0 to 0.8

days showing in all diabetics an improvement of the diabetic control during infusion. The MBG improved from 12.0 ± 2.4 mmol/l during the NPH day, and 9.2 ± 1.4 on the SC short acting insulin ($p < 0.01$), respectively, to 6.4 ± 1.0 mmol/l during infusion ($p < 0.01$). Glucose excretion was significantly lower during infusion ($p < 0.01$). Ketonuria was not found.

Figure 2 shows a comparison of MBG and MAGE values of the individual patient on the experimental days. The MBG of the infusion day was significantly higher than the MBG of a comparable normal control group (4.4 ± 0.4 mmol/l) ($p < 0.01$). MAGE was not significantly affected by the change to short acting insulin four times daily (8.9 ± 4.8 mmol/l to 7.4 ± 3.6 mmol/l), however, during insulin infusion MAGE improved significantly to 4.7 ± 0.9 mmol/l ($p < 0.01$). MAGE on the infusion day, however, was significantly greater ($p < 0.001$) in diabetic patients as compared to normals (1.8 ± 0.6 mmol/l).

Figure 3 illustrates the blood glucose profile of patient 7 during IV infusion of 62 U/24 h. It can be seen that near normal glucose profiles were obtained. Severe hypoglycaemic episodes were not seen. Only 1.7% of all blood glucose determinations were less than 2.5 mmol/l on the infusion day. The maximum and minimum glucose levels are given in Table 2.

Discussion

Better metabolic control in diabetic patients has been demonstrated using open-loop systems for IV infusion of insulin [2, 4, 7–9, 13, 20], and for SC infusion

Fig. 2. Capillary blood glucose (top) and mean amplitude of glycaemic excursions (MAGE) (bottom) of the individual patients during: Conventional insulin twice daily; short acting insulin SC four times daily; and IV insulin infusion. Solid and dotted lines represent mean $\pm$ 2SD of the control group

Fig. 3. Capillary blood glucose levels in a longstanding, insulin-dependent diabetic patient during IV insulin infusion with the portable pump. The SC calculated insulin dose (62 U/24 h) was used for infusion. The insulin infusion rate varied between 15 and 240 mU/min. Meals (hatched area), snacks (S) and exercise (E) are shown at the top of the figure

[16–18, 21, 22], respectively. Preplanned IV insulin infusion with the open-loop delivery system used in this study appeared capable of improving the metabolic control of most diabetic patients. Overall blood glucose values were lower with IV infusion than with SC injections. The MBG, however, was not normoglycaemic during the short-term infusion.

With the preplanned programme comprising basal, peak and intermediate infusion rates, lowering of blood glucose towards normal values did not require a greater amount of insulin than had previously been administered by conventional means. This is of special interest as none of the diabetic patients had endogenous insulin secretion, and thus could not contribute essentially to the improvement of blood glucose regulation. The maximal infusion rate of insulin was chosen after having observed a similar increase in 5 insulin-dependent diabetic patients – with no endogenous insulin secretion – connected to the Biostator® (unpublished results). The peak delivery rate was given from start of main meals so that plasma insulin concentration would rise before absorption of food.

The short-term peak rate and the intermediate rates resulted in fewer hypoglycaemic episodes. A constant basal rate of insulin was maintained overnight in order to produce a normal fasting glucose concentration. In accordance with previous observations [4, 8, 12] an increased insulin requirement was found during the morning hours, so from 0600 h the insulin rate was doubled.

Recently results from patient-controlled insulin infusion pumps (Siemens) have been published [9, 13]. Control of blood glucose was similar to our findings. Endogenous insulin secretion was not investi-

gated however, and probably existed in some cases [9]. We believe that in diabetic patients with no endogenous insulin secretion at least three rates of infusion are needed for normalisation of blood glucose values.

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Dr. Klaus Kølendorf
Steno Memorial Hospital
DK-2820 Gentofte
Denmark