Comparison of the Biologic Activity of Porcine and Semisynthetic Human Insulins Using the Glucose-controlled Insulin Infusion System in Insulin-dependent Diabetes

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Semisynthetic human insulin is prepared from porcine pancreas by chemical methods involving the substitution of porcine insulin B-30 alanine with threonine. To compare the effectiveness of porcine and semisynthetic human insulins, eight insulin-dependent diabetic patients were evaluated during two separate periods using a glucose-controlled insulin infusion system. During each 36-h period, patients received either porcine or semisynthetic human insulin. Patients ingested mixed meals. The mean daily insulin requirements for porcine and semisynthetic human insulins were 84 ± 9 U and 85 ± 6 U (± SEM), respectively (P = NS). Mean blood glucose values were similar at 95 ± 1 mg/dl for porcine and 101 ± 3 mg/dl with semisynthetic human insulin (P = NS). Prior metabolic control or insulin antibody levels did not correlate with intravenous insulin requirements. These studies indicate that semisynthetic human insulin is as effective as porcine insulin in maintaining near-normal blood glucose control in short-term intravenous studies using artificial pancreas techniques in insulin-dependent diabetes. DIABETES CARE 6: 193–196, MARCH–APRIL 1983.

If human insulin were metabolically effective, it could decrease or eliminate clinical problems associated with antibody production, e.g., allergy and ease of metabolic control.[1] Two different approaches to the preparation of human insulins are described. Biosynthetic human insulin is produced by recombinant DNA techniques.[2] This insulin has been evaluated extensively in vitro and in vivo using both animal and human studies.[3] In addition, biosynthetic human insulin has been shown to be similar to porcine insulin, using glucose-controlled insulin infusion systems.[4–6]

Semisynthetic human insulin has been produced from porcine pancreas by an enzymatic reaction in which the C terminal B-30 alanine is substituted with threonine.[7] Chemical and physical methods indicate that semisynthetic human insulin is identical to native human insulin.[8] Pharmacologic studies in animals and human studies in Europe have shown similar drug potency, onset, and duration of action for semisynthetic human and porcine short-acting insulins.[9] In the present study, we compared the intravenous insulin requirements and effectiveness of porcine and semisynthetic human insulins associated with mixed-meal ingestion using the glucose-controlled insulin infusion system in insulin-dependent diabetic subjects.

METHODS

Eight insulin-dependent diabetic patients (four women and four men of mean age 32 yr having a mean duration of diabetes of 13 yr) were evaluated (Table 1). Daily outpatient insulin requirements ranged between 26 and 56 U given in divided doses or as a continuous subcutaneous infusion with a portable insulin infusion pump (Table 1). After explanation of this study, subjects gave informed consent. Five of eight patients had a history of ketoacidosis, and in all subjects no C-peptide secretion was observed 1 or 2 h after 75 g of oral glucose (Table 1). C-peptide, hemoglobin A_{1c}, and insulin antibody measures were determined as previously described.[10–12]

Intermediate-acting insulin was discontinued 36 h before study in an attempt to avoid residual subcutaneous insulin action during the study. Glucose control during these 36 h was maintained using subcutaneous porcine short-acting insulin injections before meals, or every 4–6 h, and these doses were discontinued 4–6 h before the study. Short-acting semisynthetic human insulin (Human Actrapid, Novo Industries, Wilton, Connecticut) was used. Patients initiated glucose-controlled insulin infusion system (GCIIS Biostator,

TABLE 1
Patient clinical data

Patient	Age (yr)	Duration of diabetes (yr)	Percent ideal body weight	Outpatient insulin dose (U/day)	Hemoglobin A_{1c} (%)	Insulin antibody (μU/ml)	Peak C-peptide after oral glucose (ng/ml)
1	34	16	86	27	11.3	116	< 0.8
2	33	15	105	55	9.5	4895	< 0.8
3	26	10	91	56	9.5	2780	< 0.8
4	27	11	96	54	4.3	438	< 0.8
5	25	12	108	55	10.0	2585	< 0.8
6	47	3	92	26	8.6	567	< 0.8
7	33	28	100	35	8.5	1550	< 0.8
8	29	4	102	36	5.4	50	< 0.8

Miles, Elkhart, Indiana) use immediately after hospital admission. Parameters for GCIIS use were selected to keep the premeal blood glucose levels between 80 and 100 mg/dl and postprandial blood glucose levels between 140 and 160 mg/dl. The GCIIS parameters used were as follows: KR 165, KF 45, BI 80, QI 25, RI 20, FI about 440, BD 50, QD 30, RD 40, and FD about 420. BD was kept at a low level to eliminate GCIIS-induced glucose infusions. We have previously described our detailed methods for GCIIS use.[13]

Isocaloric mixed meals containing 55% carbohydrate were given to patients as three meals and an evening snack comprising a minimum of 30 kcal/kg/day. The protocol consisted of (1) GCIIS assessment of intravenous insulin requirements on day 1, using either porcine or semisynthetic human insulin in a random fashion; (2) an 8-h euglycemic clamp method was used on day 2 to estimate insulin sensitivity and responsivity using the same insulin as on day 1: the remainder of day 2 consisted of an additional 12 h of GCIIS use with mixed meals—the combined GCIIS time was 36 h and referred to as study period 1; and (3) patients received the alternate insulin preparation on days 3 and 4 (period 2) and otherwise the protocol was identical to days 1 and 2. This report describes only the GCIIS intravenous insulin requirements using porcine and semisynthetic human insulins. The euglycemic clamp data will be reported elsewhere. Statistical analyses were performed using Student's unpaired and paired *t* tests. All data are expressed as mean ± SEM unless otherwise stated. The Pearson correlation method was used.

RESULTS

Blood glucose measurements and corresponding intravenous insulin requirements were recorded every minute for 36 h of GCIIS use. Figure 1 shows data for blood glucose levels and insulin infusion rates from one representative patient. As shown, postmeal and basal blood glucose levels were similar using either of the two insulins. The mean blood glucose concentrations for the group of eight patients were also similar at 95 ± 1 mg/dl with porcine insulin and 101 ± 3 mg/dl with semisynthetic human insulin as shown in Table 2. Mean daily insulin requirements using porcine or semisynthetic human insulins were 84 ± 9 U and 85 ± 6 U, respectively (Table 2). Intravenous insulin requirements did not correlate with insulin antibody levels, hemoglobin A_{1c} levels, or outpatient insulin dosages.

As implied in other studies where raw data are presented, comparison of the first and last periods of GCIIS-determined insulin requirements revealed differences between the two GCIIS treatment periods.[4,6] To determine if the first or last period insulin requirements were different, regardless of the insulin species, we observed period 1 (days 1 and 2) insulin requirements of 84 ± 12 U/day, whereas in period 2 (days 3 and 4) 100 ± 2 U/day were required (P = NS). Glucose levels were similar during the two GCIIS study periods at 79 ± 8 mg/dl and 92 ± 3 mg/dl, respectively (P = NS).

DISCUSSION

Insulin-dependent diabetic patients were evaluated during a study to compare the intravenous effectiveness of semisynthetic human insulin with porcine insulin. Six of eight patients were in poor control before entering the study, as

TABLE 2
Mean glucose-controlled insulin infusion system insulin requirements and blood glucose levels using porcine or semisynthetic human insulin

	Blood glucose levels (mg/dl)		Insulin requirements (U/day)	
Patient	Human	Porcine	Human	Porcine
1	97	92	83 (3)*	81
2	107	98	74 (1)*	109
3	97	95	84 (1)*	68
4	92	95	92 (1)*	104
5	113	98	110 (3)*	119
6	103	94	79 (3)*	46
7	89	95	58 (1)*	74
8	107	95	103 (3)*	74
Mean ± SEM	101 ± 3	95 ± 1	85 ± 6	84 ± 9
P value	NS		NS	

*Numbers in parentheses signify the study day when human insulin was used.

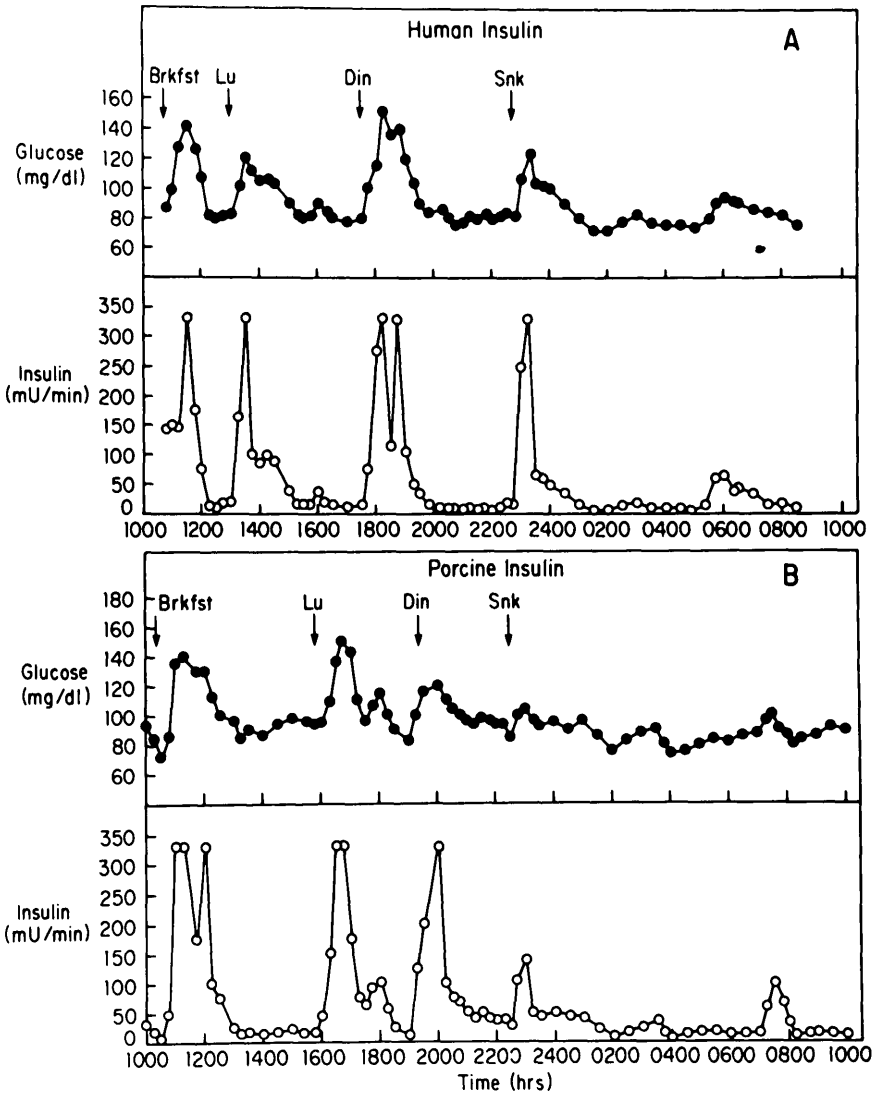

FIG. 1. Example of daily intravenous insulin requirements and blood glucose levels using the glucose-controlled insulin infusion system in one representative patient. Semisynthetic human insulin is illustrated in panel A and porcine insulin is illustrated in panel B. Arrows indicate the time when breakfast (Brkfst), lunch (Lu), dinner (Din), and a snack (Snk) were ingested.

assessed by hemoglobin A_{1c} levels; however, their insulin requirements did not differ from those of the patients in good control. Intravenous insulin requirements, using either porcine or semisynthetic human insulins were not significantly different, and similar glucose levels were achieved using the GCIIS. No untoward side effects were noted with intravenous short-acting semisynthetic human insulin.

Intravenous insulin requirements using soluble insulins were unrelated to insulin antibody and hemoglobin A_{1c} levels regardless of whether period 1 or 2 study data were used. These data are different from our studies using subcutaneous semisynthetic human insulin in which daily outpatient insulin requirements do correlate with insulin antibody levels.[14]

It is concluded that intravenous semisynthetic human insulin is as biologically effective as porcine insulin in controlling blood glucose levels after mixed meals in short-term studies using the GCIIS. Longer-term outpatient studies using intermediate- and short-acting semisynthetic human insulins also have been shown to be successful, as we recently reported.[14]

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