Efficiency of Human Insulin (recombinant DNA) in the Treatment of Diabetic Ketoacidosis and Severe Nonketoacidotic Hyperglycemia

WERNER BACHMANN, HELMUT WALTER, NORBERT LOTZ, AND HELLMUT MEHNERT

Human insulin (recombinant DNA) was compared with pork insulin in the treatment of diabetic ketoacidosis and severe nonketoacidotic hyperglycemia using a continuous, intravenous, low-dose regimen. Seven patients (age range 48 ± 26 yr, mean ± SD) with diabetic ketoacidosis and three (52, 65, and 70 yr) with nonketoacidotic hyperglycemia were studied. In the ketoacidotic group the initial values of blood glucose, pH, and base excess were 808 ± 353 mg/dl, 7.06 ± 0.1, and −22.8 ± 5.9 mmol/L, respectively. The mean initial values of blood glucose and osmolality of the three patients with nonketoacidotic hyperglycemia were 731 ± 127 mg/dl and 355 ± 49 mosmol/kg, respectively. Within 24 h insulin therapy led to continuous improvement in blood glucose to 187 ± 90 (ketoacidotic patients) and 172 ± 28 mg/dl (nonketoacidotic group) and normalization of pH, base excess, and osmolality. The mean insulin requirement was 84 ± 45 U/24 h in ketoacidotic and 86 ± 18 U/24 h in nonketoacidotic patients, respectively. The comparison groups receiving pork insulin did not differ significantly in either clinical or initial and subsequent biochemical data or in insulin requirement.
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In extensive clinical studies human insulin (recombinant DNA) has been proven to be an effective and safe insulin preparation by subcutaneous administration in patients with insulin-dependent diabetes mellitus.[1-3] The purpose of this investigation was to study the efficiency of intravenously given human insulin in the treatment of diabetic ketoacidosis and severe nonketoacidotic hyperglycemia compared with treatment with highly purified pork insulin.

PATIENTS AND METHODS

A series of 10 patients consecutively admitted to the Third Medical Department of the Schwabing City Hospital with the diagnosis "diabetic coma" were included in the study. The diagnosis of "diabetic coma" was achieved by history, physical and mental status (comatose or stuporous), and laboratory bed-site tests.

A group of 20 patients who were admitted to the hospital in the months before this human insulin study group served as a comparison group. Clinical data of the patients are shown in Tables 1 and 2. Seven patients had a diabetic ketoacidosis (Table 1); the mean age of that group was 48 yr and the mean duration of diabetes was 8.9 yr. Before the study four of these patients were on insulin and two were on sulfonylurea therapy; in one patient diabetes manifested itself in ketoacidosis. The mean age of the comparison group of 14 patients was 47.8 yr and the mean duration of diabetes was 14.4 yr.

Three patients were admitted with a nonketoacidotic hyperglycemia (Table 2) and one had previously been on insulin. In two patients severe hyperglycemia manifested itself in diabetes. The comparison group consisted of six patients with a mean age of 64.8 yr and a mean duration of diabetes of 6.5 yr.

Before starting therapy, intradermal tests with human insulin, placebo, and histamine solutions were performed to exclude insulin allergy. Venous blood samples for laboratory tests were taken before and at least at 1, 2, 3, 6, 9, 12 and 24 h after starting therapy. In addition to fluid and electrolyte replacement, insulin was administered as a continuous i.v. infusion of 6–12 U/h during the first hours in patients with severe nonketoacidotic hyperglycemia and with additional bolus i.v. injections of 10–20 U in patients with diabetic ketoacidosis.[4,5] In some cases it was necessary to repeat bolus injections hourly. Fluid and electrolyte replacement, as well as subsequent insulin dosage, were determined by the clinical assessment of the patient and by laboratory data. Sodium bicarbonate was only used at a pH of below 7.1.

TABLE 1
Clinical data of patients with diabetic ketoacidosis treated with human insulin (recombinant DNA)

Subject no.	Age (yr)	Sex	Previous therapy	Duration of diabetes (yr)
1	76	F	Insulin	11
2	73	F	Insulin	10
3	21	M	Insulin	20
4	17	M	Insulin	4
5	32	M	—	0
6	43	M	Sulfonylurea	10
7	74	F	Sulfonylurea	7
Mean ± SD	48.0 ± 26.0			8.9 ± 6.3
Control*	47.8 ± 16.3 (24–79)			14.4 ± 9.2 (2–33)

*Mean values (± SD) of 14 patients treated with pork insulin.

TABLE 2
Clinical data of patients with severe nonketoacidotic hyperglycemia treated with human insulin (recombinant DNA)

Subject no.	Age (yr)	Sex	Previous therapy	Duration of diabetes (yrs)
8	65	M	Insulin	10
9	52	F	—	0
10	70	M	—	0
Control*	64.8 ± 12.2 (48–77)			6.5 ± 4.5 (0–10)

*Mean values (± SD) of six patients treated with pork insulin.

RESULTS AND DISCUSSION

Some of the initial biochemical data of the individual patients of the study group are listed in Tables 3 and 4. In patients with ketoacidosis in the human insulin–treated group, mean blood glucose levels were 808 mg/dl; pH was 7.06, and bicarbonate was 6.69 mmol/L compared with blood glucose of 691 mg/dl, pH of 6.95, and bicarbonate of 4.93 mmol/L in the pork insulin–treated group.

Table 5 and Figure 1A summarize the changes in blood glucose, beta-hydroxybutyrate, pH, and base excess in each group and demonstrate the similarity of response to either human or pork insulin. In both groups blood glucose was lowered constantly after starting therapy to about 190 mg/dl after 24 h. In addition, in both groups ketone bodies, pH, and base excess were normalized within 12–24 h. In spite of a high individual variety of insulin dosage, as can be seen in Table 6 for the patients on human insulin, the mean insulin

TABLE 3
Initial biochemical data of patients with diabetic ketoacidosis treated with human insulin (recombinant DNA)

Subject no.	Blood glucose (mg/dl)	pH	Bicarbonate (mmol/L)
1	718	6.94	2.9
2	1493	6.94	6.1
3	651	7.01	3.5
4	417	7.15	7.0
5	804	7.19	17.0
6	571	7.09	5.9
7	1002	7.11	4.4
Mean ± SD	808 ± 353	7.06 ± 0.10	6.69 ± 4.78
Control*	691 ± 242	6.95 ± 0.14	4.93 ± 3.89

*Mean values (± SD) of 14 patients treated with pork insulin.

TABLE 4
Initial biochemical data of patients with severe nonketoacidotic hyperglycemia treated with human insulin (recombinant DNA)

Subject no.	Blood glucose (mg/dl)	Osmolality (mosmol/kg)
8	606	320
9	860	390
10	728	355
Mean ± SD	731 ± 127	355 ± 49
Control*	915 ± 297	355 ± 33

*Mean values (± SD) of six patients treated with pork insulin.

TABLE 5
Change in plasma pH, base excess, and beta-hydroxybutyrate during continuous intravenous insulin therapy in diabetic ketoacidosis (mean ± SD)

	Hours of therapy				
	0	3	6	12	24
Human insulin (N = 7)					
pH	7.06 ± 0.10	7.13 ± 0.10	7.27 ± 0.06	7.35 ± 0.07	7.38 ± 0.05
base excess (mmol/L)	−22.8 ± 5.9	−17.9 ± 6.5	−10.6 ± 5.6	−4.4 ± 4.3	−1.6 ± 3.8
β-HOB (mg/dl)	11.4 ± 1.5	12.7 ± 2.9	12.0 ± 3.0	9.3 ± 3.4	6.2 ± 4.7
Pork insulin (N = 14)					
pH	6.95 ± 0.14	7.11 ± 0.12	7.23 ± 0.10	7.33 ± 0.08	7.39 ± 0.12
base excess (mmol/L)	−26.6 ± 6.4	−20.1 ± 6.9	−13.1 ± 7.3	−7.2 ± 6.3	−7.1 ± 7.1
β-HOB (mg/dl)	12.8 ± 1.9	13.2 ± 2.2	12.9 ± 2.3	12.4 ± 1.7	8.6 ± 3.7

requirement during the first 24 h of treatment was almost identical, with 84 U for human and 87.5 U for pork insulin. The same was valid for fluid and potassium replacement: mean potassium substitution in the human insulin–treated patients was 174 ± 88 mmol and mean volume replacement was 6.1 ± 2.5 L/24 h. In patients with severe nonketoacidotic hyperglycemia of the human insulin group, initial mean blood glucose was 731 mg/dl; it was 915 mg/dl in the pork insulin–treated group (Table 4). Initial plasma osmolality was 355 mosmol/kg, identical in both groups. According to the higher initial blood glucose in patients on pork insulin, the insulin requirement was 105 ± 14 U/24 h, higher than in the human insulin–treated group (86 ± 18 U/24 h). The different starting situation accounted for the higher insulin requirement reaching a comparatively good blood glucose compensation within 12 h of treatment (Figure 1B). After this period of treatment, the blood glucose concentration was about 250 mg/dl in both groups, and after 24 h about 170 mg/dl. Again, fluid and potassium replacement did not differ in these patients; potassium substitution in the human insulin–treated group was 137 ± 10 mmol and fluid substitution was 8.4 ± 1.7 L/24 h. As demonstrated by other authors,[6–8] the continuous i.v. low-dose insulin regimen has been very effective in the treatment of diabetic ketoacidosis as well as in severe nonketoacidotic hyperglycemia. No differences could be observed in the use of pork and human insulin. As far as human insulin was concerned, no side effects, especially no allergic or toxic reactions, could be seen. Therefore, human insulin may also be considered as a safe and effective insulin preparation for intravenous application in metabolic emergency situations.

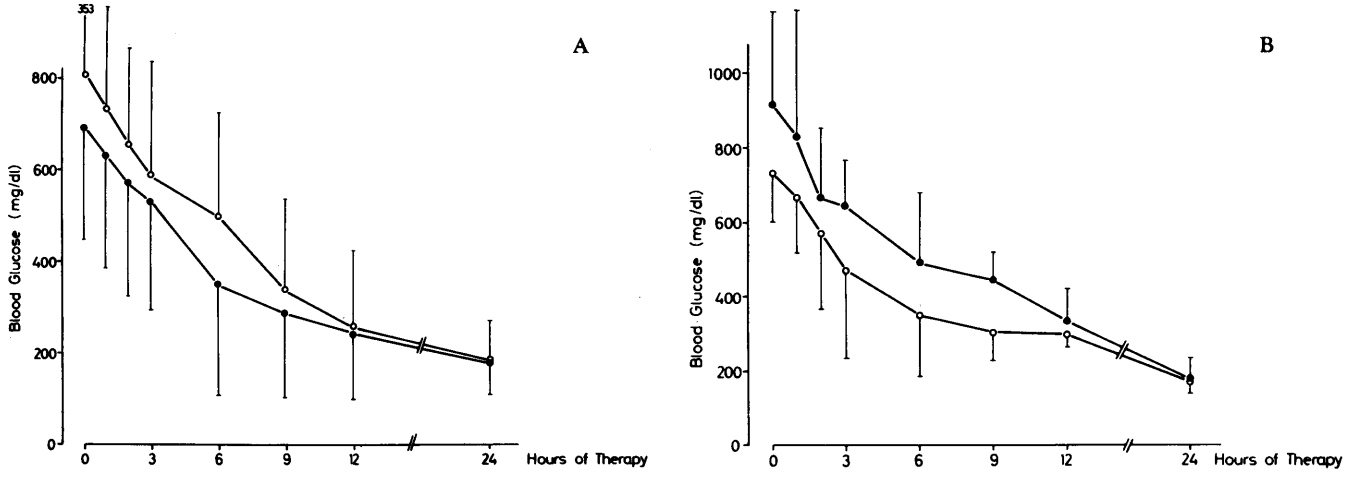

FIG. 1. (A) Changes in blood glucose during continuous intravenous insulin therapy in patients with diabetic ketoacidosis. ○——○ human insulin (N = 7), ●——● pork insulin (N = 14) (mean ± SD). (B) Changes in blood glucose during continuous intravenous insulin therapy in patients with severe hyperglycemia without ketoacidosis. ○——○ human insulin (N = 3), ●——● pork insulin (N = 6) (mean ± SD).

TABLE 6
Insulin requirement during continuous intravenous insulin therapy in patients with diabetic ketoacidosis and nonketoacidotic hyperglycemia treated with human insulin (recombinant DNA)

Subject no.	Duration of i.v. insulin	Insulin requirement/24 h	
		U (total)	U/h
1	48	86	3.56
2	222	173	7.20
3	51	82	3.42
4	20	62	2.58
5	21	25	1.04
6	72	68	2.83
7	41	90	3.75
8	43	68	2.83
9	38	86	3.58
10	41	104	4.33
$\bar{X}$ ± SD	59.7 ± 58.9	84 ± 38	3.51 ± 1.57
Control*	—	92 ± 28	3.83 ± 1.17

*Mean values (± SD) of 20 patients treated with pork insulin.

From the Schwabing City Hospital, Kölner Platz 1, 8000 München 40, West Germany.

Address reprint requests to W. Bachmann, III Medizinische Abteilung, Krankenhaus München-Schwabing, Kölner Platz 1, 8000 München 40, West Germany.

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