Comparative Study of NPH Human Insulin (recombinant DNA) and NPH Bovine Insulin in Diabetic Subjects

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The hypoglycemic potencies of human insulin (recombinant DNA) and bovine NPH insulin were compared in insulin-dependent diabetic subjects. The same dosages of the two preparations were alternately injected, for two successive 5-day periods, on a twice-a-day schedule. Blood glucose profiles were monitored by finger pricking 6 times/day. Slight but significant differences in glucose time appeared, suggesting that human NPH insulin acts faster than bovine NPH, and for a shorter time. DIABETES CARE 5 (SUPPL. 2): 63–66, 1982.

Human insulin (recombinant DNA) is now available for clinical trials. Most of the studies performed to date dealt with regular human insulin,[1] and NPH human insulin was used only once, in healthy subjects.[2] We report here some preliminary results of human NPH insulinotherapy in diabetic subjects in a short-term pragmatic experiment. In order to compare the hypoglycemic potencies of human and bovine NPH preparations in the conditions of usual monitoring and treatment, 18 insulin-dependent diabetic subjects received at random each of these two preparations, at similar dosage, for two successive periods of 5 days. Glucose monitoring was performed 6 times/day at predetermined intervals of time.

PATIENTS AND METHODS

Patients

Eighteen patients, 9 men and 9 women, aged 21–72 yr, gave informed consent for the study. Main clinical features appear in Tables 1 and 2. Briefly, the dependency for insulin treatment had been established by the usual clinical criteria, i.e., the development of marked hyperglycemia and ketonuria in absence of insulin injections. The duration of diabetes had been 8 ± 3 yr (mean ± SEM). Renal function was normal in all except patient no. 6, whose serum creatinine concentration was 149 μmol/L. Liver function, assessed by serum alkaline phosphatase, transaminase and γ-glutamine transferase concentrations, was normal in all of them. Lipodystrophies on thighs, due to prior insulin injections, were detectable in only patient no. 15. None of the drugs administered concomitantly displays known interference with insulin action, and their dosage was not modified throughout the study.

All patients had been trained to glucose self-monitoring using finger pricking, glucose-oxidase strips, and strip-reading devices. All were hospitalized, performed standard physical exercise, and received a constant (individually prescribed) diet appropriate to their body weight and condition. Meals included breakfast, lunch and dinner, plus three intermediate snacks, and all meals were given at constant clock hours. Carbohydrate calories were distributed 15% at breakfast, 30% at lunch, and 25% at dinner. All patients had previously been treated by intermediate insulin twice a day—bovine NPH (all patients), or first Rapitard then bovine (5 of them). Two of them had been treated for less than 3 wk (patients no. 13 and 16).

Methods

Insulin injections. The two preparations used were: NPH human insulin (recombinant DNA), batches no. CT50-82-IF (Eli Lilly and Company, Indianapolis, Indiana) and purified bovine NPH (Organon, Saint-Denis, France), 40 U/ml in both instances.

Insulin was injected subcutaneously in the anterior abdominal wall, at the same site throughout the study, in order to minimize variations in resorption due to injection site.[3] Injections were performed at 8:15 a.m. and 7:15 p.m., i.e., 20 min before breakfast and dinner, respectively. Individual insulin dosages appear in Table 2. Mean morning dosage was 34 ± 3 U, and mean evening dosage was 17 ± 2 U. The same doses were maintained in all patients but patients no. 16 and 17. In these two patients readjustments had to be

TABLE 1
Clinical features of patients studied

Patient	Sex	Age (yr)	Duration of diabetes (yr)	Retinopathy	Neuropathy	Proteinuria (g/24 h)	Plasma creatinine μmol^{L-1}	Blood pressure (mmHg)	
								Supine	Upright
1	F	28	8	No	No	0	65	110/70	110/70
2	F	30	11	Yes	No	0	74	110/70	110/70
3	M	45	5	No	No	0	69	120/80	120/80
4	F	72	12	Yes	No	0	87	190/90	138/90
5	M	25	9	Yes	Yes	0	71	140/100	90/70
6	M	57	9	Yes	Yes	2	149	190/100	160/100
7	F	67	10	No	No	0	104	180/90	180/100
8	F	72	17	No	No	0	61	170/90	160/90
9	M	53	4	No	No	0	100	120/70	110/60
10	M	43	5	No	No	0	70	106/80	100/82
11	M	51	8	No	Yes	0	65	120/80	90/60
12	M	22	5	No	No	0	89	120/60	120/60
13	M	34	1	No	No	0	97	126/70	110/70
14	M	71	10	No	No	0	90	140/80	140/80
15	F	26	12	Yes	No	0.18	49	150/90	150/90
16	M	21	1	No	No	0	66	120/70	120/70
17	F	54	11	Yes	Yes	0	90	160/70	130/86
18	F	29	4	Yes	No	0	59	100/70	90/72
M	9/9	44	8				81		
± SEM		4	1				5		
Range		(21–72)	(1–17)				(49–149)		

performed during the first 2 days of study; dosages were not modified later on. With these two exceptions, insulin doses were strictly identical for each individual case, for the time of study.

Patients were randomly assigned to human or bovine NPH for two successive 5-day periods.

Determination. Blood glucose was determined on venous blood samples twice a day, at 800 and 1400 h, using a glucose-oxidase method adapted for the Technicon Autoanalyzer. Capillary blood glucose was determined daily 6 times/day (8, 10, 12 a.m., and 4, 7, 10 p.m.) using Dextrostix strips (Ames Co., Elkhart, Indiana) and Glucometer devices (Ames).

Expression of results. Results are presented as mean values ± SEM. Comparison of values for the corresponding sampling times was performed by Student's *t* test for paired and unpaired values.

The following parameters were considered: (1) comparative blood glucose profile for each of the 5 days; (2) mean of the 5 successive daily profiles; (3) number of hypoglycemic episodes and other adverse reactions.

RESULTS

Time course of glucose concentration. On the first day of study, the fasting glucose value was 140 ± 10 mg/dl in venous blood and 142 ± 20 mg/dl in capillary blood ($N = 18$; $r = 0.91$; $P < 0.001$). A marked glucose rise occurred after breakfast, of similar magnitude in the human and bovine insulin–treated groups at 1000 (Figure 1), followed by a progressive decline. In all instances, the glucose profile was lower in patients treated with human insulin than in the bovine NPH–treated group. The glucose values were significantly lower at 1200 (first day) and at 1200, 1600, 1900 and 2200 (third day) in the human-treated group (Figure 1). On the cumulative profile over 5 days, the differences between the two groups were significant at 2200 ($P < 0.05$).

Contrastingly, on the fasting samples collected at 0800, before renewal of human NPH injections, blood glucose values were slightly but significantly higher than in the bovine NPH–treated group ($P < 0.05$ on the third day) (Figure 1).

Hypoglycemic attacks and adverse reactions. Four hypoglycemic episodes were detected: three during treatment with human NPH and one during treatment with bovine NPH insulin. In no instance did the patients become comatose. Hypoglycemia occurred on the second or third day of treatment, at 12:00 a.m. and 4:00 p.m. for human NPH, and 4:00 p.m. for bovine insulin.

No other adverse general or local reaction (at the site of injections) attributable to insulin treatment was detected.

DISCUSSION

Our results suggest that: 1. Treatment with NPH insulin twice a day for 10 days did not yield a satisfactory control of blood glucose profile, in the conditions of the present study, whichever insulin preparation was used.

TABLE 2
Further clinical features of patients studied

Patient	% ideal body weight	Diet Total (kcal)	Diet Glucides (g)	Insulin dosage NPH (U) Morning	Insulin dosage NPH (U) Evening	Lipodystrophy	Associated pathological condition
1	87	2500	410	26	14	No	Chronic calcified pancreatitis
2	78	2000	230	24	12	No	—
3	94	2000	310	46	12	No	Chronic calcified pancreatitis
4	142	1200	140	30	30	No	Hypertension
5	76	1800	210	26	12	No	—
6	140	1800	210	10	8	No	Hypertension
7	145	1000	115	20	10	No	Hypertension
8	145	1450	175	48	34	No	Hypertension
9	96	2500	385	50	38	No	Chronic calcified pancreatitis
10	106	1950	300	36	4	No	Chronic calcified pancreatitis
11	92	2000	300	56	18	No	Chronic calcified pancreatitis
12	104	1800	180	44	16	No	—
13	89	2200	230	40	20	No	—
14	85	2000	210	34	16	No	Lower limb arteriopathy
15	125	1000	115	32	14	Yes	—
16	95	2000	200	36	18	No	—
17	131	900	130	30	18	No	Hypertension
18	110	1600	160	25	15	No	—
M	108			34	17		
± SEM	6			3	2		
Range	(76–145)			(10–56)	(4–38)		

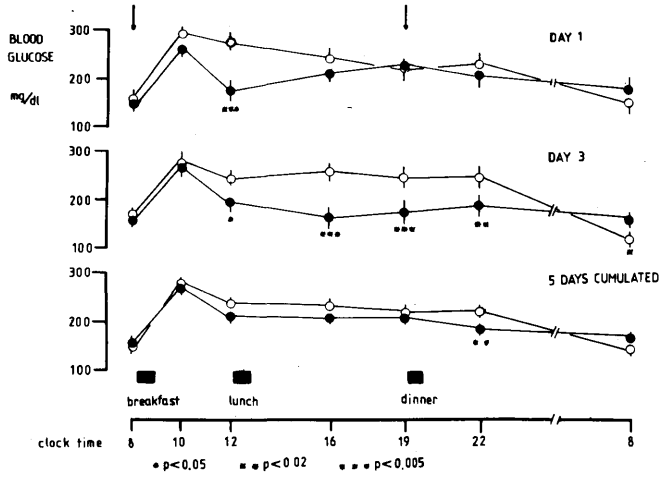

FIG. 1. Blood glucose concentrations in 18 IDD patients treated with NPH injections twice a day. Times of insulin injections are symbolized by vertical arrows; times of main meals are symbolized by black bars. The black circles symbolize determinations under human insulin NPH (●) and the white circles symbolize determinations under bovine NPH (○). Results are presented as mean values ± SEM. Statistical significance is denoted on the figure.

2. Human NPH insulin may induce at similar dosage slightly more pronounced hypoglycemic effects for 4–11 h following injections. Conversely, beyond the 13th h after the evening injections, the hypoglycemic effect had vanished more rapidly than following bovine NPH insulin.

These differences between the effects of human and bovine NPH preparations, although minute, were significant on several successive days and remained detectable on the overall mean of treatment period.

3. The differences in insulin actions could not be correlated with the duration or history of previous insulin treatments on analysis of individual cases.

If confirmed by further studies, the different speed of actions for human NPH insulin could be explained by some differences in bioavailability, catabolism, or interactions with target tissues.

Potential differences in bioavailability cannot be ascribed, in present work, to the site of injection, which remained the same, but a faster resorption of the insulin depot may be due to the slightly higher hydrosolubility of human insulin[4] as compared to bovine insulin.

A difference in protamine or zinc content should be checked. No difference in the respective biologic potencies of human

and bovine or porcine insulin was detectable in vitro.[5] But further studies are needed to clarify the hypothetical differences in hormone binding to circulating antibodies,[6] hepatic uptake, or catabolism of the hormone.[7]

Albeit faster than bovine NPH, the human NPH preparations should be complemented with regular insulin in order to minimize the postbreakfast glucose peak.

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