Comparative Study of NPH Human Insulin (recombinant DNA) and Pork Insulin in Diabetic Subjects: Preliminary Report

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Continuous blood glucose monitoring in six insulin-dependent diabetic patients shows that the biologic action of NPH human insulin (recombinant DNA) and pork insulin is similar. Nevertheless, the activity of NPH human insulin seems faster and more pronounced since minimal glycemia is lower and more rapidly reached after human insulin. The speed of glycemic increase is slightly lower and the decrease is faster with NPH human insulin; thus the area under the NPH human insulin–induced glycemic curve is less wide, but differences are not significant. Our data favor a faster and more potent effect of NPH human insulin. DIABETES CARE 5 (SUPPL. 2): 60–62, 1982.

The production of human insulin constitutes one of the first practical applications of DNA recombinant technology and may be of fundamental importance in the future treatment of diabetes mellitus. This insulin has been shown to be strictly identical to native human pancreatic insulin in terms of physiochemical, immunologic, and biologic properties.[1] Nevertheless, these in vitro and in vivo studies have dealt with unmodified human insulin (recombinant DNA)[2] and we are aware of only one published report dealing with the biologic properties of NPH human insulin.[3]

We here report on the first comparative study of NPH human insulin and NPH pork insulin in diabetic patients.

MATERIALS AND METHODS

Six patients, three men and three women, aged 17–47 yr and presenting with insulin-dependent diabetes treated for at least 3 yr were included in this trial. Principal clinical characteristics of this population are summarized in Table 1. Briefly, the last injection of intermediate-acting insulin was administered 36 h before the beginning of the study; on the day preceding the test, patients received subcutaneous injections of regular (fast-acting) insulin (Actrapid, Novo) at 8:00 a.m. and 12:00 a.m. At 8:30 p.m., after an intramuscular injection of Actrapid, a manually adjusted syringe pump (Sage Instruments, Orion Research, Inc.) was attached to an i.v. line and Actrapid insulin (concentration, 1 U/ml) was administered continuously for 12 h, until the beginning of the study; during this last step, insulin infusion rates were adjusted every 2 h to maintain capillary blood glucose levels at between 0.80 and 1.50 g/L (Dextrostix strips, Dextrometer reader, Ames Company, Elkhart, Indiana). At 9:00 a.m. a double-lumen catheter[4] was placed in a forearm vein for continuous recording of blood glucose, using the glucose-oxidase technique (AAI Technicon, reagents GOD-PAP, Boehringer-Mannheim) with an autoanalyzer. After stopping the pump at 9:30 a.m. patients were randomly assigned to treatment groups receiving either Lilly NPH human insulin, batch CT-5082, or pork insulin, batch CT-5322. Insulin was injected s.c. over the right shoulder immediately after breakfast. Patients ate lunch 3 h later and dinner after a further 6 h, at which time continuous glucose monitoring was stopped. Using a crossover sequence, this same protocol was then repeated, injecting the second variety of NPH at the same dose level and the same site. Throughout the study, food intake remained constant for all subjects, 1600–2800 cal, with 40% as carbohydrates distributed among the three meals, 26% of the carbohydrate calories at breakfast and 37% each at lunch and dinner.

The following parameters were studied: comparative analysis of blood glucose curves (continuous recording), peak and trough glucose levels and times at which these were attained, and determination of the slope of the rising and descending segments of the blood glucose curve. Results were expressed as means ± SEM for the six patients, and comparisons were carried out using the Student's *t*-test for paired series.

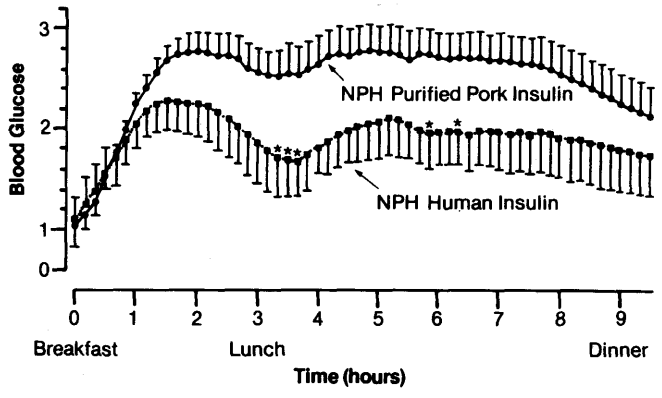

*FIG. 1. Comparison between curves of continuous blood glucose recording (means ± SEM) after subcutaneous injection of NPH human insulin and NPH pork insulin in six insulin-dependent diabetic subjects. *P < 0.05.*

RESULTS

There was no significant difference between glucose values during the period of nocturnal insulin infusion preceding injection of NPH (before pork insulin: 1.53 ± 0.16 g/L; before human insulin: 1.49 ± 0.21 g/L).

The mean curve for blood glucose levels is shown in Figure 1, with indication of values obtained at 10-min intervals; only levels between the 200th and the 220th min, and between 350 and 380 min were significantly lower after administration of NPH human insulin.

Table 2 shows the various parameters characterizing the effects of human and pork NPH; the only significant difference was for minimal glucose levels, which were lower after NPH human than after NPH pork insulin.

DISCUSSION

Our results reveal no fundamental difference between blood glucose patterns after NPH human or NPH pork insulins. We thus partially confirm results of Galloway et al.[3] who found no significant difference between these two types of insulin when injected into normal fasting subjects. Nevertheless, unlike these authors, we have found that NPH human insulin acts slightly faster than does the pork variety; while formal statistical significance was not attained, peak and trough glucose values were seen more rapidly after NPH human insulin. On the other hand, while peak glucose values were identical for the two forms of insulin, in all patients minimal glucose values were lower after human NPH, and this difference was significant. This fact was consistently observed in the six patients treated.

This moderate increase in efficacy was also seen on the charts for continuous glucose monitoring; minimal values after breakfast and lunch were lower with NPH human insulin. Furthermore, the slope of the decreasing segment of the glucose curve after human NPH was sharper, while the rate of increase was slower, although these differences did not attain statistical significance. Examination of individual

TABLE 1
Clinical characteristics of the patient population

Patient no.	Sex	Duration (yr)			Complications		HbA_1 (%)†
		Age	Diabetes	Insulin treatment	Microangiopathy*	Macroangiopathy*	
1	M	26	5	5	Np		11.4
2	F	18	5	4			11.5
3	F	47	11	8	Np	Cp	12.0
4	F	43	22	22	Rp, Np	Mi	11.0
5	M	42	23	23	Rp		7.0
6	M	17	4	4			10.5

*Abbreviations: Np = neuropathy, Rp = retinopathy (nonproliferative), Cp = coronary arteriopathy, Mi = arteriopathy of the legs.
†Normal value: 6.5–8.5%.

TABLE 2
Numerical values for curve showing continuously recorded glucose values

	Maximum blood glucose		Minimum blood glucose		Area under blood glucose curve	Mean rate of change (g/L/min)	
	Value (g/L)	Time (min)	Value (g/L)	Time (min)		Rise	Fall
NPH human insulin	2.45 ± 0.34	110.2 ± 14.2	1.53 ± 0.32*	220.7 ± 9.8	1107.1 ± 191.4	12.8 ± 1.5	8.5 ± 0.9
NPH pork insulin	2.88 ± 0.20	117.5 ± 11.5	2.36 ± 0.24	235.3 ± 23.8	1432.9 ± 126.6	15.8 ± 1.4	5.3 ± 0.9

*P < 0.05.

curves demonstrated smaller areas under the curve and lower blood glucose values in five of six patients with NPH human versus NPH pork insulin.

Thus human NPH appears, with the same dosage, at least as effective as pork NPH, in the conditions of the study, that is, with 1 injection/day.

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