Search for the Most Practical Regular/NPH Mixtures for Type I Diabetic Patients

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After 2 wk of good control 9 type I diabetic patients were hospitalized and treated in a randomized fashion with different human insulin mixtures (regular: NPH), containing 10, 15, or 20% regular insulin. In the case of the 15:85% mixture, mean blood glucose was found to be in the range of 70–150 mg/dl. Significant differences occurred at certain time points between the curves obtained with the 10:90% and the 15:85% mixtures, and the 10:90% and the 20:80% preparations, respectively. Prolongation of the interval between hormone injection and start of breakfast from 30 to 45 min abolished the postprandial glucose excursion in the 15:85% and the 20:80% mixture, but not the 10:90% mixture. DIABETES CARE 5 (SUPPL. 2): 53–56, 1982.

Recent reports indicate that the conventional treatment of insulin-dependent diabetes can be markedly improved by intensive patient education and application of more than two s.c. hormone injections.[1,2] Moreover, it has been shown that the use of adequate insulin preparations can be of considerable importance.[3–7] There is also evidence for a circadian rhythm of insulin requirement in diabetic patients, probably due to fluctuating cortisol levels.[8–15] A higher need of insulin per unit carbohydrate exists during morning hours compared with midday or evening.[16] On account of this fact, a morning injection containing a certain amount of short-acting hormone (regular) in the insulin mixture is superior to pure intermediate-acting insulin preparations. Part of our clinical studies with human insulin (recombinant DNA) (Eli Lilly, Indianapolis, Indiana) was undertaken to characterize insulin mixtures or regular/NPH in type I diabetic patients.

Experimental design. Five men and four women were examined, all having fasting C-peptide levels below 0.16 nmol/L that could not be increased by i.v. injection of 1 mg glucagon. Their age varied from 17 to 72 yr, duration of diabetes from 5 to 26 yr, and with one exception, they were near to the ideal body weight (Table 1). Most patients had already insulin mixtures of porcine NPH and porcine regular. The portion of short-acting insulin in the morning dose varied between 10 and 20% (Table 2). According to HbA_1 levels, however, only two patients were well controlled.

With the exception of patient no. 4, all others were known to us from former stays in the hospital and had remained under medical supervision. All had learned to perform self-monitoring by urine and blood glucose measurement and to adapt their insulin requirement to changing muscular activity or intercurrent infections.

Two weeks before admission, the patients were asked to intensify their usual conventional therapy. Only if glucose measurements during ambulatory control and the first 2 days in the hospital showed mean blood glucose levels below 150 mg/dl and the fasting value was repeatedly near 100 mg/dl, the experimental protocol was started.

The aim was that effects of small differences between insulin mixtures tested according to a randomized schedule could only be detected in patients with good control and with a minimum of residual insulin secretion. During the test period, all meals were identical and the patients were asked to observe an exercise program that was repeated every day.

At 6:30 p.m., patients received the second insulin injection consisting of that dose of a porcine regular/NPH mixture which was found to furnish good glycemic control during the night.

Human insulin mixtures containing 10, 15, or 20% regular were prepared at least 24 h before use. The amount of the morning dose varied from 22 to 45 U. The time interval between injection and start of meal was 30 min in five and 45 min in four patients. Blood was drawn from a plastic cannula at the patient's forearm vein at least every hour.

TABLE 1
Clinical characteristics of the patients studied

Patient No.	Sex	Age (yr)	Duration (yr)	Height (cm)	Weight (kg)	Percent of ideal weight	Complications	Additional diagnoses
1	M	50	26	170	68	108	retinopathy nephropathy polyneuropathy	peripheral macroangiopathy hyperlipoproteinemia hypertension, coronary heart disease
2	W	72	12	165	57	103		coronary heart disease
3	M	20	5	178	68	97	polyneuropathy	recurrent acute pancreatitis acne vulgaris
4	M	17	13	173	59	90		
5	W	45	5	163	64	119		recurrent cholecystolithiasis euthyroid goiter
6	M	19	7	179	74	104		
7	W	34	15	169	62	105	retinopathy nephropathy	hypercholesterolemia
8	M	40	6	169	59	95		
9	W	21	7	168	55	95		diffuse goiter

Glucose was measured from 25 μl of whole blood using a GOD-enzyme electrode (glucose analyzer YSI 23 A, Yellow Springs Instruments, Yellow Springs, Ohio).

RESULTS

Mean blood glucose concentration ± SEM of nine type I diabetic patients after application of the 15:85 (Regular:NPH) human insulin mixture is shown in Figure 1. The curve reaches its highest point with 147 mg/dl at 8:30 a.m. and its lowest point with about 70 mg/dl at noon, and climbs slowly to 140 mg/dl at 6:30 p.m. Each meal is followed by glucose peaks. This curve is now compared with two other mean blood glucose curves from the 20:80 and 10:90 mixtures (Figure 2). All three curves begin within a comparable range. As expected, the highest glucose peak after breakfast is obtained with the 10:90 mixture. The higher the amount of regular insulin per mixture, the earlier the curve declines and the earlier it rises again during the afternoon. Significant differences occur between the 10:90 and the 15:85 curves

TABLE 2
Previous therapy and treatment with human insulin

Patient No.	HbA_1 under conventional therapy (% of HBA_0*)	Previous insulin therapy	Morning dose of human insulin (U)	Interval between injection and breakfast (min)
1	13.3	32 U 20:80 mixture Nordisk 18 U 5:95 mixture Nordisk	32	45
2	10.8	16 U 10:90 mixture Nordisk 14 U 10:90 mixture Nordisk	26	45
3	11.6	28 U 10:90 mixture Nordisk 26 U Mixtard Nordisk	26	30
4	12.4	30 U Depot Hoechst CR 30 U Depot Hoechst CR	42	45
5	14.2	26 U 10:90 mixture Nordisk 15 U 10:90 mixture Nordisk	26	30
6	11.0	25 U 15:85 mixture Nordisk 14 U 10:90 mixture Nordisk	22	30
7	13.1	30 U Ultralente at 11 a.m. 10-6-8 U Acrapid before main meals	45	30
8	9.0	20 U 10:90 mixture Nordisk 10 U 10:90 mixture Nordisk	25	30
9	9.9	28 U 15:85 mixture Nordisk 24 U 10:90 mixture Nordisk	28	45

*Normal range: 5–8%.

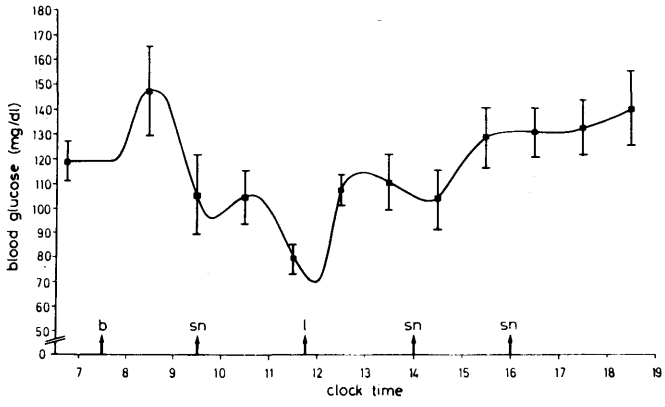

FIG. 1. Mean blood glucose concentration ± SEM of nine insulin-dependent diabetic patients after injection of 30 ± 8 U (mean ± SD) of a 15:85 regular/NPH mixture. Arrows indicate begin of meals. b = breakfast; l = lunch; sn = snack.

during the morning (0830, 0930, 1030, and 1130 h) and between the 10:90 and 20:80 curves at the same period in the morning and additionally in the late afternoon (1730 and 1830 h) ($P < 0.05$). The steep increase of the 20:80 curve after lunch cannot only be assigned to meal intake but also suggests an influence of counterregulatory hormones, since applying this regimen three patients had hypoglycemic attacks before noon. The strong glucose lowering potency of the 20:80 mixture can also be derived from the fact that compared with the other curves, the morning snack at 0930 is not followed by an increase. Most hypoglycemic episodes occurred with this mixture (Table 3).

The differentiation of the whole group into patients with a 30-min interval between hormone injection and start of breakfast and those with a 45-min interval revealed an old truth: prolongation of the interval by 15 min can totally abolish the postprandial glucose peak. This proved to be true for the 15:85 mixture (Figure 3) and for the 20:80 mixture (not shown). Using the 10:90 mixture, however, a difference

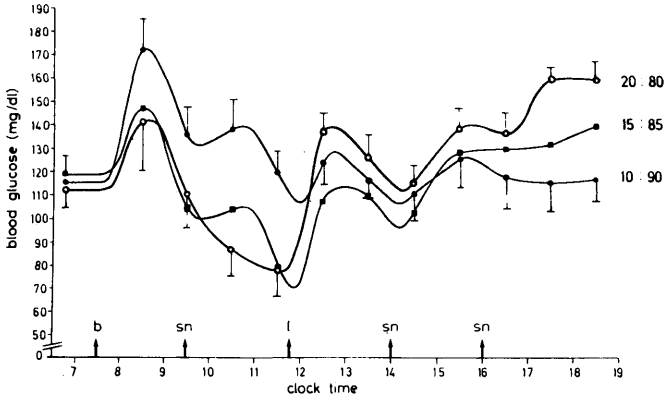

FIG. 2. Mean blood glucose concentrations of nine insulin-dependent diabetic patients after injection of different human insulin mixtures.

TABLE 3
Frequency of hypoglycemia in 9 insulin-dependent diabetic patients treated with different insulin mixtures

Blood glucose (mg/dl)	Human insulin mixtures		
	20:80	15:85	10:90
<60	5	3	1
<50	5	1	0
<40	0	0	0

cannot be demonstrated, suggesting that now the critical minimum of regular insulin has been reached (Figure 4).

DISCUSSION

With human insulin mixtures containing only a 10% or 15% portion of regular, glucose homeostasis in type I diabetic subjects was excellent. Of course, another decisive factor for good control was the strict adherence of all patients to a schedule of time-related insulin injections, meal supply, and muscular activity. Despite these favorable conditions, which cannot be achieved during the out-clinic study, it was not possible to discriminate between the neighboring 15:85 and 20:80 curves. However, statistical significance could be obtained between the 10:90 and 15:85 curves and between the 10:90 and 20:80 curves at certain time periods.

In five of nine patients, hypoglycemia occurred after application of the 20:80 mixtures. Clinical appearance of these attacks and recognition by the patient was not different from comparable episodes under their former treatment with porcine or bovine insulin.

Although a more rapid onset of blood glucose decrease after s.c. injection of human insulin compared with porcine insulin has been noted in healthy fasting volunteers,[17] a shortening of the 30-min time interval between hormone injection and start of the meal seems not to be justified.

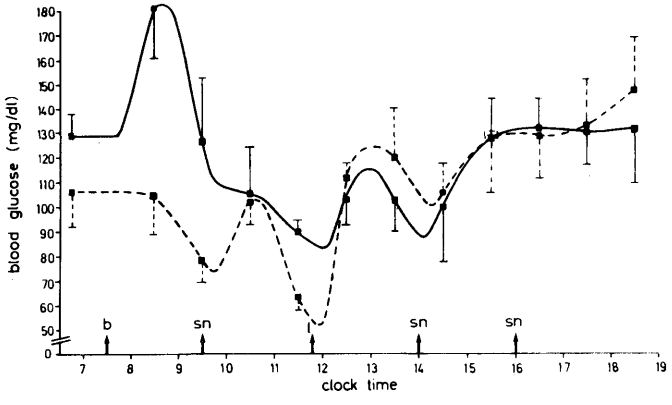

FIG. 3. Glucose curves after application of a 15:85 human insulin mixture in IDDM with different time intervals between injection and breakfast. ■——■ 30-min interval, N = 5; ■---■ 45-min interval, N = 4.

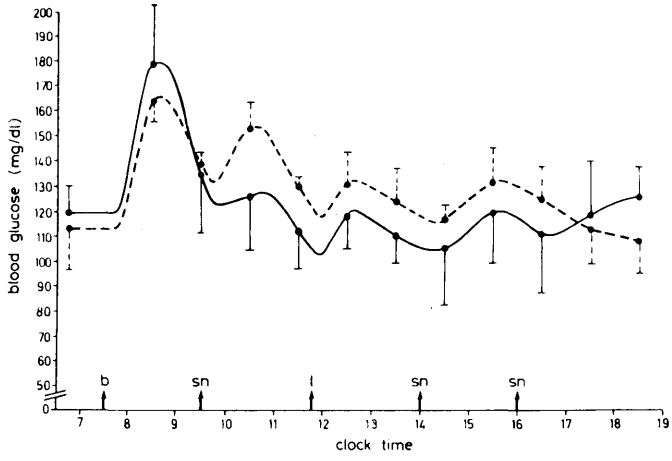

FIG. 4. Glucose curves after application of a 10:90 human insulin mixture in IDDM with different time intervals between injection and breakfast. ●——● 30-min interval, N = 5; ●---● 45-min interval, N = 4.

However, a prolongation of this interval for several minutes may be beneficial for some patients.

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