Prevention of Early-Morning Hyperglycemia in IDDM Patients With Long-Acting Zinc Insulin

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OBJECTIVE — To evaluate whether an insulin regimen with a long-acting zinc insulin (Ultratard HM) could help control fasting hyperglycemia in insulin-dependent diabetes mellitus (IDDM) patients.

RESEARCH DESIGN AND METHODS — A randomized sequential crossover trial with 6-wk treatment periods was used. Ten IDDM patients from the diabetes clinic at the Medical School who had persistent fasting hyperglycemia (>10 mmol/L) were studied. Patients with nocturnal hypoglycemia were excluded. All patients completed the study. Insulin regimens consisted of three daily injections of a short-acting insulin (Actrapid HM) before meals and either a long-acting zinc insulin (Ultratard HM) or an intermediate isophane insulin (Protaphane HM) before the evening meal. Each regimen was followed for 6 wk.

RESULTS — Fasting blood glucose levels (at 06:00 and 08:00) were significantly lower after the long-acting insulin regimen (6.26 ± 0.88 vs. 10.82 ± 4.27 mM, $P < 0.05$ and 9.26 ± 1.02 vs. 14.03 ± 1.08 mM, $P < 0.05$, respectively). Plasma-free insulin levels mirrored blood glucose concentrations because they were significantly higher at 06:00 and 08:00 after the long-acting insulin regimen (49.5 ± 10.1 vs. 20.1 ± 4.3 pM, $P < 0.05$ and 31.6 ± 5.0 vs. 16.5 ± 3.4 pM, $P < 0.05$, respectively). At any other time of the day, blood glucose and plasma insulin levels were not significantly different with either one of the two insulin regimens.

CONCLUSIONS — A long-acting zinc human insulin injected before the evening meal can help to control persistent fasting hyperglycemia in IDDM patients.

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RECEIVED FOR PUBLICATION 14 AUGUST 1990 AND ACCEPTED IN REVISED FORM 23 APRIL 1991.

Control of early-morning hyperglycemia in patients with insulin-dependent diabetes mellitus (IDDM) is not always an easy task. Some patients treated with intensified insulin regimens have blood glucose concentrations under reasonable control for most of the day, but during the first hours of the morning, hyperglycemia often develops. Early-morning hyperglycemia in IDDM patients is either a consequence of the Somogyi effect (hypoglycemic, often asymptomatic, episodes occurring during the night), or it is due to a combination of two important factors: the waning effect of the dose of insulin injected in the evening and the dawn phenomenon (1,2).

In the latter case, the only effective therapeutic measure, so far, has been to delay the intermediate insulin injection until bedtime (3); thus, increasing the number of insulin administrations to 4/day (4,5). Obviously, some patients might find 4 injections/day inconvenient, and this could have a negative effect on their compliance to therapy.

However, with the introduction of human insulin, a new insulin preparation has now become available: a long-acting zinc human insulin, which has a time of action that ranges between the intermediate-acting insulins and the long-acting ultralente insulins (6,7). This preparation, used instead of the intermediate insulin in the evening injection (before dinner), may represent, in theory, an appropriate tool for keeping the levels of plasma insulin sufficiently high in the morning (to contrast the dawn phenomenon) without adding a fourth injection at bedtime.

Against this background, we have designed a controlled study with the aim of evaluating whether an insulin regimen with a long-acting zinc human insulin is effective in controlling fasting blood glucose concentrations in IDDM patients with early morning hyperglycemia.

Table 1—*Patient characteristics*

Patients	Age (yr)	Body mass index (kg/m^2)	Diabetes duration (yr)	HbA_{1c} (%)	Daily insulin (U)
1	19	22.2	12	7.5	66
2	24	22.7	5	9.2	72
3	22	21.9	28	9.8	46
4	40	18.2	4	5.2	52
5	28	22.7	20	5.6	36
6	29	25.7	17	5.7	66
7	24	21.8	14	6.8	52
8	37	28.7	7	7.5	76
9	29	26.5	15	8.8	23
10	28	26.2	11	10.4	60
Mean ± SE	28 ± 2	23.7 ± 1.0	12 ± 2	7.6 ± 0.6	55 ± 5

RESEARCH DESIGN AND METHODS— Ten ketosis-prone IDDM patients (5 women, 5 men) were consecutively recruited from our outpatient clinic on the basis of a persistent increase in fasting blood glucose levels (>10 mM) that could not be corrected by adjusting their usual insulin regimen (short-acting insulin before breakfast and lunch and short-acting insulin and intermediate insulin before dinner). All patients were C-peptide negative and free of either proliferative retinopathy, nephropathy, or neuropathy. Their clinical characteristics at the time of recruitment are listed in Table 1. All patients were able to perform self-monitoring of blood glucose and recognize hypoglycemic symptoms. Patients with nocturnal hypoglycemia (symptoms and/or blood glucose values <4 mM at 0300) were excluded from the study. Informed consent was obtained by each participant.

This study was based on a controlled randomized crossover design with a run-in period of 4 wk and an investigation period of 6 wk for each treatment. During the run-in period, dietary advice (based on the American Diabetes Association's recommendations) was given to tailor the energetic needs of each subject (8). The ability of each patient to perform blood glucose monitoring and to recognize hypoglycemia was checked. All patients continued their insulin regimen, which consisted of short-acting human insulin before breakfast and lunch and short-acting plus intermediate human insulin before dinner. During the run-in period, the dosage of both the short-acting and intermediate insulins was adjusted to obtain blood glucose values as close as possible to normal throughout the 24 h, trying to minimize the risk of hypoglycemic episodes. At the end of the run-in period, the mean total daily insulin dose was 50.9 ± 4.9 U (0.77 ± 0.21 $U \cdot kg^{-1} \cdot day^{-1}$), of which 15.0 ± 4.3% was given at breakfast, 29.6 ± 5.4% at lunch, and 55.4 ± 8.4% at dinner. After the run-in period, patients were randomly allocated to one of two insulin regimens that consisted of three daily injections of short-acting human insulin (Actrapid HM) before meals and a long-acting zinc human insulin (Ultratard HM) for the first regimen or an intermediate human isophane-protamine insulin (Protaphane HM) before dinner for the second regimen. After the first 6-wk period on one insulin regimen, they were switched to the other one. Patients were instructed to keep the insulin dosage and its distribution during the day constant throughout the study. Changes were only allowed in case of either two (or more) hypoglycemic episodes (plasma glucose <2.8 mM) or ketonuria.

All insulin preparations were semisynthetic human insulin from Novo (Copenhagen). Short-acting human insulin (Actrapid HM) had the time peak between 2 and 5 h after subcutaneous injection, the long-acting zinc human insulin (Ultratard HM) between 8 and 20 h and the isophane human insulin (Protophane HM) between 4 and 12 h. Patients were instructed to prepare insulin mixtures extemporarily in the syringe (regular insulin was always drawn up first) and to inject them immediately.

Patients always had breakfast, lunch, and dinner at 0800, 1300, and 2000, respectively, with snacks at 1000, 1630, and 2230. The content of meals and snacks did not vary during the study. The bedtime snack contained ~15 g carbohydrates and consisted of fruit.

Patients reported to the outpatient clinic every 2 wk during the 1st mo and every week thereafter. At the end of each investigation, patients were hospitalized; plasma free insulin and blood glucose levels were then measured at 0600, 0800, 1300, 1500 (2 h after lunch), 2000 and 2200 (2 h after dinner). Moreover, fasting HbA_{1c} was measured. The number and severity of symptomatic hypoglycemic episodes (sweaty, dizziness, or blurred vision remitting with the intake of glucose) were recorded.

Blood glucose was measured by a glucose-oxidase method (Boehringer Mannheim, Mannheim, Germany). Plasma free insulin was analyzed by a radioimmunoassay method (Sorin Biomedica, Sallugia, Italy) in a single run for each patient. Plasma was treated immediately

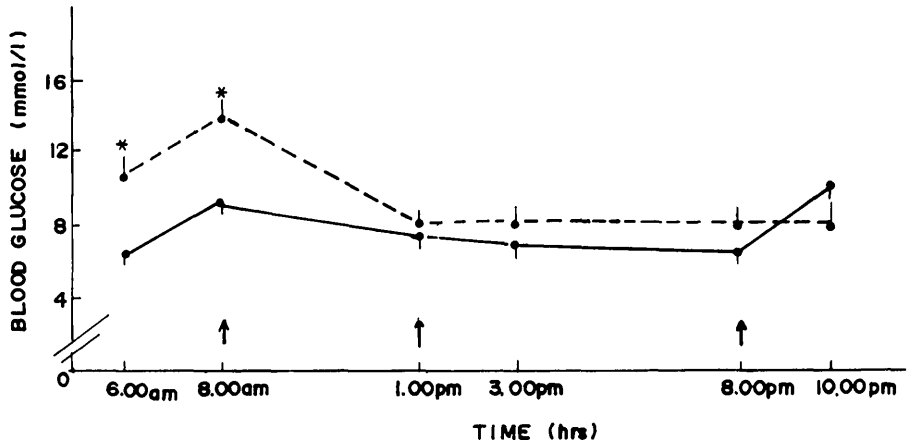

Figure 1—*Daytime blood glucose profile at end of treatment with long-acting zinc (solid line) and isophane (dashed line). Arrows indicate 3 main meals. *P < 0.05.*

after sampling with polyethylene glycol 6000 (25% wt/wt for precipitation of insulin antibodies) (9). The intra-assay coefficient of variation was 10.2%. HbA_{1c} was measured with high-performance liquid chromatography (10).

Data are presented as means ± SE. The significance of differences was evaluated by the Student's paired *t* test, setting the level of significance for the two-tailed distribution at $P = 0.05$.

RESULTS— Plasma glucose profiles at the end of the two treatment periods are shown in Fig. 1. Early-morning blood glucose levels (at 0600 and 0800) were significantly lower, with the long-acting insulin compared with the intermediate insulin regimen (6.26 ± 0.88 vs. 10.82 ± 4.27 mM, $P < 0.05$ and 9.26 ± 1.02 vs. 14.03 ± 1.08 mM, $P < 0.05$, respectively).

Plasma free insulin levels mirrored blood glucose concentrations (Fig. 2); compared with intermediate-acting insulin long-acting zinc insulin gave significantly higher values at 0600 and 0800 (49.5 ± 10.1 vs. 20.1 ± 4.3 pM, $P < 0.05$ and 31.6 ± 5.0 vs. 16.5 ± 3.4 pM, $P < 0.05$). At any other time of the day, both blood glucose and plasma insulin values were not statistically different with either one of the insulin regimens (Figs. 1 and 2, Table 2).

HbA_{1c} values were similar after the two treatments: 7.2 ± 0.4% with the long-acting insulin and 7.4 ± 0.3% with the intermediate insulin regimen. Blood glucose fluctuations within the day were reduced by the long-acting zinc insulin, as indicated by the intraindividual standard deviations of blood glucose concentrations measured throughout the day, which were lower with the zinc insulin than with the isophane insulin (3.35 ± 0.39 vs. 4.24 ± 0.42, $P < 0.05$) (Table 2).

Hypoglycemic reactions were not frequent. In particular, among all the patients, only one symptomatic episode was recorded for each treatment period. Moreover, the total number of low blood glucose values (<4 mM) on the last day of each treatment period was similar for the two insulin regimens: eight for the long-acting zinc insulin and seven for the isophane insulin. There was a random distribution of blood glucose values <4 mM throughout the whole day. The mean daily insulin dose at the end of the two treatment periods was similar for the two regimens, as was the amount of insulin given at each injection and the amount of regular insulin (Tables 2 and 3).

CONCLUSIONS— This study clearly demonstrates that an intensified insulin

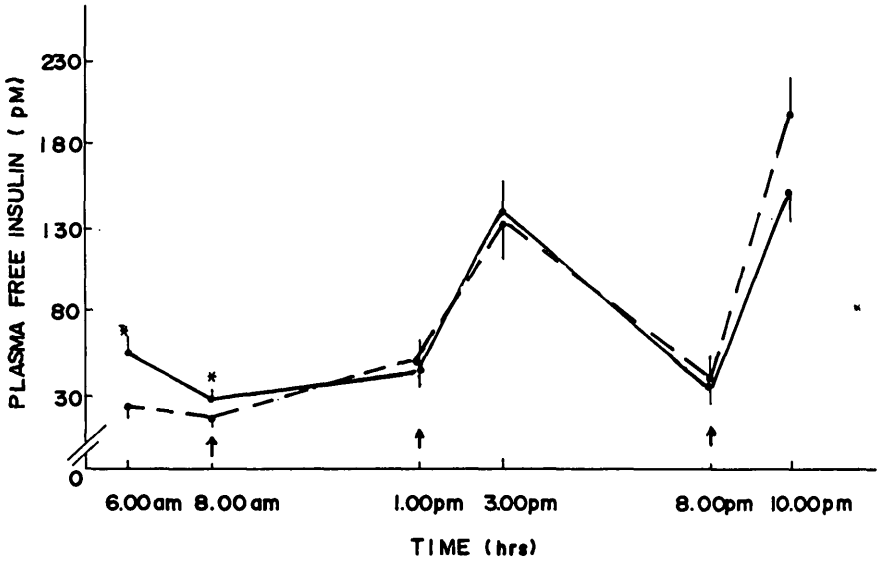

Figure 2—*Daytime plasma free insulin profile at end of treatment with long-acting zinc (solid line) and isophane (dashed line). Arrows indicate 3 main meals. *P < 0.05.*

Table 2—*Metabolic control and insulin dose at end of two periods of treatment*

	LONG-ACTING ZINC	ISOPHANE
BLOOD GLUCOSE (MM)		
AT 0600	6.26 ± 0.88	10.82 ± 4.27*
AT 0800	9.26 ± 1.02	14.03 ± 1.08*
DAILY MEAN†	7.71 ± 0.34	9.13 ± 0.66
INTRAINDIVIDUAL SD	3.35 ± 0.39	4.24 ± 0.42*
DAILY INSULIN		
TOTAL (U)	51.9 ± 4.4	54.9 ± 5.2
% OF REGULAR INSULIN	69.4 ± 7.2	67.2 ± 7.1

Values are means ± SE.
*$P < 0.05$.
†Calculated on 6 measurements performed on last day of each therapeutic regimen.

treatment, based on the basal/bolus model with 3 injections/day, is more effective in controlling early-morning hyperglycemia in IDDM patients if a long-acting zinc human insulin is administered before dinner instead of the intermediate insulin. Morning hyperglycemia in most patients with IDDM is due either to the dawn phenomenon or to the waning effect of the insulin injected the previous evening or, very often, the combination of these two factors (1). Overnight metabolic studies have shown that the amount of insulin necessary to maintain euglycemia in patients with IDDM increases between 0200 and 0700, when unmet, this increased need for insulin can cause hyperglycemia (2). The waning effect of the intermediate insulin, injected in the evening, can either lead, by itself, to hyperglycemia in the early morning or accentuate the dawn phenomenon (3).

Early-morning hyperglycemia may also represent a consequence of the Somogyi effect (hypoglycemic episodes occurring during the night) in a minority of IDDM patients (11). However, in this study, the presence of nocturnal hypoglycemia (blood glucose values <4 mM) was checked in every patient before entering the trial and represented an exclusion criterion. Therefore, the results presented herein cannot be extrapolated to this particular group of patients.

In this study, we compared the effects of two different insulin preparations in IDDM patients with persistent fasting hyperglycemia. The preparations were a long-acting zinc human insulin (Ultratard HM) and an intermediate isophane human insulin (Protaphane HM) having a longer duration compared with other human isophane insulins (12,13); both were mixed with soluble insulin in the evening injection before dinner. The hypothesis tested was that the long-acting insulin could lead to higher concentrations of plasma insulin early in the morning which in turn would allow for better control of the dawn phenomenon.

Our data support this hypothesis, because blood glucose values, measured early in the morning and before breakfast, were significantly lower with the long-acting insulin. This can be interpreted as an effect of the higher plasma insulin values obtained with the long-acting insulin regimen from early morning until breakfast time. As a consequence of the reduction of the fasting blood glucose values (without other major effects on the daily blood glucose profile), the excursions of blood glucose concentrations during the day decreased with the long-acting insulin regimen, as shown by the significantly lower standard deviations of the daily blood glucose concentrations (14; Table 2).

No significant effect of the two therapeutic regimens on HbA_{1c} was observed in this study. The improvement obtained with the long-acting zinc insulin was confined to blood glucose values registered during prebreakfast, whereas glycemic control during the remaining part of the day did not change (Fig. 1).

Table 3—*Individual short-acting insulin dose*

	LONG-ACTING ZINC			ISOPHANE		
PATIENTS	BREAKFAST	LUNCH	DINNER	BREAKFAST	LUNCH	DINNER
1	6	12	16	6	10	14
2	10	16	16	10	16	16
3	6	6	8	6	6	8
4	12	22	16	12	22	16
5	10	16	10	12	16	10
6	6	12	10	6	12	10
7	8	16	12	8	18	14
8	8	20	26	10	20	26
9	10	10	10	12	10	10
10	12	12	8	12	16	8
MEAN ± SE	8.8 ± 0.7	14.2 ± 1.5	13.2 ± 1.7	9.4 ± 0.8	14.6 ± 1.4	13.2 ± 1.7

Use of the long-acting insulin injected in the evening before dinner did not seem to increase the risk of hypoglycemia. Among all patients, only one clinically manifest hypoglycemic attack was recorded with each insulin regimen throughout the study and, moreover, the number of low blood glucose values (<4 mM) was similar for both long-acting and intermediate insulins.

A possible drawback of the use of insulin preparations containing zinc in combination with a short-acting insulin is the delay of the absorption rate of the latter, probably due to a recombination with the free zinc present in the solution containing the long-acting insulin (15,16). This phenomenon is particularly important when the mixture of insulin is left in the syringe for several minutes. Our patients were educated to inject insulin soon after preparing the mixture. This might explain why postdinner-free insulin levels were not statistically different between the two treatment periods (although slightly higher with the isophane insulin), and postdinner blood glucose values were remarkably similar.

In summary, a long-acting zinc human insulin injected before dinner can help to control persistent fasting hyperglycemia in IDDM patients.

Acknowledgments— This work was supported by a grant from the Novo Farmaceutici Italia SPA and by a grant from the Italian Ministry of Research.

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