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Split-Mixed Insulin Regimen With Human Ultralente Before Supper and NPH (Isophane) Before Breakfast in Children and Adolescents With IDDM

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Objective: Fasting hyperglycemia is common in patients with insulin-dependent diabetes mellitus (IDDM) treated with twice-daily subcutaneous insulin regimens. We postulated that substituting human ultralente insulin for the presupper dose of intermediate-acting insulin would improve overnight glycemic control in children and adolescents with IDDM. Research Design and Methods: This 6-mo double-blind crossover study compared a conventional insulin regimen, a mixture of human NPH and regular given before both breakfast and supper (NPH), with a novel twice-daily regimen in which human ultralente replaced NPH before the evening meal (ultralente). This study was comprised of 20 children and adolescents (mean age and duration of IDDM 11.3 ± 2.9 and 2.4 ± 1.3 yr, respectively) from the Youth Clinic of the Joslin Diabetes Center, all of whom regularly performed self-monitoring of blood glucose (SMBG) and had been treated exclusively with human insulin (mean daily dose 0.75 ± 0.22 U/kg). Subjects performed SMBG on a prescribed schedule with a glucose meter with an electronic memory, and recorded results of blood glucose measurements, insulin dosages, and episodes of hypoglycemia. Monthly measurements were obtained for height, weight, and HbA_1, and mean daily insulin dosages and average blood glucose level before breakfast, lunch, supper, bedtime snack, and between 0200 and 0300 were calculated. Nonfasting serum lipids were measured at entry, crossover, and the end of the study. Results: After 3 mo, mean HbA_1 did not differ significantly (9.1 ± 1.7 vs. 9.5 ± 1.4%, NPH and ultralente, respectively). Mean fasting blood glucose was significantly lower on ultralente (9.6 ± 1.9 vs. 10.3 ± 2.2 mM, $P < 0.05$, and blood glucose showed a similar trend ($0.05 < P < 0.1$) before lunch (8.9 ± 1.7 vs. 9.8 ± 2.6 mM. Mean blood glucose before bedtime snack was significantly lower ($P < 0.01$) on NPH (8.4 ± 1.9 vs. 10.0 ± 2.1 mM) but did not differ significantly before supper or between 0200 and 0300. On the two regimens, growth and serum lipids were normal and similar, and no differences were observed in the incidence or severity of hypoglycemia. Conclusions: Compared with a mixed dose of regular and NPH, a similar dose of a mixture of regular and human ultralente insulin before supper caused a modest reduction in fasting blood glucose levels but was associated with higher blood glucose levels before the bedtime snack. Overall glycemic control, reflected in HbA_1 values, was not significantly improved. *Diabetes Care* 14:1100–106, 1991

Hyperglycemia before and after breakfast occurs in most patients with insulin-dependent diabetes mellitus (IDDM) treated with twice-daily subcutaneous insulin regimens (1,2). When the second dose of a standard split-mixed insulin regimen

is given before supper, the maximal effect of the intermediate-acting insulin occurs between 2400 and 0300 h, thereafter, plasma free insulin levels tend to wane. Therefore, it is not surprising that symptomatic or asymptomatic hypoglycemia frequently occurs during sleep (3–9) and declining plasma levels of insulin result in a tendency for blood glucose concentrations to rise before breakfast (7,8,10–14). A reduction in the presupper dose of intermediate-acting insulin to avoid nocturnal hypoglycemia often results in unacceptably high blood glucose concentrations before breakfast.

Regimens of insulin administration that have been most successful in optimizing overnight glycemic control use an injection of intermediate-acting insulin at bedtime, necessitating three or four daily injections of insulin (15–18) or continuous subcutaneous insulin infusion (CSII) by pump (19–22). However, bedtime for infants and young children usually follows within 2–3 h of the evening meal, so the potential benefit from an additional injection of intermediate-acting insulin at bedtime may be negated by its relatively early administration. Many older children and adolescents are loathe to take more than two injections of insulin each day, and most are unsuitable candidates for CSII. For these reasons, a recommendation to use a more intensive insulin regimen in youth is frequently impractical or rejected.

Human ultralente insulin has a slower onset of action, blunted peak, and longer duration of action (23–25) compared with intermediate-acting insulins such as NPH or lente (26–30). Therefore, we postulated that human ultralente insulin could be used in a simple regimen requiring only two daily injections to improve fasting blood glucose levels in children and adolescents without increasing the risk of nocturnal hypoglycemia. This study compared a classic twice-daily insulin regimen (a mixture of human NPH [isophane] and regular insulin given before breakfast and supper) with a novel insulin regimen in which human ultralente replaced NPH insulin before the evening meal.

RESEARCH DESIGN AND METHODS

This 6-mo study was a randomized double-blind crossover trial involving 20 (10 boys, 10 girls) children and adolescents with IDDM who attended the Youth Clinic of the Joslin Diabetes Center and had previously demonstrated satisfactory compliance with their diabetes care, including regular self-monitoring of blood glucose (SMBG). All patients had been treated exclusively with human insulin since diagnosis and were receiving a total combined daily insulin dose of at least 0.5 U/kg provided in a split-mixed insulin program (regular and lente in 9 subjects and regular and NPH in 11 subjects). Patients were ineligible if they had recurrent diabetic ketoacidosis, recurrent severe hypoglycemia, or other medical diseases. The mean ± SD age of the subjects was 11.3 ± 2.9 yr (range 7.3–17.2 yr) and their mean duration of diabetes was 2.4 ± 1.3 yr (range 1–5.5 yr). Nine patients remained prepubertal throughout the study; 11 were either pubertal at commencement or entered puberty during the course of the study. At entry, a complete history was obtained, and a physical examination was performed; all patients had a normal biochemical profile (Du Pont ACA IV, Wilmington, DE), thyroid function tests, and blood count. Written informed consent was obtained from subjects and their parents.

With only human insulin (Humulin, Lilly, Indianapolis, IN), we compared two regimens of overnight insulin replacement: ultralente and regular, and NPH and regular given before the evening meal. The daytime regimen of NPH and regular insulin given before breakfast was kept constant throughout the study. Both the morning and evening dosages of insulin were given as a mixture drawn into the same syringe immediately before injection. The insulin dose used during the screening phase served as the basis for dose selection. Subjects were instructed to give their injections 30 min before meals unless the concentration of blood glucose was <3.9 mM in which case they were instructed to consume a source of rapidly absorbed carbohydrate and to proceed with the meal within 15 min. To reduce the risk of nocturnal hypoglycemia, subjects were instructed to increase the size of their bedtime snack if blood glucose at this time was ≤6.7 mM (6).

Ten subjects were randomly assigned in a double-blind fashion to the ultralente regimen and the remainder received the NPH regimen. After 12 wk, the subjects were crossed over from ultralente to NPH, or vice versa, and continued for a further 12 wk. Four separate vials of insulin (for the morning and evening dosages of regular, the morning dosage of NPH, and the evening dosage of NPH or ultralente) were provided monthly. Although the physical appearance of the two cloudy insulins (NPH and ultralente) differed, all NPH and ultralente bottles were masked with a special study label to discourage subjects from trying to discover the identity of the cloudy insulin.

Throughout the study, subjects were requested to perform SMBG at least twice every day, four times on 1 weekend day and five times (once between 0200 and 0300) on 1 day/wk. On 1 day each month, subjects were requested to perform a profile that included blood glucose measurements before and 90 min after meals, before the bedtime snack, and between 0200 and 0300. All subjects' blood glucose measurements were performed with a glucose meter with an electronic memory (One Touch, Lifescan, Milpitas, CA) provided by the study together with an ample supply of test strips. The accuracy of SMBG was validated monthly by comparing subjects' blood glucose measurements obtained with their glucose meters with those performed on an aliquot of the same blood sample sent to the clinical chemistry laboratory. Deviations >10% were followed up by additional instruction in the technique of SMBG, and the glucose meter was checked for performance accuracy.

TABLE 1
Height, weight, insulin dose, HbA_1, and serum lipids at start, crossover, and end of study

Month	Weight (kg)	Height (cm)	Total dose/24 h (U/kg)	HbA_1 (%)	Cholesterol (mM)		Triglycerides (mM)
					Total	High-density lipoprotein	
0	42.8 ± 13.0	145.8 ± 13.8	0.75 ± 0.22	9.4 ± 1.5	4.03 ± 0.55	1.51 ± 0.36	1.36 ± 0.8
3	43.7 ± 13.4	147.0 ± 13.7	0.78 ± 0.20	9.0 ± 1.3	3.98 ± 0.42	1.48 ± 0.26	1.22 ± 0.5
6	45.2 ± 13.5*	148.5 ± 13.3*	0.89 ± 0.19*	9.6 ± 1.8	3.95 ± 0.62	1.46 ± 0.34	1.31 ± 0.6

Month 0, baseline; month 3, crossover; month 6, end of study.
*$P \leq 0.01$ vs. corresponding baseline value.

During the 1st wk after randomization and again after the crossover, a member of the research team had daily telephone contact with the subject/family to review the SMBG results and to guide the subject to adjust the dose(s) of insulin according to standard guidelines (31).

Subjects were seen monthly, and measurements were obtained for height, weight, blood pressure, and heart rate. Insulin dosages were adjusted as indicated by growth, changes in physical activity, and results of SMBG. A blood sample was obtained for measurement of blood glucose, HbA_1 (normal range 5.4–7.4%; 32), and a urine sample was tested for glucose and ketones. Nonfasting measurements of total cholesterol, high-density lipoprotein cholesterol, and triglycerides (as part of an automated serum chemistry profile) were obtained at entry into the study, at the crossover visit, and when the study ended after 6 mo. The concentration of low-density lipoprotein cholesterol was calculated as total cholesterol − (high-density lipoprotein cholesterol + triglycerides × 0.2) (33).

Subjects were instructed to document suspected hypoglycemia, whenever possible, with a blood glucose measurement before they treated their symptoms and to record all such events. For the purpose of this study, biochemical hypoglycemia was defined as a blood glucose concentration ≤3.3 mM. Subjects kept a written record of insulin dosages, results of SMBG, episodes of hypoglycemia (severity, time, circumstances), and any other untoward events, that was reviewed monthly. The record of blood glucose measurements and the times they were performed was "downloaded" from the memory of the glucose meter with a "Data Manager (Lifescan)." The average insulin dosages and the mean blood glucose concentrations at each time point (before breakfast, lunch, supper, bedtime snack, and between 0200 and 0300) were determined monthly.

At the end of the study, subjects selected the regimen they thought gave the best glycemic control with the fewest adverse effects.

Statistical analysis. All data were presented as means ± SD unless otherwise stated. The significance of differences between the means of paired data were determined by Wilcoxon's rank-sum test and the Mann-Whitney *U* test was used to compare unpaired data. Repeated-measures analysis of variance was used to determine the significance of differences of measurements performed repeatedly in the same subjects. Statistical analyses were performed with Statview SE + Graphics (Abacus, Berkeley, CA) on a Macintosh SE/30 computer.

Biochemical variables were initially analyzed separately for prepubertal and pubertal subjects. No significant differences between the results of prepubertal and pubertal subjects were found, therefore, all subsequent analyses were performed on the entire group of 20 subjects.

RESULTS

All subjects maintained normal rates of linear growth and weight gain, and the mean dose of insulin increased with growth, increasing insulin requirements of puberty, and, in some patients, as a result of intensification of their diabetes (Table 1). Mean weight, height, and total daily insulin dose after 6 mo were all significantly

TABLE 2
Comparisons of insulin dosages

Month	Total dose (U/kg)		Morning dose (regular/NPH)		Evening dose (regular/NPH or ultralente)		Morning/evening dose	
	NPH	Ultralente	NPH	Ultralente	NPH	Ultralente	NPH	Ultralente
0	0.77 ± 0.16	0.77 ± 0.25	0.30 ± 0.17	0.27 ± 0.16	0.44 ± 0.34	0.33 ± 0.23*	2.02 ± 0.88	2.07 ± 0.90
3	0.84 ± 0.22	0.83 ± 0.19	0.31 ± 0.15	0.27 ± 0.16*	0.34 ± 0.23	0.41 ± 0.23†	1.90 ± 0.75	1.95 ± 0.81

*$P \leq 0.05$, †$P < 0.05 < P < 0.1$ NPH vs. ultralente regimen.

greater than their corresponding baseline values. On ultralente, the ratio of regular to NPH before breakfast was slightly lower than on NPH (0.27 ± 0.16 vs. 0.31 ± 0.15, $P < 0.05$, whereas the ratio of regular to ultralente before supper was slightly greater than the ratio of regular to NPH (0.41 ± 0.23 vs. 0.34 ± 0.23, P $0.05 < P < 0.1$). The ratio of the morning to evening dosages of insulin, however, were similar after 3 mo on each regimen (Table 2).

The average number of blood glucose measurements performed by each subject in the 3 mo on each regimen was similar (310 ± 43 on NPH and 300 ± 51 on ultralente). Mean fasting blood glucose concentrations were significantly lower in 2 of the 3 mo on the ultralente regimen, whereas, the mean blood glucose concentration before the bedtime snack was significantly lower in 2 of the 3 mo on the NPH regimen (Table 3). Mean blood glucose concentrations before lunch and supper, and between 0200 and 0300 were not significantly different between the two regimens; however, measurements at the latter time point were sparse.

Mean coefficients of variation of blood glucose values before breakfast, lunch, and supper, at bedtime and at 0200 to 0300 in the 3rd mo on NPH and ultralente were 34 ± 9 vs. 39 ± 9 ($P < 0.05$), 45 ± 16 vs. 51 ± 14, 45 ± 11 vs. 45 ± 10, 45 ± 12 vs. 44 ± 15, and 42 ± 18 vs. 38 ± 21, respectively.

Table 1 shows the mean HbA_1 concentration at entry to the study, at the time of crossover, and at the end of the study, regardless of the insulin regimen used. After 2 mo, the mean HbA_1 concentration decreased significantly from the baseline value (0 mo) (9.0 ± 1.3 vs. 9.4 ± 1.5%, $P < 0.05$), suggesting a study effect. However, the early improvement in glycemic control waned, and after 6 mo the mean HbA_1 concentration was 9.6 ± 1.8%, which was not significantly different from the baseline value. Table 3 shows a comparison of the HbA_1 values on the two regimens.

Biochemical hypoglycemia was demonstrated by SMBG on 12 ± 10 occasions (3.9 ± 3.5% of all blood glucose measurements) on NPH and on 13 ± 8 occasions (4.4 ± 2.9% of all blood glucose measurements) on ultralente. There were no differences in the frequency of biochemical hypoglycemia in any of the 3 mo on either regimen. However, the distribution of the occurrence of biochemical hypoglycemia differed between the two regimens. On NPH, the mean number of blood glucose concentrations ≤3.3 mM was equally distributed among the intervals from breakfast to lunch (2.9 ± 3.4%), lunch to supper (2.3 ± 2.8%), supper to bedtime snack (4.0 ± 4.7%), and bedtime snack to breakfast (2.8 ± 3.0%). In contrast, biochemical hypoglycemia on the ultralente regimen was significantly more common between breakfast and lunch (5.6 ± 4.5%) than during the other periods of the day (3.2 ± 2.6, 2.7 ± 2.9, 1.6 ± 3.7%, respectively). Biochemical hypoglycemia between breakfast and lunch on ultralente (5.6 ± 4.5%) was significantly ($P = 0.01$) more frequent than on NPH (2.9 ± 3.4%).

TABLE 3
Mean monthly self-monitoring of blood glucose and HbA_1 data

Month	Breakfast		Lunch		Supper		Bedtime		0200–0300 (n = 17)		HbA_1	
	NPH	Ultralente	NPH	Ultralente	NPH	Ultralente	NPH	Ultralente	NPH	Ultralente	NPH	Ultralente
1	10.6 ± 2.4 (33)	9.7 ± 2.2 (33)*	9.9 ± 2.3 (11)	8.6 ± 2.8 (12)†	10.9 ± 2.7 (32)	10.2 ± 2.0 (32)	8.5 ± 2.2 (22)	9.9 ± 2.7 (21)*	10.0 ± 3.4 (4)	11.2 ± 3.8 (4)	9.3 ± 1.4	9.0 ± 1.1
2 (n = 19)	10.0 ± 2.3 (32)	9.5 ± 2.0 (31)	9.7 ± 3.3 (12)	8.9 ± 2.2 (11)	10.9 ± 2.9 (32)	11.1 ± 2.4 (31)	8.3 ± 2.3 (21)	9.5 ± 2.5 (19)†	10.9 ± 2.6 (4)	9.7 ± 3.4 (3)	9.0 ± 1.5	9.1 ± 1.4
3	10.4 ± 2.4 (35)	9.5 ± 1.8 (34)*	9.5 ± 3.1 (12)	9.1 ± 2.3 (11)	10.7 ± 2.7 (35)	10.7 ± 1.8 (34)	8.4 ± 2.1 (21)	10.3 ± 2.2 (29)‡	9.7 ± 2.9 (4)	10.8 ± 3.5 (3)	9.1 ± 1.7	9.5 ± 1.4
All 3 mo	10.3 ± 2.2	9.6 ± 1.9*	9.8 ± 2.6	8.9 ± 1.7†	10.8 ± 2.6	10.7 ± 1.7	8.4 ± 1.9	10.0 ± 2.1‡	10.2 ± 2.1	10.6 ± 2.7	9.2 ± 1.5	9.3 ± 1.1

n = 20 except where indicated. Numbers in parentheses indicate average number of blood glucose measurements performed by each subject at respective times of day in each interval of ~1 mo. HbA_1 measurements in mo 1 and 2 were performed on 19 subjects.
*$P < 0.05$ mean monthly blood glucose concentrations between ultralente and NPH regimens.
†P $0.05 < P < 0.1$. ‡$P < 0.01$.

Three episodes of severe hypoglycemia (defined as loss of consciousness, seizure, an episode requiring treatment with glucagon or intravenous glucose) occurred during the study. Two episodes occurred in the same subject, once in the 2nd mo on ultralente (immediately before lunch at school; HbA_1 was 8%) and the second occurred in the 3rd mo on the NPH regimen (at 0200; HbA_1 was 8.8%). The third episode of severe hypoglycemia occurred at summer camp when the subject was in the 2nd mo on the NPH regimen (this event occurred at 0700; HbA_1 was 7%). In addition, three episodes of moderate hypoglycemia (defined as episode of hypoglycemia in which the patient exhibited symptoms and signs of neuroglycopenia and treatment required assistance by another person) were documented. Two episodes occurred on the ultralente regimen (both were in the same subject and occurred in each of the first 2 mo on the ultralente regimen with HbA_1 values of 10.4 and 10.6%, respectively), and the third episode of moderate hypoglycemia occurred while the subject was in the 1st mo on the NPH regimen when his HbA_1 value was 10.9%.

Mean serum lipid values did not change significantly over the course of the study (Table 1). After 3 mo on the NPH and ultralente regimens, nonfasting mean serum total cholesterol (3.93 ± 0.52 vs. 3.96 ± 0.52 mM), high-density lipoprotein cholesterol (1.45 ± 0.34 vs. 1.47 ± 0.26 mM), calculated low-density lipoprotein cholesterol (1.84 ± 0.52 vs. 1.97 ± 0.47 mM) and triglycerides (1.38 ± 0.52 vs. 1.14 ± 0.53 mM) were similar and not significantly different from baseline values.

After completion of the study, 11 subjects chose to use the ultralente regimen and were still using it 1 yr later. Two subjects reverted to a twice-daily mixture of regular and lente insulin, and 7 chose the NPH regimen. One year after completion of the study, 1 subject who chose the NPH regimen was on three daily dosages of insulin with the second dose of NPH at bedtime.

CONCLUSIONS

This study was undertaken to explore the possibility that human ultralente insulin, because of its slower onset of action, blunted peak, and longer duration of action compared with intermediate-acting insulins such as NPH or lente, could be used in a twice-daily insulin regimen to optimize overnight glycemia in youth with IDDM. A mixture of regular and NPH insulin was chosen for the morning dose because it was thought that the early peak effect of the latter would provide the insulin action necessary to cover the midday meal (30).

Hildebrandt et al. (24) found that human ultralente insulin was absorbed significantly faster than beef ultralente insulin and suggested that an evening dose of human ultralente insulin might be of value for basal insulin delivery, especially in children in whom the duration of the relatively small evening dose of intermediate-acting insulin is often too short to meet the increasing need for insulin in the morning. Francis et al. (34) compared pork lente to human ultralente insulin in subjects with raised fasting blood glucose concentrations and found that the latter was associated with significantly lower mean blood glucose concentrations before and after breakfast. This observation led to the suggestion that subjects with poor overnight metabolic control and raised fasting blood glucose concentrations may benefit from human ultralente insulin as part of a twice-daily insulin regimen. Tunbridge et al. (35) compared a twice-daily human ultralente regimen with a lente-based injection regimen in adults with IDDM and found that ultralente improved fasting blood glucose concentrations but offered no clinical advantage over lente insulin in subjects with more marked fasting hyperglycemia.

Despite slightly improved fasting and prelunch concentrations of blood glucose with use of ultralente insulin before the evening meal, higher levels of blood glucose from supper to bedtime presumably accounted for the failure to demonstrate a significant improvement in the concentrations of glycosylated hemoglobin. Despite similar presupper dosages of regular insulin on the two regimens, blood glucose concentrations before the bedtime snack were significantly lower on the NPH regimen. This could have resulted from the early hypoglycemic effect of human NPH, which is known to lower blood glucose within 2–4 h of subcutaneous injection (30). In addition, the higher concentrations of blood glucose before the bedtime snack on ultralente may have resulted from a blunting of the action of regular insulin when mixed in the same syringe with human ultralente insulin (36,37). A better result from the use of ultralente insulin administered before the evening meal might require a larger fraction of regular insulin in the mixture than was used in this study, injection of the mixture at least 60 min before the evening meal, or separate injections of regular and ultralente insulins. However, the latter option would defeat the purpose of using ultralente insulin.

Although this study did not demonstrate a dramatic improvement in the concentration of blood glucose before breakfast when human ultralente insulin was substituted for NPH insulin before supper, the effect might have been greater had we selected children with persistently high fasting concentrations of blood glucose or subjects with a pronounced dawn phenomenon. Before resorting to three injections of insulin each day (a bedtime injection of intermediate-acting insulin), we recommend a trial of this regimen for young children who have supper early, children with recurrent nocturnal hypoglycemia, and children with pronounced fasting hyperglycemia as a result of an early morning rise in blood glucose concentrations. Further study is needed to determine whether altering the proportion of regular to ultralente insulin in the presupper injection and reducing the size of the bedtime snack would result in further improvement in overnight glycemia.

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