Effect of the Fast-Acting Insulin Analog Lispro on the Risk of Nocturnal Hypoglycemia During Intensified Insulin Therapy

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OBJECTIVE — To measure the effectiveness of insulin lispro, a fast-acting insulin analog, in reducing hypoglycemic episodes when used in a basal bolus regimen by patients with type 1 diabetes using intensive insulin therapy.

RESEARCH DESIGN AND METHODS — In 11 diabetes outpatient clinics in the U.K., 165 subjects with type 1 diabetes were enrolled in a randomized crossover open-label study with a 2-month run-in period and then treated with a basal bolus regimen. Patients used human NPH insulin at night with either premeal insulin lispro for 4 months followed by human regular insulin for another 4 months or human regular insulin for 4 months followed by insulin lispro for another 4 months. The main outcome measures were the number of hypoglycemic episodes during both treatments and HbA_{1c} level.

RESULTS — A total of 135 patients were randomized, with 68 receiving insulin lispro and 67 receiving human regular insulin for the first 4 months. The data for the first 4 months of treatment only were compared as two independent groups because of a period effect and a treatment–period interaction. Glycemic control was equally tight during treatment with human regular insulin (HbA_{1c}, 6.2 ± 0.8%) and insulin lispro (6.0 ± 0.9%). A total of 1,156 hypoglycemic episodes occurred during treatment with human regular insulin compared with 775 hypoglycemic episodes that occurred during treatment with insulin lispro ($P = 0.04$). This difference was chiefly because of a reduced number of nocturnal episodes (181 vs. 52, $P = 0.001$) in the insulin lispro group.

CONCLUSIONS — The use of a fast-acting insulin analog, insulin lispro, as part of a basal bolus regimen reduces nocturnal hypoglycemia in patients with type 1 diabetes who maintain tight glycemic control during intensive insulin therapy.

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Recent prospective studies have confirmed the benefits of maintaining blood glucose levels as close to normal as possible for patients with diabetes (1,2). The resulting reduced risk of microvascular disease, particularly diabetic nephropathy, offers patients the opportunity to have a near-normal life expectancy. However, maintaining more normal blood glucose levels may result in more frequent episodes of hypoglycemia (3). The high risk of severe hypoglycemia is partly because of both acquired defects in glucose counterregulation and fewer hypoglycemia warning symptoms (4). However, the principal cause is the presence of inappropriately raised insulin levels in the postabsorptive period, particularly at night (5–7). Even the fastest-acting conventional insulin (regular insulin) fails to reproduce "physiological" insulin profiles after subcutaneous injection as a result of the molecules aggregating as hexamers (8).

The use of genetic engineering to produce insulin analogs has the potential of replacing insulin more effectively. Reversal of the normal proline-lysine sequence in the insulin β-chain at position 28 and 29 produces a molecule with less self-association (9). Insulin lispro enters the bloodstream more rapidly than conventional insulin, and this can limit the increase in blood glucose after eating (10–12). Furthermore, the more rapid decrease in insulin concentration should reduce postabsorptive hypoglycemia (13).

Previous studies have generally suggested that insulin lispro in a basal bolus regimen achieves equivalent but not improved glycemic control compared with regular insulin (14,15). Any advantage of lower postprandial glucose values is offset by a tendency for premeal values to rise as circulating insulin decreases (16). Hypoglycemia is less common (15–17), although the decrease is usually slight, with mild episodes reduced by ~20% (14).

One explanation for the modest clinical benefit demonstrated for lispro thus far may relate to the glycemic control of subjects who participated in previous studies. Even in studies in which subjects were described as "well-controlled," the glycemic goals of intensive insulin therapy were rarely met, and mean HbA_{1c} levels did not indicate tight metabolic control. We hypothesized that patients who would benefit most from fast-acting insulin analogs are those at greatest risk for hypoglycemia, namely those who kept their blood glucose levels close to normal. We tested this hypothesis in a multicenter trial.

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Abbreviations: DCCT, Diabetes Control and Complications Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of subjects*

	Drop outs in run-in period	Patients receiving insulin lispro	Patients receiving regular insulin
n	30	68	67
Sex (M/F)	13/17	35/33	36/31
Age (years)	35 ± 9	37 ± 11	39 ± 11
BMI	25.3 ± 3.7	25.2 ± 2.6	25.4 ± 2.9
Duration of diabetes (years)		16.4 ± 9.6	16.7 ± 8.8

Data are means ± SEM.

RESEARCH DESIGN AND METHODS

Study design

We used a randomized crossover open-label design carried out in 11 diabetes clinics throughout the U.K. Eligible patients had type 1 diabetes for at least 2 years, had been using a basal-bolus regimen for at least 3 months, had an HbA_{1c} level <8%, and had expressed a desire to achieve tight glucose control. We excluded patients if they had active proliferative retinopathy, symptomatic peripheral neuropathy, or a serum creatinine level >250 μmol/l or if they had been admitted to the hospital on more than three occasions with severe hypoglycemia in the previous 12 months.

Suitable patients entered a 2-month run-in period during which their glucose control was optimized with multiple injections of human regular insulin (Humulin R; Lilly, Basingstoke, U.K.) before the three main meals and human NPH insulin (Humulin I; Lilly, Basingstoke, U.K.) at bedtime. Patients were asked to maintain the Diabetes Control and Complications Trial (DCCT) glycemic targets of premeal concentrations of 4–7 mmol/l (72–126 mg/dl) and postprandial concentrations of 7–10 mmol/l (126–180 mg/dl). Patients were in regular contact with diabetes nurses who advised patients on insulin adjustment to meet the glucose targets based on patients' own glucose profiles, which were recorded at least weekly in specially designed diaries. Details of hypoglycemic episodes were also recorded in the diaries.

In addition, every 2 weeks, patients collected a seven-sample glucose profile for 1 day into capillary tubes, which were analyzed at a central laboratory. Any patient who failed to maintain at least 70% of capillary samples within the above targets or had an HbA_{1c} level >8% at the end of the run-in period was not randomized.

Eligible patients were randomized after 2 months to receive either insulin lispro for 4 months followed by human regular insulin for an additional 4 months or human regular insulin therapy for 4 months followed by insulin lispro for 4 months. We instructed patients to inject human regular insulin ~30 min before each of their main meals, and insulin lispro was injected immediately before eating.

The main end points were the number of hypoglycemic episodes experienced by the subjects during both treatments. Mild episodes were defined as symptoms or signs associated with hypoglycemia experienced by the patient or observed by another person or a home blood glucose measurement of <3 mmol/l. Severe episodes were defined as those in which patients needed the assistance of another person (e.g., coma or seizure). Secondary end points included HbA_{1c} level (measured by high-performance liquid chromatography ion-exchange chromatography, normal range 3.8–5.5%), daily blood glucose profiles, weight, and insulin dose.

Seven-point capillary glucose profiles were collected at monthly intervals and analyzed centrally.

Statistics

Continuous data expressed generally as means ± SD were analyzed by Student's *t* test, and categorical data were analyzed by χ^2 test after testing for period and treatment–period interactions. Because analysis of the two periods showed significant period and treatment–period interactions, only the data for the first 4 months of the study were analyzed as two independent parallel groups on an intention-to-treat basis (18). A two-sided analysis was carried out with significance set at 0.05.

RESULTS — We invited 165 patients (84 men, 81 women) with a mean weight of 75 ± 12 kg, a mean BMI of 25.3 ± 3 kg/m², and a mean duration of diabetes of 16.6 ± 7.8 years to participate in the study (Table 1). Of the 165 subjects, 48 had background retinopathy, and 26 had peripheral neuropathy.

Crossover analysis and dropouts

Of the 165 patients who entered the run-in period, 30 were not randomized, including 21 who chose not to enter the study, 6 who failed to meet the entry criteria, and 3 who were withdrawn at the physician's discretion. Of the remaining 135, 68 received insulin lispro for the first 4 months, and 67 received human regular insulin. No significant differences in demographic characteristics existed between the two groups (Table 1). We tested the appropriateness of crossover analysis by using the total number of episodes of hypoglycemia (Table 2), our main end point of interest. This demonstrated both a period and a treatment–period interaction (Table 3). Therefore, during the analysis, only the data for the first period were compared as two independent groups. One patient died after a prolonged seizure that was possibly related to hypoglycemia during the second phase of the study while taking regular insulin.

Rates of hypoglycemia

Period 1. There were 8 episodes of severe hypoglycemia (4 involving coma and 4 requiring glucagon) in two patients taking insulin lispro (3%) and 12 episodes of severe hypoglycemia (2 involving coma and 10 requiring glucagon) in six patients taking human regular insulin (9%). This was not statistically different.

There were 1,156 hypoglycemic episodes during treatment with human regular insulin compared with 775 during treat-

Table 2—*Total number of hypoglycemic episodes in each period*

Patients grouped according to allocation of preprandial insulin	Number of episodes	
	Period 1	Period 2
Insulin lispro followed by Humulin R	775	702
Humulin R followed by insulin lispro	1,156	883

Table 3—*Crossover trial analysis*

Period effect*	Mean difference, d_1 versus mean $-d_2$	1.4 vs. 4.5
Treatment–period interaction†	Mean average, a_1 versus a_2	22.8 vs. 27.3

Total number of hypoglycemic episodes in each period. Group 1 received lispro followed by human regular insulin. Group 2 received human regular insulin followed by lispro. In the light of a significant period effect, we discarded the data from the second period and analyzed the first period as two independent groups. *P = 0.002; †P = 0.034.

ment with insulin lispro (P = 0.04) (Table 2). The difference in the rate of hypoglycemia was chiefly due to a reduction in the number of episodes between 12:00 and 6:00 A.M. in subjects taking insulin lispro (181 vs. 52, P = 0.001) (Table 4 and Fig. 1). Episodes were also reduced between 12:00 and 6:00 P.M. (380 vs. 277, P = 0.04).

Period 2. There were 13 episodes of severe hypoglycemia (8 involving coma and 5 requiring glucagon) in three patients taking insulin lispro (3%) and 4 episodes of severe hypoglycemia (2 involving coma and 2 requiring glucagon) in one patient taking regular insulin (1.5%). A total of 702 hypoglycemic episodes occurred during treatment with human regular insulin compared with 883 hypoglycemic episodes during treatment with insulin lispro.

HbA_{1c}

Period 1. Glycemic control as measured by HbA_{1c} improved in both groups but was not different for treatment with human regular insulin versus insulin lispro either at the start (6.4 ± 0.9 vs. 6.2 ± 1.1%) or at the end (6.2 ± 0.8 vs. 6.0 ± 0.9%) of the period (Fig. 1).

Period 2. HbA_{1c} levels during treatment with human regular insulin were 6.0 ± 0.9% at the start and 6.4 ± 1.1% at the end of 4 months. Values during treatment with insulin lispro were 6.2 ± 0.8 and 6.4 ± 1.1%, respectively.

Capillary glucose profiles

The capillary glucose values for the seven-point profiles measured centrally during period 1 are shown in Fig. 2 and represent the means ± SEM of between 90 and 128 samples at each time point. Values taken after breakfast and lunch were significantly lower during treatment with insulin lispro versus treatment with human regular insulin (7.4 ± 0.5 vs. 8.5 ± 0.4 mmol/l, P = 0.048; 6.6 ± 0.3 vs. 7.2 ± 0.3 mmol/l, P = 0.043, respectively). Values at bedtime were significantly higher during treatment with insulin lispro versus treatment with human regular insulin (8.1 ± 5 vs. 7.5 ± 0.4 mmol/l, P = 0.03).

Weight

Weight increased in patients taking human regular insulin (from 73.5 ± 10.1 to 75.7 ± 10.2 kg, P = 0.048) but not in patients taking insulin lispro (from 74.8 ± 11.4 to 74.7 ± 11.7 kg).

Insulin dose

Basal (intermediate-acting) insulin doses were not different either at the start of the study for patients taking human regular insulin (0.26 ± 0.02 U/kg) versus patients taking insulin lispro (0.24 ± 0.02 U/kg) or at the end of the study (0.27 ± 0.02 vs. 0.27 ± 0.02 U/kg). Total daily preprandial insulin doses were not different for the two groups at either the start (0.45 ± 0.02 vs. 0.47 ± 0.02 U/kg) or the end (0.43 ± 0.02 vs. 0.43 ± 0.02 U/kg) of the study.

CONCLUSIONS — We demonstrated that patients taking an insulin analog, insulin lispro, in an intensified regimen can achieve glycemic control that is as equally effective as that of patients using conventional regular insulin with less hypoglycemia. There were fewer hypoglycemic episodes between 12:00 and 6:00 P.M., but the greatest effect was evident with nocturnal episodes, which were reduced by threefold. Eight episodes of severe hypoglycemia were experienced by patients taking insulin lispro compared with 12 episodes experienced by patients taking regular insulin, but this was not significant.

We used a crossover design with a 2-month run-in period by including only patients capable of maintaining near normoglycemia for two 4-month periods during intensive insulin therapy and by using regular and insulin lispro in random order. There was a marked period effect on the incidence of hypoglycemia in our study. We observed lower rates of hypoglycemia among patients who took insulin lispro first compared with patients who took regular insulin first, and these lower rates were relatively maintained when patients switched back to human regular insulin. In contrast, patients who used human regular insulin first experienced more hypoglycemic episodes than patients taking insulin lispro first and fewer episodes when they switched to insulin lispro. Other studies of insulin lispro that have used a crossover design have not reported such an effect, and we do not know why it occurred in this study.

One possible explanation may be that the protective responses to hypoglycemia are influenced by recent prior glycemic experience. Perhaps defective glucose counterregulation associated with recurrent mild hypoglycemia (19) and intensified insulin therapy (20) was restored by the period of relatively infrequent exposure to hypoglycemia (21,22), which persisted throughout the next 4 months. However, this explanation is speculative and is not supported by a recent study in which glycemic control was comparable and in which a period effect was not observed in a crossover design (23). An alternative expla-

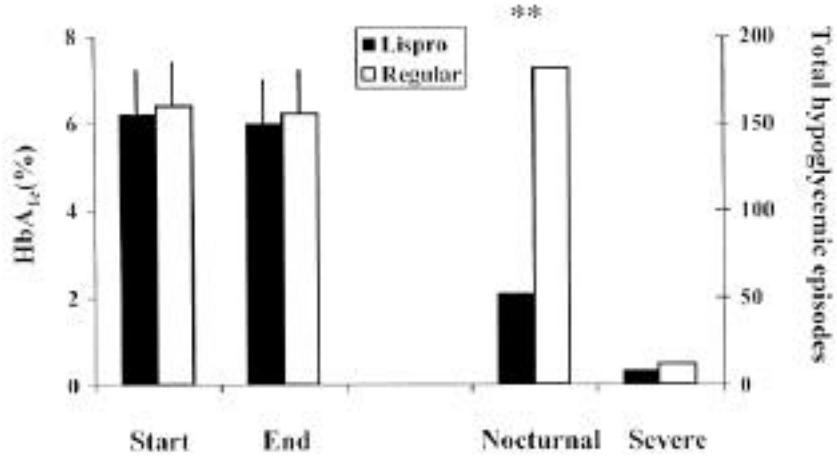

Figure 1—*HbA_{1c} and severe and nocturnal hypoglycemic episodes during period 1 of the study.* **P < *0.01.*

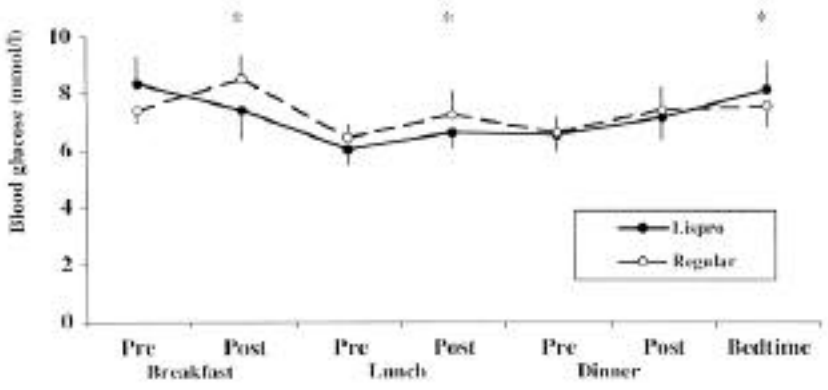

Figure 2—*Capillary glucose profiles (means ± SEM) measured centrally during period 1 of the study. *P < 0.05.*

nation is that, while using insulin lispro, both patients and the nurses working with them developed techniques to avoid hypoglycemia, which carried over to the period when they used regular insulin.

We were unable to draw any conclusions about severe hypoglycemia because these episodes occurred infrequently during the 4 months. Nevertheless, 8–12 episodes in each group of ~60 patients is comparable with the DCCT and other studies of intensive insulin therapy that have reported rates of ~30%/year (3). One patient died of probable hypoglycemia during the second 4 months of the study while using regular insulin, which highlights the potential risks of intensive insulin therapy.

A lower rate of nocturnal hypoglycemia has been described in other studies of insulin lispro, but in these studies, the decrease has been more modest at ~20–30%. Holleman et al. (23) recently reported a decrease of 46%. Our data suggest that the greatest benefit of short-acting analogs will be gained by patients at highest risk for hypoglycemia. In the DCCT, severe hypoglycemia was common at night and accounted for 30% of all episodes. Patients who try to maintain their blood glucose levels close to normal by using intermittent subcutaneous insulin experience relatively high free insulin concentrations in the postabsorptive period (24). Replacing regular insulin with an analog may reduce insulin levels at vulnerable times and thus reduce the risk of hypoglycemia.

Our data indicate that daytime regular insulin has a greater effect on the risk of nocturnal hypoglycemia than previously believed. Presumably, regular insulin taken before the evening meal is largely responsible, but insulin levels may rise throughout the day with repeated doses. Whatever the exact cause, we believe that the ability of insulin analogs to reduce nocturnal hypoglycemia is a significant therapeutic advancement.

The capillary glucose profiles in this study confirm previous findings that fast-acting insulin analogs modestly reduce the increase in postprandial glucose levels compared with regular insulin. Unlike previous studies, we did not observe higher glucose values before the evening meal during treatment with insulin lispro, although none of the patients received morning NPH insulin (15). Fasting glucose values were not significantly higher in patients treated with an insulin analog. Furthermore, although patients were free to adjust the dose of NPH at bedtime, we observed no differences in the NPH dose between the two groups. One explanation for these differences is that preprandial "escape" of blood glucose may be less of a problem in patients who maintain very tight glycemic control. Alternatively, the higher blood glucose levels we observed in patients treated with insulin lispro before bedtime suggests that these observations may merely reflect the tendency of British patients to eat their evening meal relatively early, between 5:00 and 6:00 P.M.

We chose not to conduct a blind study because we wanted to compare insulin lispro and regular insulin taken in a way that would offer the best possible glycemic control. Thus, we asked patients to inject regular insulin 30–45 min before eating, whereas insulin lispro was taken just before the meal. In an open study, the reliability of data, which depend on patients reporting hypoglycemic episodes, must be questioned. We cannot rule out the possibility of bias, particularly if participants believed they were using a more effective insulin. This especially applies to hypoglycemic episodes during the day. However, because most episodes recorded between 12:00 and 6:00 A.M. awaken patients from sleep, nocturnal episodes are less likely to be affected by bias.

We believe that insulin lispro in a basal bolus regimen should be considered in patients with type 1 diabetes who attempt to maintain near-normal glucose values, particularly if they experience nocturnal hypoglycemia. This approach may allow more patients to achieve lower glycemic targets safely and in turn reduce their risk of developing microvascular complications.

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Table 4—*Time distribution of hypoglycemic episodes during period 1*

Time of episode	Lispro (*n*)	Regular (*n*)
12:01–6:00 A.M.*	52	181
6:01 A.M. to 12:00 P.M.	245	245
12:01–6:00 P.M.†	277	380
6:01 P.M. to 12:00 A.M.	150	266

Data are *n*. *P = 0.001; †P = 0.048.

APPENDIX

Study group members

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