Postprandial Insulin Lispro

A new therapeutic option for type 1 diabetic patients

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OBJECTIVE — For intensified insulin therapy of type 1 diabetes, bolus injection of regular human insulin 30–15 min before a meal is currently recommended. This randomized study is aimed to determine whether insulin lispro (LIS), a new insulin analog with a rapid onset of action, can provide comparable blood glucose (BG) control by injection after the meal.

RESEARCH DESIGN AND METHODS — Eighteen type 1 diabetic subjects injected regular insulin (REG) at 40, 20, or 0 min before or LIS at 20 or 0 min before or 15 min after the start of a standardized test meal. BG excursions and area under the curve of BG excursions (AUC) at the six visits were compared by analysis of variance. Hypoglycemic events (BG ≤2.78 mmol/l) were evaluated in relation to the achieved postprandial BG control.

RESULTS — Mean AUC values were 2.00, 2.55, and 3.33 mmol · h · l^{-1} for REG given 40, 20, and 0 min before the test meal, respectively, and −2.19, −2.15, and 1.98 mmol · h · l^{-1} for LIS given 20 and 0 min before and 15 min after the start of the test meal, respectively. LIS injected 20 min (−20) or immediately (0) before the meal was significantly more effective in controlling postprandial BG excursion ($P < 0.001$) than any REG treatment. Postprandial injection of LIS (15) did not compromise postprandial BG control and resulted in less hypoglycemia. REG −40 and LIS −20 were associated with early hypoglycemia, but other hypoglycemic events were equally distributed among groups.

CONCLUSIONS — The optimal time for bolus insulin injection was 20 min before the meal for REG and immediately before the meal for LIS. LIS injected immediately after a standard meal provided postprandial BG control at least as good as REG injected from 40 to 0 min before the meal. Postprandial injection of LIS is an attractive new therapeutic option.

The Diabetes Control and Complications Trial demonstrated that intensified insulin therapy can reduce the risk of primary and secondary long-term complications in type 1 diabetic patients (1). Intensified insulin (basal-bolus) therapy is administered as basal insulin with short-acting bolus insulin, requiring at least four injections per day. Most textbooks and publications recommend that bolus insulin be injected 15–30 min before the meal, but these standards were based mainly on kinetic considerations and clinical practice. A few studies have tried to determine the optimal time for preprandial injection of bolus insulin (2–7). These studies indicated that postprandial glucodynamic control was significantly improved with earlier injection of the preprandial bolus, i.e., in a range of 60–15 min compared with 5–0 min before the meal. To mimic the physiological insulin time-action profile, regular insulin (REG) has to be injected ~60 min before the meal.

However, most studies were conducted when insulin regimens were less stringent than those in current practice and with heterogeneous patient populations and questionable designs, some of them enrolling only very few patients. A glucose clamp study came to the conclusion that in patients with a tight regimen, even an injection 30 min before the meal carried a risk of hypoglycemia soon after eating, while an injection immediately before the meal led to postprandial hyperinsulinemia and suboptimal postprandial blood glucose (BG) control (8). The authors concluded that this dilemma could only be overcome by an ultrafast-acting insulin analog designed by DNA technology.

Such an ultrafast insulin analog is now available in the form of insulin lispro (LIS). Because of its rapid onset of action of 0–15 min and duration of action of 2–4 h, it can be injected just before the meal, significantly improving postprandial BG values compared with REG (9,10). The aim of the present study was to elucidate the relationship of insulin bolus timing with postprandial BG excursions and to determine whether LIS injected after the meal could control BG values at least as well as REG or LIS injected before the meal. The defined optimal regimen from among the times selected was evaluated from the best postprandial BG control without increasing the danger of hypoglyemic events.

RESEARCH DESIGN AND METHODS

Patients

The study, carried out under ethical committee approval, involved 18 type 1 diabetic patients with intensified insulin therapy and good metabolic control (HbA_{1c} ≤8%). All patients gave written informed consent, were diagnosed under the age of 40 years, injected insulin three or moretimes a day, had a BMI <35 kg/m^2, and had no evidence of rapidly progressing complications. Patients were excluded if they had advanced diabetic complications, other significant disease, a history of clinically significant hypoglycemia, or insulin allergy or resistance. Of the 18 patients, 15 (83.3%) were men, and 3 (16.7%) were women. Baseline patient characteristics (means ± SD) were as follows: age 35 ± 7 years, weight 73 ± 9 kg, height 177 ± 5 cm, BMI 23 ± 2 kg/m^2, HbA_{1c} 6.9 ± 0.8% (normal range: 4.0–6.0%), and duration of

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Abbreviations: AUC, area under the curve of blood glucose excursion; BG, blood glucose; LIS, insulin lispro; REG, regular insulin.

diabetes 11 ± 7 years. All 18 enrolled patients completed all of the required visits.

Study design

A randomized replicated Latin square design with six treatments and six study days was chosen to give all 18 patients an equal chance to perform all of the six different visits comparing both inter- and intraindividual differences. At each visit, REG or LIS bolus injection was given relative to the start of the test meal to provide the following treatment groups:

REG −40	REG administered 40 min before the start of the meal
REG −20	REG administered 20 min before the start of the meal
REG 0	REG administered immediately (0 min) before the start of the meal
LIS −20	LIS administered 20 min before the start of the meal
LIS 0	LIS administered immediately (0 min) before the start of the meal
LIS +15	LIS administered 15 min after the start of the meal

The timing of REG −40 was chosen to reflect the findings of previous studies (2–7), REG −20 to follow textbook recommendations, and REG 0 as advocated by some diabetologists. LIS −20 was an experimental treatment to examine whether postprandial control could be further improved, LIS 0 reflected the current clinical standard recommendation, and LIS +15 was chosen to determine whether this was a viable option.

Lunchtime was selected for the study visits, since it was expected to provide the most stable physiological situation because the dawn phenomenon and nocturnal hypoglycemia would lead to higher variation in fasting glucose earlier in the day. Serum samples for BG analysis were drawn at −40, −20, 0, 15, 60, 90, 120, 150, and 180 min relative to the start of the meal through an indwelling venous catheter. All BG concentrations were determined by a central laboratory using a glucose oxidase method. Patients maintained their basal regimen and breakfast stable and identical on the study days. All patients injected basal insulin twice a day, in the early morning (6:00–7:00 A.M.) and before bedtime (10:00–11:00 P.M.), and some used zinc-depot insulin in the morning and NPH insulin at night, while others used NPH insulin for both. The basal insulin regimen remained constant throughout the entire study period. The bolus dose required for the standardized meal was calculated for each individual patient and was kept identical for all visits. The mean bolus dose injected by the 18 patients to match the test meal was 5.3 IU (range: 4–8 IU). The test meal for all patients and visits comprised 350 g of beef stroganoff: 584.5 kcal, 35 g protein, 45.5 g carbohydrates, 28 g fat. BG values had to be within a range of 3.3–11.1 mmol/l at the start of the study visit. All six visits had to be performed within six weeks to keep the physical conditions as stable as possible.

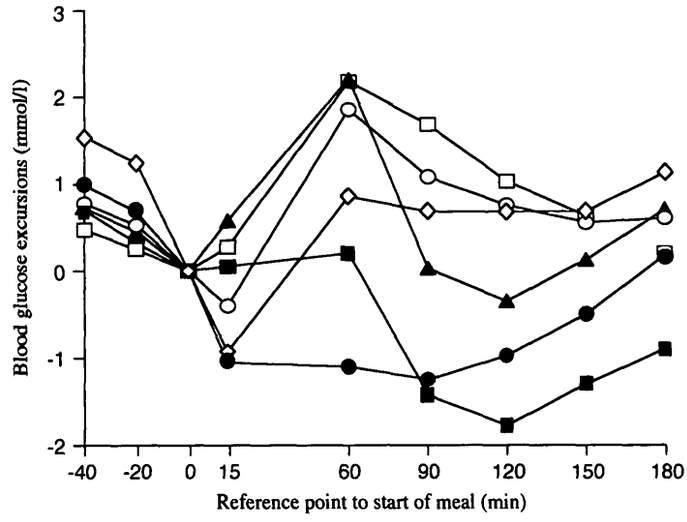

Figure 1—*BG concentrations were measured in type 1 diabetic patients given either REG (open symbols) or LIS (closed symbols) at specified times in relation to the start (time 0) of a standard meal. Excursion levels were calculated with reference to the value at time 0 for each patient. REG was given 40 min before (REG −40) (◇), 20 min before (REG −20) (○), or immediately before (REG 0) (□) the meal, and LIS was given 20 min before (LIS −20) (●), immediately before (LIS 0) (■), or 15 min after (LIS +15) (▲) the set meal. n = 18 for each point.*

Statistical methods

Postprandial BG excursions at 60, 90, and 120 min (calculated as 60, 90, or 120 min BG − 0 min BG) were evaluated for each of the six treatment groups. The six treatments were compared for each of the measurements (BG and postprandial BG excursions) using an analysis of variance model incorporating the effects of treatment and study day. Treatment group means were compared in a pair-wise fashion using the Student-Neuman-Keuls test. In addition, because of considerable variability in the time-action profiles of BG levels when compared on the basis of 1-h and 2-h values, the area under the curve of BG excursions (AUC) for each treatment was estimated by the trapezoidal rule and compared to express the overall postprandial BG excursion over the 3-h measurement period.

The number of hypoglycemic events, defined as BG ≤2.78 mmol/l, was evaluated for each patient on each insulin regimen. Additionally, hypoglycemic events were classified as early if they occurred within 0–60 min after the start of the meal or as late if they occurred >60 min after the start of the meal. Events that started in the early period but continued into the late period were counted only once and as an early event.

RESULTS

Postprandial BG excursions

There was no significant difference (P = 0.407) between treatment groups for the mean BG concentrations at 40 min before the administration of study insulin. The BG excursions throughout the study period are shown in Fig. 1 and the excursions at 60, 90, and 120 min in Table 1. For the excursion at 60 min, the mean value of treatment LIS 0 was significantly lower than the means of treatments REG −20, REG 0, and LIS +15, and the mean value of treatment LIS −20 was significantly lower than means of all other treatments. The mean value of treatment LIS +15 was not significantly different from any of the REG treatments. For the excursion at 90 min, the means of treatments LIS −20 and LIS 0 were significantly lower than the means of each of the

Table 1—*BG excursions by treatment*

Treatment	REG −40	REG −20	REG 0	LIS −20	LIS 0	LIS +15
Excursion						
60 min	0.84 ± 1.52*	1.84 ± 1.65*†	2.16 ± 1.70*‡	−1.12 ± 2.13	0.19 ± 1.72*	2.20 ± 1.49*†
90 min	0.65 ± 1.72*†	1.05 ± 2.20*‡	1.67 ± 2.55*†	−1.27 ± 1.89	−1.44 ± 1.60	0.02 ± 1.99
120 min	0.67 ± 1.69†	0.74 ± 2.40†	1.02 ± 2.73*†	−0.99 ± 1.89	−1.79 ± 1.66	−0.37 ± 2.05

Data are means ± SD and are given in millimoles per hour per liter. *$P < 0.05$ compared with LIS −20; †$P < 0.05$ compared with LIS 0 (Student-Newman-Keuls test).

REG treatments. However, the means of each of the REG treatments were not significantly different from each other or from the mean of treatment LIS +15, although numerically the value of LIS +15 was lower than that of each of the REG treatments. For the 120-min excursions, the mean value of treatment LIS −20 was significantly less than the mean of treatment REG 0, and the mean of treatment LIS 0 was significantly less than the means of all REG treatments. Again, the REG treatments did not statistically differ from each other or from LIS +15, but LIS +15 was numerically considerably lower than each of the REG groups.

Analysis of the AUCs of all six treatments showed LIS −20 (−2.19 mmol · h · l^{-1}) and LIS 0 (−2.15 mmol · h · l^{-1}) to be significantly ($P < 0.001$) lower than all other treatments (Fig. 2). The AUC of LIS +15 (1.98 mmol · h · l^{-1}) was numerically, but not statistically, lower than that of each of the REG groups (REG −40: 2.00; REG −20: 2.55; and REG 0: 3.33 mmol · h · l^{-1}).

Hypoglycemic events

Hypoglycemic events occurred in 7 of the 18 patients, and all were observed postprandially. Of the 7 patients, 2 had hypoglycemic events only with REG and 2 only with LIS, while 3 had hypoglycemic events with both insulins. Thus, five (27.8%) patients had hypoglycemic events during treatment with REG and five (27.8%) during treatment with LIS. However, this was a patient population with a very tight insulin regimen, as reflected by the low baseline HbA_{1c} levels. Also, the influence of the morning basal insulin could not be precisely differentiated, and the standard meal was not high-caloric.

In total, 13 hypoglycemic events were experienced by the 7 patients, of which seven occurred during treatment with REG and six during treatment with LIS. For early hypoglycemias, there were three in the REG −40 group, one in REG −20, two in LIS −20, and one in LIS +15. There was one late hypoglycemia in each of the REG −40, REG −20, and REG 0 groups and three in the LIS +15 group. No hypoglycemic events were seen with LIS 0. Of the events that started in the early period but extended into the late, there were one in REG −20, two in LIS −20, and one in LIS +15, and these were counted only in the early period corresponding with the onset of the event. No significant changes in other clinical laboratory measurements were noted at any time during the study.

CONCLUSIONS — Good glucodynamic control with minimal hypoglycemic events is a major aim of diabetes treatment. Surprisingly, few studies have examined the relationship between time of bolus insulin administration and glycemic control in patients with basal-bolus regimens. Patients prefer to inject their insulin very shortly before a meal (11), although it is recommended that REG be injected at least 30 min before (12). For REG in the present study, 40 min before the meal (REG −40) was the most effective regimen in terms of glucodynamic control but was associated with early hypoglycemic events, as has been reported in other studies (8,13). Similarly, LIS administered 20 min before the meal (LIS −20) was the most effective treatment in terms of glucodynamic control but may also lead to early hypoglycemic events. Several long-term studies, however, have reported that LIS resulted in fewer hypoglycemic events than REG (14,15).

The most appropriate time for injection of REG bolus appeared to be 20 min before the meal (REG −20), which is within the time range recommended in most textbooks. REG administered immediately before the meal (REG 0) was, by far, the worst treatment in terms of postprandial BG control and should not be recommended. From BG excursions and AUCs of the excursions, LIS 0 was significantly more effective than all REG treatment groups in controlling postprandial BG. Also, LIS 0 was not associated with either early or late hypoglycemic events. Postprandial injection of LIS (LIS +15), did not compromise the BG control and resulted in less hypoglycemia. Even though in this treatment LIS was injected up to 55 min after REG

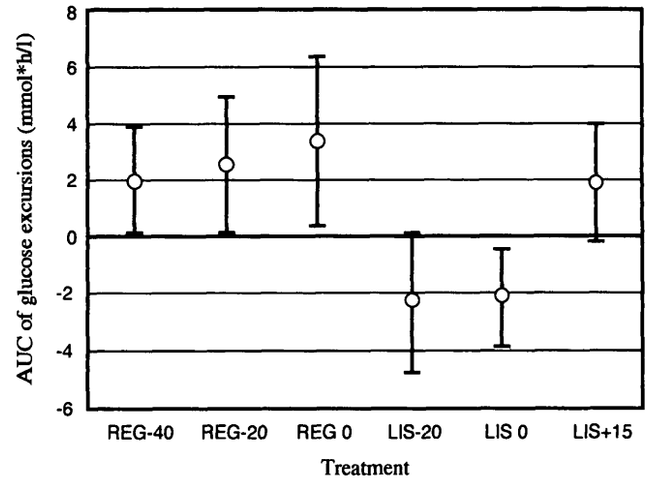

Figure 2—*The AUCs were estimated using the trapezoidal rule. The values shown are means and 95% CIs for each treatment.* n = *18 for each group.*

−40, its effects were much more rapid, providing better postprandial control than any of the REG treatments.

Postprandial injection of bolus LIS is an attractive new option, since it would allow patients to adjust their insulin units according to the calories ingested. There would be less pressure on the patient to eat quickly, which might be a particular benefit for children (and their parents). Although the present study showed that postprandial LIS did not cause a deterioration of glucodynamic control, it cannot be predicted from these results whether this is true for all meals with different carbohydrate and fat composition. Optimal postprandial injection times in relation to composition of meals requires further clinical study, and long-term safety should be determined from changes in HbA_{1c} levels. In a recent pilot study, however, LIS was given to patients for 4 weeks in a postprandial fashion with no negative findings in HbA_{1c} or other physiological parameters (16).

The results of the present clinical trial may lead to a better understanding of the timing complex involved in the administration of bolus insulin. The best time for administration of REG was between 20–40 min before a meal. For LIS, the best time for administration was immediately before the meal, but postprandial administration still provided good glucodynamic control.

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