A Randomized Clinical Trial Comparing Breakfast, Dinner, or Bedtime Administration of Insulin Glargine in Patients With Type 1 Diabetes

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OBJECTIVE — Insulin glargine (Lantus), a long-acting human insulin analog, provides effective glycemic control when administered at bedtime. This open-label, randomized, parallel group, multicenter study investigated whether insulin glargine is equally effective if administered before breakfast, before dinner, or at bedtime.

RESEARCH DESIGN AND METHODS — Patients with type 1 diabetes on basal-bolus therapy (n = 378, 18–68 years, HbA_{1c} 5.5–9.8%) were treated with once-daily individually titrated insulin glargine in combination with prandial insulin lispro for 24 weeks.

RESULTS — Baseline characteristics were similar in the three groups (overall age 40.9 ± 11.9 years, diabetes duration 17.3 ± 11.5 years). Median total daily insulin dose was similar at baseline (0.65, 0.65, and 0.66 IU/kg for breakfast, dinner, and bedtime, respectively) and remained relatively constant over the study period; however, the insulin glargine–to–total insulin dose ratio increased more in the breakfast group than in the dinner and bedtime groups. A similar reduction of adjusted mean HbA_{1c} from baseline to end point occurred in all patients (7.6–7.4, 7.6–7.5, and 7.6–7.5% for breakfast, dinner, and bedtime, respectively), and a similar percentage achieved HbA_{1c} <7.0% at end point in all groups (29.5, 29.8, and 25.8%, respectively). The 24-h blood glucose profiles in relation to injection time were similar in all groups. The incidences of total symptomatic and severe hypoglycemia did not differ between the three treatment groups; however, nocturnal hypoglycemia occurred in significantly fewer patients in the breakfast group (59.5%) compared with the dinner (71.9%) and bedtime (77.5%) groups (P = 0.005).

CONCLUSIONS — These data suggest that insulin glargine, in combination with insulin lispro, is safe and effective when administered before breakfast, before dinner, or at bedtime.

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Abbreviations: FBG, fasting blood glucose; ITT, intent to treat.

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

Patients with type 1 diabetes have an absolute deficiency of insulin secretion. Current strategies for the treatment of type 1 diabetes, therefore, use a basal-bolus principle to imitate physiological insulin secretion, composed of a basal insulin with a 24-h duration of action and supplementary injections of a fast-acting insulin before meals. The development of short-acting recombinant insulin analogs such as insulin lispro and insulin aspart have provided a means of supplying a more physiological prandial insulin, resulting in improved postprandial glucose control and less hypoglycemia (1). The introduction of short-acting insulin analogs has also increased the need and demand for an optimal basal insulin because only with the combination of both prandial and basal insulin is it possible to achieve improved HbA_{1c} (2).

Traditional protracted-acting insulin preparations such as NPH insulin have a duration of action of ~14 h, and plasma insulin levels peak 4–6 h after administration (3). As a consequence, NPH insulin may need to be administered up to three times daily in some patients with type 1 diabetes in order to provide sufficient insulin supply throughout the day, especially when combined with short-acting insulin analogs (4). Indeed, even four daily injections of NPH insulin has been cited as the optimal way to provide constant basal insulin substitution (4). Multiple dosing regimens are less optimal than a once-daily regimen in terms of adherence, flexibility, and choice for the patient to adapt treatment to their individual lifestyle.

To satisfy the need for an optimized basal insulin, insulin glargine (Lantus; Aventis Pharma), a recombinant human insulin analog with a modified molecular structure, has been developed. Two additional arginine residues at the COOH terminus of the B-chain and a substitution of glycine for asparagine in position 21 of the A-chain induce a shift of the isoelec-

tric point from pH 5.4 in native human insulin to pH 6.7 in insulin glargine. These structural modifications provide a means for the desired protraction of the glucose-lowering action of insulin glargine.

Indeed, the time-action profile of insulin glargine has been demonstrated to provide a continuous, smooth supply of insulin with no pronounced peak over a 24-h period (3). This unique action profile should enable individual tailoring of the timing of basal insulin injection. In a combination regimen with prandial insulin lispro, insulin glargine provided equivalent levels of glycemic control in terms of HbA_{1c} and a significantly greater reduction of fasting blood glucose (FBG) levels, when compared with NPH insulin (5). Furthermore, insulin glargine–treated patients experienced significantly less weight gain than those treated with NPH insulin (0.12 vs. 0.54 kg, $P < 0.05$) (5). Other studies in patients with type 1 diabetes showed that patients treated with insulin glargine had a lower risk of nocturnal hypoglycemia (6–7). Availability of a once-daily insulin preparation that can provide effective glycemic control regardless of the timing of administration during the day would significantly enhance the flexibility of patients' dosing regimens.

In all previous studies, insulin glargine was administered at bedtime. The aim of this study was to investigate whether appropriately titrated insulin glargine provides similar glycemic control regardless of whether it is administered before breakfast, before dinner, or at bedtime, in a combination regimen with prandial insulin lispro.

RESEARCH DESIGN AND METHODS

Patients

A total of 448 patients with type 1 diabetes were screened for entry into this trial at ~30 centers. According to the protocol, eligible patients were aged 18–65 years with an HbA_{1c} of 6.0–8.5%. However, a few exceptions of patients with values outside these inclusion criteria were included in the study, such that the actual range of values at baseline were age 18–68 years and an HbA_{1c} of 5.5–9.8% (two, one, and two patients in the breakfast, dinner, and bedtime groups, respectively). These were patients who, according to the study investigator, usually had an HbA_{1c} within the criteria and were permitted inclusion at the discretion of the study manager. They had been treated with an intensified insulin regimen for at least 1 year and with an intermediate- or long-acting insulin in combination with a short-acting insulin analog for at least 6 months. Patients who were screened and met these criteria (381 patients) were randomized to one of the three treatment groups.

Study design

The study had an open-label, randomized, parallel group, multicenter design that consisted of a screening phase (1–4 weeks) and a 24-week treatment phase plus 2 days' observation. During the screening phase, patients continued their usual insulin regimen (intermediate- or long-acting insulin and a fast-acting insulin analog) and were encouraged to strive for optimal glycemic control. At the end of the screening phase, participants were randomized to receive once-daily subcutaneous insulin glargine either before breakfast (0600–0900), before dinner (1800–2000), or at bedtime (2100–0000). Randomization was generated by a schedule of linked sequential numbers to treatment codes allocated at random by Aventis Pharma. The schedule was prepared by center on a 1:1:1 basis so that each investigator had patients in the three groups. An independent agency (Parexel) arranged central telephone randomization. In those patients who previously injected their basal insulin once daily, the first dose of insulin glargine was identical to the previous total daily basal insulin dose. In those patients who previously injected their basal insulin more than once daily (>80% of all patients in the study), the first dose of insulin glargine was 20% lower than the previous total daily basal insulin dose. The dose of insulin glargine was individually titrated by the patient according to a predefined titration algorithm toward a target prebreakfast blood glucose of 4.4–6.7 mmol/l. Insulin lispro was individually titrated as necessary, after preprandial glucose values had reached the target defined by the insulin glargine titration algorithm, and injected subcutaneously before or immediately after a meal, according to the patient's usual routine.

Efficacy measures

The primary objective was to show equivalent efficacy, based on HbA_{1c} at end point, and this was based on the per-protocol population, with intent-to-treat (ITT) analysis performed as a secondary confirmatory analysis. Blood samples for determination of HbA_{1c} levels were taken at visits 1 (screening), 2 (baseline), 9 (week 12), and 11 (week 24). HbA_{1c} for visit 1 was analyzed in the local laboratory, and HbA_{1c} for all other visits was measured in the central laboratory (ClinServ, Hamburg, Germany). Secondary efficacy measures were based on the ITT population and included blood glucose values from 4-point and 8-point blood glucose profiles determined by self-monitoring of blood glucose, incidence of hypoglycemia, insulin doses, and responder rates. Symptomatic hypoglycemia was defined as an event consistent with symptoms of hypoglycemia. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the patient required the assistance of another person and had a blood glucose level <2.8 mmol/l or the event was associated with prompt recovery after oral carbohydrate or intravenous glucose or subcutaneous glucagon administration. Nocturnal hypoglycemia was defined as symptomatic hypoglycemia that occurred while the patient was asleep between bedtime (and after the evening injection of insulin glargine in the bedtime group) and before getting up in the morning (before the morning determination of blood glucose and any insulin injection in the breakfast group). Symptomatic, severe, and nocturnal hypoglycemia were further categorized as confirmed by a blood glucose level <2.0 mmol/l.

Safety data

Adverse events were reported by the patient in a patient diary or noted by the investigator. Hypoglycemia reported as a serious adverse event was reported and analyzed separately from all other serious adverse events.

Quality of life

Quality of life, as assessed by treatment satisfaction according to the Diabetes Treatment Satisfaction Questionnaire, was assessed. The results of this analysis are the subject of a separate report.

Statistical methods

The mean HbA_{1c} level at end point was evaluated for the per-protocol population (patients with no major violation and with a treatment duration of at least 20 weeks). The mean HbA_{1c} achieved with each regimen at end point was compared in a pairwise manner using ANCOVA with the corresponding baseline value as covariate. Two treatment groups were determined to be equivalent if the two-sided 95% observed treatment difference was within 0.4% of the HbA_{1c} level. An ITT analysis of HbA_{1c} at end point was performed on all patients randomized and treated and having both a baseline and at least one during-treatment value as confirmation of the per-protocol analysis. Blood glucose variables were compared at end point using an ANCOVA model with the blood glucose values as the dependent variable, treatment and (pooled) center as fixed effects, and the blood glucose baseline value as the covariate. The Cochran-Mantel-Haenzel test stratified by (pooled) center was used to test for differences in the rate of hypoglycemia.

A sample size of 100 patients per group provided 80% power that the two-sided 95% CI for the adjusted mean difference for each pairwise comparison did not exceed ±0.4% HbA_{1c}, which was the predefined equivalence margin. The sample size calculation was based on a common SD of 1% for HbA_{1c} at end point, based on previous studies with insulin glargine. Taking into account an expected 20% major protocol violation or early withdrawal, 375 patients (125 in each group) enabled 300 patients to be available for analysis. The study conformed with the ethical principles of the Helsinki Declaration.

RESULTS

Patient characteristics

The patients in each treatment group were similar in terms of age, BMI, and baseline glycemic control (Table 1). Overall, the study population had a mean (± SD) age of 40.9 ± 11.9 years and a mean diabetes duration of 17.3 ± 11.5 years. Eight patients had been previously treated with insulin glargine injected once daily, and one patient had been previously treated with insulin glargine injected twice daily (one, three, and five patients for breakfast, dinner, and bedtime, respectively). The majority of patients (71.4%) were treated with NPH insulin before the study, with injections ranging from 1 to 6 per day (45% injected NPH insulin twice daily). The remaining patients used lente (7.1%), other insulins (1.3%), or various combinations of the above-mentioned insulins (14.6%), and information on prior basal insulin was not available for 4.5% of patients. The three treatment groups were similar with respect to their prior basal insulin regimen.

Table 1—*Baseline characteristics of patients treated with insulin glargine at breakfast, dinner, or bedtime*

Characteristic	Breakfast	Dinner	Bedtime
n	121	128	129
Male (%)	55.4	59.4	46.5
Age (years)	41.8 ± 12.3	40.8 ± 11.4	40.2 ± 12.0
BMI (kg/m^2)	25.5 ± 3.7	25.6 ± 3.3	25.1 ± 3.4
Diabetes duration (years)	17.4 ± 11.0	17.2 ± 11.0	17.3 ± 12.5
Duration of intensified insulin treatment (years)	8.5 ± 5.5	8.6 ± 6.1	8.0 ± 6.6
HbA_{1c} (%)	7.6 ± 0.8	7.5 ± 0.8	7.6 ± 0.8
FBG (mmol/l)	9.2 ± 2.5	9.1 ± 2.3	9.1 ± 2.3

Data are means ± SD, unless otherwise noted.

Patient flow

Of the 448 patients screened, 381 were randomized. One patient in each group did not receive the intervention, leaving a total of 121, 128, and 129 patients in the breakfast, dinner, and bedtime groups, respectively. More patients were withdrawn from the breakfast group (17 patients) than either the dinner (5 patients) or the bedtime group (4 patients). In the breakfast group, patients withdrew owing to hypoglycemia (two patients, one of whom experienced 20 hypoglycemic events [none severe], and the other experiencing two severe hypoglycemic events), other adverse events (two patients), lack of efficacy (six patients), deviation from entry criteria (two patients), and protocol violation (one patient), and four patients in this group no longer wished to continue. In the dinner group, three patients did not wish to continue, one patient was lost to follow-up, and one withdrew owing to unsatisfactory blood glucose control (according to the investigator's comment). In the bedtime group, three patients did not wish to continue, and one patient withdrew owing to adverse events. The majority of the withdrawals in the breakfast group occurred in the initial study period (during the first 6 weeks), when marked changes in the insulin dosing were still occurring.

Insulin dose

In all three treatment groups, there was a decrease of ~20% in the basal insulin dose at baseline compared with screening. Median total daily insulin dose per kilogram body weight was similar at baseline among the three treatment groups (0.65, 0.65, and 0.66 IU/kg for breakfast, dinner, and bedtime, respectively), with minor changes over the study period. The median ratio of insulin glargine to total insulin dose changed to the greatest extent from baseline to end point in the breakfast group. Whereas 42% of the total daily basal insulin was insulin glargine at baseline, this increased to 51% by end point, compared with a change of 44–47% in the dinner group, and 43–45% in the bedtime group. Although the adjustments to the ratio of insulin glargine and mealtime insulin lispro doses were carried out gradually over the study duration, most of the dose adjustment in the breakfast group was complete after the first month of treatment.

Glycemic control

Only minor reductions in HbA_{1c} from baseline to end point were observed over the study duration (Table 2), and end point HbA_{1c} values were similar among the three treatment groups (7.6–7.4, 7.6–7.5, and 7.6–7.5% for breakfast, dinner, and bedtime, respectively). The 95% CIs for the difference in HbA_{1c} between treatment groups at end point lies entirely within the predefined equivalence margin of −0.4% and +0.4%. The analysis of the ITT population confirmed these results. A similar proportion of pa-

Table 2—*Pairwise comparison of the adjusted mean HbA_{1c}*

	Adjusted means					
	Breakfast	Dinner	Bedtime	Adjusted mean	Difference (95% CI)	*P* value
Per-protocol population						
n	100	121	123			
Dinner versus bedtime						
Baseline*	—	7.6	7.6	−0.1	(−0.26 to 0.13)	0.53
End point†	—	7.5	7.5	−0.1	(−0.25 to 0.12)	0.47
Breakfast versus bedtime						
Baseline*	7.6	—	7.6	−0.1	(−0.26 to 0.15)	0.58
End point†	7.4	—	7.5	−0.1	(−0.19 to 0.09)	0.31
Breakfast versus dinner						
Baseline*	7.6	7.6	—	0.0	(−0.20 to 0.21)	0.97
End point†	7.4	7.5	—	0.0	(−0.23 to 0.16)	0.73
Intention-to-treat analysis						
n	112	124	128			
Dinner versus bedtime						
Baseline*	—	7.6	7.6	−0.1	(−0.25 to 0.13)	0.52
End point†	—	7.4	7.5	−0.1	(−0.27 to 0.09)	0.31
Breakfast versus bedtime						
Baseline*	7.6	—	7.6	−0.1	(−0.25 to 0.13)	0.54
End point†	7.4	—	7.5	−0.1	(−0.32 to 0.05)	0.15
Breakfast versus dinner						
Baseline*	7.6	7.6	—	0.0	(−0.19 to 0.20)	0.99
End point†	7.4	7.4	—	0.0	(−0.23 to 0.14)	0.65

*Adjusted means, 95% CI, and *P* value from an ANOVA model with treatment and (pooled) center as fixed effects; †adjusted means, 95% CI, and *P* value from an ANOVA model with treatment and (pooled) center as fixed effects and baseline as covariate.

tients achieved an HbA_{1c} <7.0% at end point in the breakfast (baseline 22.5%, end point 29.5%), dinner (25.0, 29.8%), and bedtime (20.9, 25.8%) groups. Thus, glycemic control was achieved independently of the timing of administration of insulin glargine.

The relatively low number of patients achieving an HbA_{1c} <7.0% suggests that a longer treatment period or more intensive insulin titration may have been required to achieve this ambitious target. A subgroup analysis of the patients reaching an FBG <6.7 mmol/l (120 mg/dl) showed that these patients achieved HbA_{1c} values of 6.5% in the breakfast group, compared with 7.0% in the dinner group (P = 0.054) and 7.4% in the bedtime group ($P < 0.005$).

Mean blood glucose results obtained from eight-point profiles for each of the three treatments are presented in relation to time of insulin glargine administration (Fig. 1). The 24-h blood glucose profiles were comparable, regardless of time of insulin glargine administration, and confirmed the flat, reproducible glucodynamic profile following once-daily administration of insulin glargine. Small changes in average preprandial glucose values from baseline to end point occurred in each group, and there were no significant between-treatment differences (Table 3). However, in the breakfast group, there was a larger decrease in mean 24-h blood glucose values from baseline to end point compared with the other two groups; this difference was statistically significant compared with the bedtime group (P = 0.036). Nocturnal blood glucose values were slightly higher at baseline in the bedtime group than in the other two treatment groups. Only minor changes were observed over the study duration, with no significant differences detected between treatment groups (Table 3). FBG decreased from baseline to end point in the dinner and bedtime groups but remained almost unchanged in the breakfast group, suggesting that the insulin could have been titrated more in the breakfast group. Variability in FBG levels was significantly lower in the breakfast

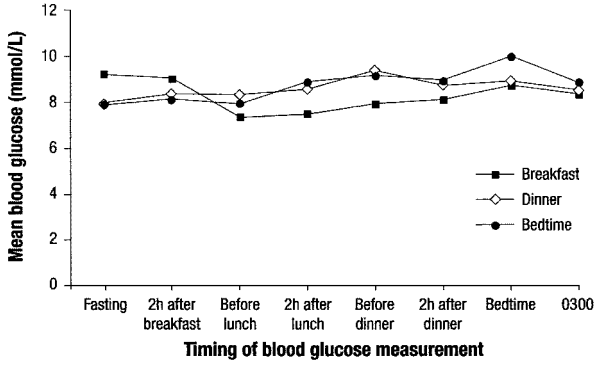

Figure 1—*The 24-h blood glucose profile of patients treated with insulin glargine at breakfast, dinner, or bedtime.*

Table 3—*Blood glucose control (mean change from baseline to end point) in patients with type 1 diabetes treated with insulin glargine at breakfast, dinner, or bedtime*

Parameter	Breakfast	Dinner	Bedtime
FBG (mmol/l)*	101	115	110
n	9.1 ± 0.2	9.1 ± 0.2	9.1 ± 0.2
Baseline (mean ± SEM)	9.2 ± 0.2	7.9 ± 0.2	8.0 ± 0.2
End point (mean ± SEM)			
Mean change from baseline to end point (mean ± SD)	+0.1 ± 2.6	−1.2 ± 2.7	−1.3 ± 2.5
Preprandial blood glucose (mmol/l)†			
n	100	112	108
Baseline (mean ± SEM)	8.7 ± 0.2	8.4 ± 0.2	8.5 ± 0.2
End point (mean ± SEM)	8.2 ± 0.2	8.6 ± 0.2	8.4 ± 0.2
Mean change from baseline to end point (mean ± SD)	−0.4 ± 1.7	+0.1 ± 1.7	−0.2 ± 1.7
24-h average blood glucose (mmol/l)‡			
n	107	114	113
Baseline (mean ± SEM)	8.7 ± 0.2	8.6 ± 0.2	8.4 ± 0.2
End point (mean ± SEM)	8.0 ± 0.2	8.3 ± 0.2	8.6 ± 0.2
Mean change from baseline to end point (mean ± SD)	−0.6 ± 2.2	−0.21 ± 2.7	+0.1 ± 2.2
Nocturnal blood glucose (mmol/l)§			
n	95	101	96
Baseline (mean ± SEM)	8.3 ± 0.4	8.4 ± 0.4	9.2 ± 0.4
End point (mean ± SEM)	8.4 ± 0.4	8.6 ± 0.4	8.8 ± 0.4
Mean change from baseline to end point (mean ± SD)	+0.2 ± 4.7	+0.2 ± 5.0	−0.2 ± 5.3

*FBG: pre-breakfast blood glucose; †preprandial blood glucose: calculated as mean of consecutive preprandial blood glucose values (pre-breakfast [FBG], pre-lunch, pre-dinner); ‡24-h average blood glucose: mean of eight-point blood glucose profile; §nocturnal blood glucose: measured at 0300. Note: mean values provided for baseline and end point are adjusted means from the analysis model, whereas those for changes from baseline to end point are unadjusted means.

group (32.8%) than in the dinner (40.3%, $P < 0.001$) or bedtime (42.5%, $P < 0.001$) groups at the end of the study.

Hypoglycemia

There was no difference between the three groups with respect to the percentage of patients reporting at least one episode of symptomatic hypoglycemia (Table 4). Severe symptomatic hypoglycemia was reported by 14.7% of patients in the bedtime group, compared with 17.4% in the breakfast group and 18.0% in the dinner group (between-treatment differences were not significant). The percentage of patients reporting severe symptomatic hypoglycemia confirmed by a blood glucose <2.0 mmol/l was low in all three treatment groups, with a slightly smaller percentage of patients in the bedtime group (3.9%) compared with the breakfast (6.6%) and dinner (4.7%) groups ($P = 0.7$). Nocturnal symptomatic hypoglycemia was reported in statistically significantly fewer patients in the breakfast group (59.5%) compared with the dinner (71.9%, $P = 0.029$) and bedtime (77.5%, $P = 0.0013$) groups; the pattern was similar when nocturnal hypoglycemia was confirmed by a blood glucose level <2.0 mmol/l. After dosing adjustment to a new regimen in the first month of treatment, the mean number of symptomatic hypoglycemic events per 28-day interval was similar in all treatment groups (3.2, 3.2, and 4.2 for breakfast, dinner, and bedtime, respectively). When calculated per 28-day interval, the rate of nocturnal hypoglycemic events was significantly lower

Table 4—*Frequency of symptomatic hypoglycemia over the entire treatment phase*

	Breakfast		Dinner		Bedtime		
Type of hypoglycemia	*n/N*	(%)	*n/N*	(%)	*n/N*	(%)	*P* value*
All symptomatic	112/121	92.6	120/128	93.8	125/129	96.9	0.28
With blood glucose <2.0 mmol/l	66/121	54.4	69/128	53.9	75/129	58.1	0.67
Severe symptomatic	21/121	17.4	23/128	18.0	19/129	14.7	0.72
With blood glucose <2.0 mmol/l	8/121	6.6	6/128	4.7	5/129	3.9	0.70
Nocturnal symptomatic	72/121	59.5	92/128	71.9	100/129	77.5	0.005
With blood glucose <2.0 mmol/l	16/121	13.2	27/128	21.1	32/129	24.8	0.05

n, number of patients reporting at least one episode of symptomatic hypoglycemia; *N*, number of patients evaluatable. **P* value from Cochran-Mantel-Haenszel test.

in the breakfast group (0.37 nocturnal hypoglycemic events per patient per 28 days) than in the dinner (0.92 events, $P < 0.01$) or bedtime (0.81 events, $P < 0.001$) groups over the whole treatment period.

Safety

Analysis of the laboratory safety data and vital signs did not reveal any special issues with regard to tolerability. Other than hypoglycemia, the only adverse event that was different between the groups was injection site reactions. More injection site reactions were noted in patients treated with insulin glargine at bedtime (12 patients) than before breakfast (3 patients) or before dinner (8 patients); however, this effect is unlikely to have clinically significant meaning. Hypoglycemia reported as a serious adverse event was reported in fewer patients in the breakfast group (five patients) compared with the dinner (nine patients) or bedtime (seven patients) groups. Only 19 (5.0%) of the 378 patients treated reported serious adverse events other than hypoglycemia, and the proportion was similar in the three treatment groups. Hypersensitivity reactions occurred in eight patients; four of these reactions were described as reactions to a known allergen, and four were described as pruritus (one patient), rash (one patient), and urticaria (two patients). None of these reactions were considered by the investigator to be related to the study medication.

CONCLUSIONS — The aim of this study was to investigate whether the efficacy and safety of insulin glargine would be affected by the timing of administration. The data clearly shows that there was no clinically relevant difference in efficacy between the three treatment groups, achieving the primary objective to show equivalence, based on the observed CIs, between the three treatment groups with respect to HbA_{1c} at end point. The mean baseline HbA_{1c} (7.6%) indicated that most patients had a relatively well-controlled glucose metabolism at the start of the study. Minor reductions in HbA_{1c} after 24 weeks of treatment were noted in all three groups, demonstrating that once-daily insulin glargine had equivalent efficacy when administered before breakfast, before dinner, or at bedtime.

The 24-h blood glucose profile of all three groups confirmed the sustained activity of insulin glargine achieved with a once-daily injection. Patients in the breakfast group underwent a greater adjustment of their insulin dose compared with the dinner and bedtime groups. The dose of insulin glargine increased, whereas the dose of insulin lispro was slightly reduced. At the end of the study, the ratio of insulin glargine to total insulin was highest in the breakfast group, but there were no significant differences in total insulin dose in each group compared with the start of the study. Potentially, patients in the breakfast group may have been willing to more aggressively titrate their insulin regimen because they may have felt that any side effects of an increased dose would occur while they were awake and that they would, therefore, have been able to compensate in some way. However, the FBG decreased from baseline to end point in the dinner and bedtime groups but remained almost unchanged in the breakfast group, suggesting that the dose of insulin glargine could have been titrated even higher in the breakfast group. It is also possible, given that the greatest basal-bolus dosing adjustments from baseline occurred in the breakfast group, that the dose of insulin lispro may not have been appropriately titrated in relation to the increased dose of insulin glargine, which could have resulted in a slow rise in blood glucose in a 24-h period.

The incidence of hypoglycemia and severe hypoglycemia seen in this study corresponds well with that reported in other studies in patients with type 1 diabetes, where 75–95% of patients treated with either regular human insulin or insulin aspart experienced at least one minor hypoglycemia event (8), 83.8–94.3% of patients treated with subcutaneous and inhaled insulin experienced mild to moderate hypoglycemia, and 13.3–14.3% experienced severe hypoglycemia (9). There was no difference in the percentage of patients experiencing at least one episode of symptomatic hypoglycemia between the three groups. A slightly higher rate of hypoglycemic events during the daytime in the breakfast group was responsible for the equivalent rates of total hypoglycemic events over the entire treatment period. A similar number of patients experienced severe hypoglycemia in the breakfast, dinner, and bedtime administration groups. When confirmed by a blood glucose level <2.0 mmol/l, severe hypoglycemic episodes were similarly low in all groups. There was, however, a difference in the incidence of nocturnal hypoglycemia between the three treatment groups. Both the percentage of patients with at least one episode of nocturnal hypoglycemia and the rate of nocturnal hypoglycemia per 28 days were lower in the breakfast group compared with the dinner and bedtime groups. It is interesting to note, however, that lower mean nocturnal (0300) blood glucose values were seen at end point in the breakfast group (8.4 mmol/l) compared with the dinner (8.6 mmol/l) or bedtime (8.8 mmol/l) groups; thus the fewer reports of nocturnal hypoglycemia was not attributable to higher blood glucose levels as a result of insufficient insulin exposure during the night in the breakfast group.

The administration of insulin glargine at breakfast or dinner was not associated with an increased risk of adverse events, such as total rate of hypoglycemic events. Previous studies have already shown a markedly lower rate of nocturnal hypoglycemic events in patients with type 1 diabetes on a basal-bolus regimen involving insulin glargine as the basal substitution given at bedtime, compared with NPH insulin (6–7). Therefore, switching from NPH insulin to insulin glargine has evolved as a valuable option for patients with diabetes in order to reduce frequent hypoglycemic events. The option to adjust the injection time points for insulin glargine within a basal-bolus regimen to further reduce the risk for nocturnal hypoglycemic events offers an additional benefit for patients with type 1 diabetes. However, the time of administration of insulin glargine was fixed in this study and, therefore, it is not possible to clarify what dose adjustments may be necessary if a decision were made to change the time of day for dosing in an individual patient.

The results of this study demonstrate that insulin glargine, in combination with insulin lispro, is equally effective and well tolerated whether it is injected once daily before breakfast, before dinner, or at bedtime in patients with type 1 diabetes. Insulin glargine provided equivalent overall glycemic control (in terms of HbA_{1c}) and a significantly reduced rate of nocturnal hypoglycemia at breakfast compared with dinner or bedtime administration. These data suggest that insulin glargine can be administered once daily at any fixed time of the day according to individual patient preference. The time-action profile of in-

sulin glargine, with its stable activity for up to 24 h with no pronounced peak, has the potential to offer patients a broader choice in the timing of injection, providing a more convenient dosing regimen, which in turn has the potential to result in better overall glycemic control. Flexibility in the timing of administration of insulin glargine thus offers an opportunity for patients to adapt their insulin regimen according to individual needs.

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