Less Hypoglycemia With Insulin Glargine in Intensive Insulin Therapy for Type 1 Diabetes

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OBJECTIVE — Insulin glargine (21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin) is a biosynthetic insulin analog with a prolonged duration of action compared with NPH human insulin. This study compared insulin glargine with NPH human insulin in subjects with type 1 diabetes who had been previously treated with multiple daily injections of NPH insulin and regular insulin.

RESEARCH DESIGN AND METHODS — This study was a multicenter randomized parallel-group study in which subjects were randomized to receive premeal regular insulin and either insulin glargine (at bedtime) or NPH insulin (at bedtime for patients on once-daily therapy and at bedtime and in the morning for patients on twice-daily therapy) for up to 28 weeks. Dose titration of both basal insulins was based on capillary fasting whole blood glucose (FBG) levels; the goal was a premeal blood glucose concentration of 4.4–6.7 mmol/l.

RESULTS — A total of 534 well-controlled type 1 diabetic subjects (mean GHb 7.7%, mean fasting plasma glucose [FPG] 11.8 mmol/l) were treated. A small decrease in GHb levels was noted with both insulin glargine (−0.16%) and NPH insulin (−0.21%; $P > 0.05$). Significant reductions in median FPG levels from baseline (−1.67 vs. −0.33 mmol/l with NPH insulin, $P = 0.0145$) and a trend for a reduction in capillary FBG levels were achieved with insulin glargine. After the 1-month titration phase, significantly fewer subjects receiving insulin glargine experienced symptomatic hypoglycemia (39.9 vs. 49.2%, $P = 0.0219$) or nocturnal hypoglycemia (18.2 vs. 27.1%, $P = 0.0116$) with a blood glucose level <2.0 mmol/l compared with subjects receiving NPH insulin.

CONCLUSIONS — Lower FPG levels with fewer episodes of hypoglycemia were achieved with insulin glargine compared with once- or twice-daily NPH insulin as part of a basal-bolus regimen in patients with type 1 diabetes.

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Abbreviations: ANCOVA, analysis of covariance; DCCT, Diabetes Control and Complications Trial; FBG, fasting whole blood glucose; FPG, fasting plasma glucose.

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

The Diabetes Control and Complications Trial (DCCT) (1) and other studies (2,3) provide conclusive evidence that maintaining tight glycemic control can prevent or delay microvascular complications in individuals with type 1 diabetes. Attempts to achieve glycemic control are most often made by using multiple daily insulin injection (i.e., basal-bolus) therapy or by using an insulin pump. Despite prodigious efforts, our ability to reach normal GHb levels is hampered by the limiting occurrence of hypoglycemia (4). Variability in absorption, delays in action, and prolonged insulin activity peaks in traditional insulin preparations contribute to difficulty in obtaining normoglycemia. Insulin analogs have been developed to facilitate successful basal-bolus therapy. A once-daily long-acting basal insulin analog that mimics insulin secretion in nondiabetic subjects to limit hepatic glucose production has not been available for clinical use.

The currently available longer-acting human ultralente insulin has a broad peak that lasts from 8 to 16 h, with a duration of action ranging from 20 to 36 h (5). Ultralente is the least consistently absorbed insulin formulation available and has a wide intra- and interindividual variability in pharmacokinetics and pharmacodynamics (5,6). The intermediate-acting human NPH insulin has been the mainstay of insulin regimens used by subjects with type 1 diabetes (7). NPH insulin concentrations rise to a peak after 4–6 h and then steadily decline. Because an NPH insulin dose is often limited by hypoglycemia at peak concentrations, using NPH insulin twice daily is often necessary. Furthermore, the action profile of NPH insulin, when used with regular insulin in a basal-bolus regimen, leads to an increased risk of nocturnal hypoglycemia, morning fasting hyperglycemia, or both (8).

Insulin glargine (21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin) is an insulin analog produced by recombinant DNA technology. Amino acid changes shift the isoelectric point (which reduces the solubility of insulin glargine at physiological pH levels) and stabilize the hexamer (which

delays its dissociation into monomers) (9,10). Consequently, insulin glargine has a delayed and prolonged absorption after subcutaneous administration (11). Euglycemic clamp data in healthy volunteers indicate that the absorption of insulin glargine is prolonged and without peaks (6,12–14). Short-term (4-week) comparative trials in subjects with type 1 or type 2 diabetes have demonstrated that once-daily insulin glargine doses reduce fasting plasma glucose (FPG) levels to a similar extent or to a significantly greater extent than once- or twice-daily NPH insulin with a comparable or (in some studies) a significantly lower incidence of nocturnal hypoglycemia (15–18). This long-term study examines the safety and efficacy of once-daily insulin glargine versus once- or twice-daily NPH insulin as part of basal-bolus insulin regimens for subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

A total of 534 men and women 18–80 years of age with type 1 diabetes (postprandial C-peptide levels of ≤0.5 nmol/l) for at least 1 year and GHb levels of ≤12.0% were eligible. Exclusion criteria included treatment with antidiabetic drugs other than insulin within 1 month of study entry, pregnancy, impaired hepatic function, and impaired renal function. Subjects could not work a night shift. The study protocol was approved by the respective institutional review boards, and subjects gave their informed consent.

Study design

This 28-week multicenter randomized study compared the effects of insulin glargine (Hoechst Marion Roussel, Kansas City, MO) and human NPH insulin (Lilly, Indianapolis, IN) on glycemic control and the incidence of hypoglycemia when used as part of a basal-bolus insulin regimen. A double-blind design was not feasible because insulin glargine is a clear solution and is distinguishable from cloudy NPH insulin. Insulin glargine is not miscible with soluble insulin because of pH differences; therefore, all subjects receiving insulin glargine were instructed not to mix their new insulin.

After a 1- to 4-week screening phase, subjects were randomized to receive insulin glargine once daily (at bedtime) or NPH insulin once (at bedtime) or twice (at bedtime and before breakfast), depending on their pretreatment insulin regimens. Subjects in the insulin glargine group were to be switched from once-daily NPH insulin on a unit-for-unit basis, whereas a slight dose decrease was recommended for subjects who switched from twice-daily NPH insulin. Dose titration of both basal insulins was based on capillary fasting blood glucose (FBG) levels; the goal was a premeal blood glucose concentration of 4.4–6.7 mmol/l (80–120 mg/dl). Dose increases were made if morning capillary FBG levels were consistently >6.7 mmol/l with no symptomatic nocturnal hypoglycemia. Dose decreases were made if morning capillary FBG levels were <4.4 mmol/l or if symptomatic nocturnal hypoglycemia was evident. Subjects in both treatment groups used regular insulin ~30 min before meals to meet prandial insulin requirements.

The study included 8 visits: screening (1–4 weeks before randomization); randomization (week 0); and weeks 1, 4, 8, 12, 20, and 28. Subjects self-measured capillary FBG levels (LifeScan One Touch; Johnson & Johnson, Milpitas, CA) at home on 7 consecutive days preceding the baseline and at visits at weeks 8, 20, and 28. FPG levels were assessed at all clinic visits. GHb levels were measured at baseline and at weeks 8, 20, and 28 at the Diabetes Diagnostics Laboratory (University of Missouri, Columbia, MO; normal values 4.2–5.8%).

Efficacy measures

Efficacy measures included mean changes from baseline of GHb and capillary FBG levels, median change from baseline of FPG levels, incidence of hypoglycemia, and incidence of hypoglycemia with a blood glucose level of <2.0 mmol/l (36 mg/dl). Hypoglycemia was divided into 3 subsets: all events, severe hypoglycemia (a symptomatic event requiring the assistance of another individual), and nocturnal hypoglycemia (occurring while asleep after the bedtime insulin dose and before the morning capillary FBG measurement).

Safety measures

Any episode of hypoglycemia that met the criteria for a serious adverse event (e.g., death, a life-threatening episode, hospitalization, or medical intervention to prevent permanent impairment) was considered to be a treatment-related adverse event. Adverse events of special interest included systemic hypersensitivity reactions, injection site reactions, and development of or changes in insulin glargine or human insulin antibodies as measured by the Global Preclinical Laboratory (Hoechst Marion Roussel).

Statistics

All analyses were performed by using an intent-to-treat population with the last observation carried forward. An estimated 440 subjects (220 in each treatment group) were required to detect a mean difference of 0.5% in GHb levels between treatments with a type 1 error of $\alpha = 5\%$ and a statistical power of 90%.

Baseline demographics were compared by using an analysis of variance model with treatment and investigative site as fixed effects for continuous variables and the Cochran-Mantel-Haenszel test controlled for investigative site for categorical variables. Capillary FBG values were calculated by using the mean of the 7 consecutive daily measurements taken before each visit. Changes in GHb and capillary FBG values from baseline to end point were assessed by using analysis of covariance (ANCOVA) models with terms for treatment and investigative site and with the baseline measure as a covariate. A skewed distribution of residuals from the fitted ANCOVA model was observed for FPG data; therefore, an analysis of rank change from baseline in FPG level was performed by using median values in a ranked ANCOVA model.

The incidence of hypoglycemia was measured for the titration phase (month 1), month 2 to end point, and for the entire treatment period. The frequency of subjects experiencing at least 1 episode of any type of hypoglycemia in each treatment group was compared by using the Cochran-Mantel-Haenszel test stratified by investigative site. The number of hypoglycemic episodes with available blood glucose values of <2.0 mmol/l was also summarized.

Adverse events are descriptively summarized

Fisher's exact test was used to compare the proportion of subjects in each treatment group with predefined abnormal laboratory changes. Vital signs were analyzed by ANCOVA. Insulin antibody formation was evaluated by using iodinated insulin tracers, ^{125}I-labeled insulin glargine, and ^{125}I-labeled human insulin in identical serum samples. Because many subjects had insulin antibodies at baseline, a ≥20-U (% bound/total) change at end point was predefined as a relevant change.

Table 1—*Subject demographic and disease characteristics at baseline*

	Insulin glargine	NPH	Total
Demographics			
n	264	270	534
Sex			
Male	141 (53.4)	129 (47.8)	270 (50.6)
Female	123 (46.6)	141 (52.2)	264 (49.4)
Age (years)	38.2 ± 12.2	38.9 ± 11.9	38.5 ± 12.04
BMI (kg/m^2)	25.63 ± 4.01	25.93 ± 4.55	25.78 ± 4.29
Diabetes history			
Duration (years)	17.9 ± 11.66	16.9 ± 10.0	17.4 ± 10.85
Age at onset (years)	20.6 ± 11.8	22.3 ± 12.6	21.5 ± 12.25
Insulin treatment (years)	17.7 ± 11.8	16.7 ± 10.1	17.2 ± 10.92
Metabolic control at baseline			
GHb (4.2–5.8%)	7.7 ± 1.2	7.7 ± 1.1	7.7 ± 1.2
FPG (mmol/l)	11.0 (1.1–25.3)	11.3 (2.2–36.8)	11.2 (1.1–36.8)
FBG (mmol/l)	9.2 ± 2.7	9.7 ± 3.0	9.5 ± 2.9

Data are *n*, *n* (%), means ± SD, or medians (ranges).

RESULTS

Demographics

Of the total 534 subjects from 49 sites, 264 subjects received insulin glargine, and 270 subjects received human NPH insulin. No statistically significant differences were evident at baseline in demographics between treatment groups (Table 1). The means ± SD GHb level was 7.7 ± 1.2% vs. 7.7 ± 1.1% in the insulin glargine and NPH insulin groups, respectively. Before randomization, 26% (*n* = 140) of the subjects used a once-daily basal insulin regimen, and 74% (*n* = 394) used a more-than-once-daily basal insulin regimen.

Early discontinuation was similar in each treatment group (insulin glargine 11.7%, NPH insulin 8.1%). A total of 8 subjects (3.0%) in the insulin glargine group discontinued the regimen because of adverse events, 3 of which were considered possibly related to treatment (asthenia, hypoglycemic reaction, and chest and gastrointestinal pain). One subject receiving NPH insulin discontinued the regimen because of an adverse event (death secondary to cardiopulmonary arrest) that was not considered related to the study medication.

Efficacy

Glycemic control. Reductions in GHb at end point were similar in the insulin glargine and NPH insulin treatment groups. In contrast, significant reductions in median FPG levels occurred with insulin glargine compared with NPH insulin (Table 2). Reductions in capillary FBG levels occurred early with insulin glargine; at week 8, mean capillary FBG levels in subjects treated with insulin glargine and NPH insulin were reduced by 1.17 and 0.37 mmol/l, respectively ($P < 0.0001$). The reduction in capillary FBG levels with insulin glargine was sustained, whereas further reductions occurred gradually with NPH insulin until the end of the study, at which time capillary FBG changes were comparable. At each visit after baseline, a higher percentage of subjects in the insulin glargine group met target capillary FBG values (<6.7 mmol/l); by the end of the study, 28.3% of subjects taking insulin glargine and 24.0% of subjects taking NPH insulin achieved target capillary FBG levels ($P = 0.3109$), which demonstrates the success of the treatment algorithm.

The basal insulin dose for subjects in the insulin glargine group decreased by an average of 5 U on randomization (from 28.9 ± 4.6 to 23.8 ± 3.1 IU), primarily because of a decreased dose for subjects switched from more-than-once-daily NPH insulin. This decrease in insulin glargine dose was compensated for by an increase in the dose of regular insulin (from 21.8 ± 4.7 to 25.7 ± 14.8 IU), which makes the average total insulin dose at end point nearly identical to that at baseline. In contrast, to achieve target glucose levels, subjects treated with NPH insulin had a gradual increase in both daily NPH insulin (from 29.5 ± 7.7 to 31.3 ± 9.8 IU) and regular insulin (from 21.7 ± 2.7 to 23.4 ± 5.5 IU) doses; at end point, the total insulin dose was ~4 U higher than it was at baseline.

Hypoglycemia. The incidence of all symptomatic hypoglycemic episodes during the entire 28-week study was similar between treatment groups. Significantly fewer severe hypoglycemic events occurred with blood glucose levels of <2.0 mmol/l during the course of the trial in subjects taking insulin glargine ($P = 0.0307$). After the initial titration period (month 1), a significantly lower percentage of subjects receiving insulin glargine experienced at least 1 episode of hypoglycemia with blood glucose levels of <2.0 mmol/l (Fig. 1). Table 3 shows the number of episodes of hypoglycemia per 100 patient-years in each treatment group.

Safety

Insulin glargine and NPH insulin were equally well tolerated; the frequency (84.5 vs. 86.7%, respectively) and types of adverse events were similar in both groups. Other than hypoglycemia, only 2 serious events were considered possibly related to treatment, both of which resulted from a fall during a hypoglycemic episode: a laceration above the eye (insulin glargine) and a ruptured tendon (NPH insulin). No evidence existed of an immunogenic response to insulin glargine compared with NPH insulin. Few subjects in either

Table 2—*Glycemic control (change from baseline to end point)*

	Insulin glargine	NPH	*P*
GHb (%)			
n	256	262	
Means ± SEM	−0.16 ± 0.05	−0.21 ± 0.05	0.4408
Capillary FBG (mmol/l)			
n	244	258	
Means ± SEM	−1.12 ± 0.15	−0.94 ± 0.14	0.3546
FPG (mmol/l)			
n	261	265	
Medians (ranges)	−1.67 (−20.1 to 15.3)	−0.33 (–24.3 to 15.4)	0.0145

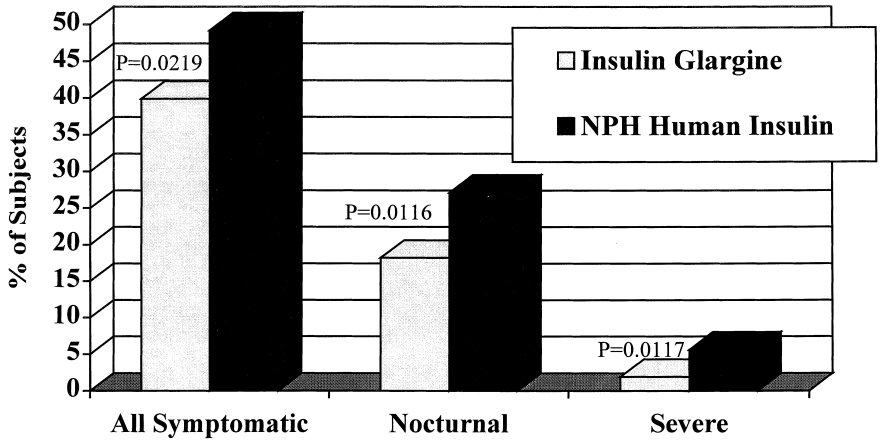

Figure 1—*Percentage of subjects reporting at least 1 episode of symptomatic, nocturnal, or severe hypoglycemia confirmed by a blood glucose level <2.0 mmol/l (month 2 to end point).*

group (1 to 2%) exhibited increases of ≥20 U in insulin glargine or human insulin antibody levels during the course of the study. No treatment-related systemic hypersensitivity reactions were evident. The proportion of subjects with treatment-emergent injection site reactions was higher in the insulin glargine group than in the NPH insulin group (15.2 vs. 10.4%, respectively) primarily because of a higher number of subjects who reported injection site pain (10 vs. 3, respectively), but all were rated mild in severity, and none required drug discontinuation.

CONCLUSIONS — This 28-week study demonstrates that once-daily insulin glargine is at least as effective as once- or twice-daily NPH insulin in achieving glycemic control but involves fewer episodes of hypoglycemia. Changes in GHb levels in both treatment groups were small and clinically insignificant but must be viewed in the context of mean GHb values of 7.7% at study initiation that limit treatment effect. The modest decreases in GHb level may also reflect a natural reticence on the part of investigators to increase dosages of an unblinded investigational drug and subject apprehension toward the use of an unknown therapy.

Insulin glargine significantly reduced morning FPG levels compared with NPH insulin. The decreases in FPG levels occurred almost immediately (week 1) with insulin glargine and were maintained for the duration of the study. In contrast, decreases in FPG levels with NPH insulin occurred gradually according to protocol-driven insulin adjustments and were maximized at week 28. Similarly, the number of subjects achieving target capillary FBG levels increased early (by week 8) in the insulin glargine group but did so more gradually in the NPH insulin group. The more rapid decrease in capillary FBG levels with insulin glargine may be related to the larger bedtime insulin dose taken by subjects who had previously used a more-than-once-daily basal insulin regimen.

The overall safety and tolerability of insulin glargine and NPH insulin were comparable. Injection site pain was reported more frequently by subjects taking insulin glargine, but we found no evidence of an immunogenic effect of insulin glargine.

Hypoglycemia, the most frequent acute complication of intensive insulin therapy, is the limiting factor in managing type 1 diabetes (4,5). The action profile of insulin glargine suggests that it may replace insulin in a more normal physiological way than NPH insulin; thus, it should decrease the risk of hypoglycemia without compromising glycemic control. When confirmed by a blood glucose level of <2.0 mmol/l, significantly fewer subjects in the insulin glargine group experienced severe symptomatic hypoglycemia during the 28-week treatment period ($P = 0.0307$). This difference is clinically meaningful when considering that the results of the DCCT show that a history ≥1 episode of severe hypoglycemia predicts further hypoglycemic episodes (1).

When the inherent variability of the dose-titration period at month 1 is excluded, the difference in the proportion of subjects in the insulin glargine group who reported any symptomatic hypoglycemia compared with that in the NPH insulin group approached statistical significance ($P = 0.0659$). Again, significantly fewer subjects taking insulin glargine experienced symptomatic, nocturnal, or severe hypoglycemic events with a blood glucose level of <2.0 mmol/l during this period.

In summary, insulin glargine lowered GHb levels to an extent comparable with NPH insulin but significantly reduced associated severe and nocturnal hypoglycemia. Because hypoglycemia is the limiting factor in achieving normoglycemia, insulin glargine may be advantageous for improving glycemic control in the type 1 diabetic population. In this study, insulin glargine was significantly more effective in reducing FPG levels with a trend for lowering capillary FBG levels. In addition to optimizing combination therapy, further study and more clinical experience with insulin glargine will indicate which subjects could benefit most from the drug and whether lower rates of hypoglycemia can be exploited to further improve glycemic control.

Table 3—*Percentage of patients reporting at least 1 episode of hypoglycemia (blood glucose <2.0 mmol/l) and the number of episodes per 100 patient-years (month 2 to end of study)*

	All hypoglycemia	Severe hypoglycemia	Nocturnal hypoglycemia
Insulin glargine			
Subjects (%)	39.9	1.9	18.2
Episodes/100 patient-years	200.5	7.9	65.1
NPH insulin			
Subjects (%)	49.2*	5.6	27.1*
Episodes/100 patient-years	345.4	16.7	101.2

Data are % or *n*. *$P < 0.05$ vs. insulin glargine.

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APPENDIX

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