Basal Insulin Glargine (HOE 901) Versus NPH Insulin in Patients With Type 1 Diabetes on Multiple Daily Insulin Regimens

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OBJECTIVE — Insulin glargine (HOE 901, 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg human insulin) is a novel recombinant analog of human insulin with a shift in the isoelectric point producing a retarded absorption rate and an increased duration of action that closely mimics normal basal insulin secretion. It recently received approval from the Food and Drug Administration. The aim of this study was to evaluate 2 formulations of insulin glargine for safety and efficacy in the treatment of patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — In a 4-week trial, 256 patients with type 1 diabetes received either NPH insulin or insulin glargine containing 30 μg/ml zinc (insulin glargine[30]) or 80 μg/ml zinc (insulin glargine[80]). Insulin glargine was given subcutaneously once daily at bedtime. NPH insulin was given either once daily (at bedtime) or twice daily (before breakfast and at bedtime), according to the patient's prestudy regimen. The initial doses of insulin glargine and NPH were based on the previous NPH total daily dose.

RESULTS — At study end point, insulin glargine–pooled groups had significantly lower fasting plasma glucose (FPG) levels than the NPH insulin group, with adjusted mean FPG levels reduced by 2.2 mmol/l (P = 0.0001). Insulin glargine was superior to NPH insulin in reducing FPG levels in patients who had previously received NPH insulin twice daily but not in patients who had previously received NPH once daily. FPG levels were more stable in patients using insulin glargine than in patients using NPH insulin. A subset of patients (n = 71) underwent hourly overnight plasma glucose measurements. Insulin glargine patients exhibited lower FPG levels after 5:00 A.M.; the difference was significant by 8:00 A.M. The adjusted mean FPG for insulin glargine[30] was 7.8 mmol/l; for insulin glargine[80], 7.3 mmol/l; and for NPH, 10.7 mmol/l. Both formulations of insulin glargine were well tolerated, similar to NPH insulin.

CONCLUSIONS — Basal insulin glargine administered once daily for 4 weeks as part of a basal-bolus multiple daily insulin regimen was safe and more effective in lowering fasting plasma glucose levels than NPH in patients with type 1 diabetes.

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Insulin secretion in healthy individuals without diabetes is characterized by continuous basal secretion with peaks immediately after meals. Current strategies for insulin treatment of diabetes have failed to reproduce the normal physiological secretion pattern (1,2). Intermediate- and long-acting insulins have been complexed with protamine (NPH insulins) or the hexamer-stabilizing agent zinc (lente and ultralente insulins) to delay absorption (3,4). These formulations fall short of maintaining optimal glycemic control because of a pronounced insulin peak after injection, variable absorption, or a duration of action that still falls short of the ideal basal insulin (5–7). Development of improved long-acting insulins constitutes an important step toward improving the quality of glycemic control and avoiding long-term complications of diabetes (8,9).

Insulin glargine (HOE 901, 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg human insulin) is a novel human insulin analog that is synthesized by recombinant DNA technology using *Escherichia coli* plasmid DNA. Insulin glargine has a modified isoelectric point that results in reduced solubility at neutral pH (10). Crystallography studies indicate an increase in the intramolecular bonding of the insulin hexamer (11). Injected as a clear solution of pH 4.0, insulin glargine forms a microprecipitate in the physiological pH of the subcutaneous space. The stabilization of the insulin hexamer and higher aggregates may influence the nature of the precipitate and the rate of its dissolution and absorption from the site of injection. Animal studies indicate that the addition of zinc as a hexamer-stabilizing agent delays the onset and further increases the duration of action of insulin glargine in a concentration-dependent manner. Consequently, insulin glargine has a delayed and prolonged absorption from the injection site after subcutaneous administration.

Early trials in healthy volunteers and in patients with type 1 diabetes confirm that insulin glargine is a long-acting insulin that can more closely mimic normal basal insulin secretion (12,13).

We evaluated 2 formulations of insulin glargine, differing only in zinc chloride content (30 or 80 μg/ml), for safety and efficacy in the treatment of type 1 diabetes in patients receiving basal-bolus multiple-

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Abbreviations: ANCOVA, analysis of covariance; FBG, fasting blood glucose; FPG, fasting plasma glucose; SMBG, self-monitoring of blood glucose.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Summary of patient demographic characteristics and diabetes history*

	Insulin glargine[30]	Insulin glargine[80]	NPH insulin	Total treated
Total subjects (*n*)	82	86	88	256
Sex (M/F)	42/40	44/42	47/41	133/123
White patients (*n*)	76	81	83	240
Age (years)	37.5 ± 11.7	37.0 ± 11.5	37.9 ± 12.5	37.5 ± 11.9
HbA_{1c} (%)	7.8 ± 1.1	7.9 ± 1.2	8.0 ± 1.2	7.9 ± 1.1
BMI (kg/m^2)	23.9 ± 2.5	24.4 ± 2.5	24.5 ± 2.7	24.3 ± 2.6
Duration of diabetes (years)	16.7 ± 11.3	15.8 ± 10.0	16.3 ± 10.8	16.3 ± 10.7
Onset age (years)	21.5 ± 10.8	22.0 ± 12.7	22.3 ± 13.1	21.9 ± 12.2

Data are means ± SD unless otherwise stated.

dose insulin therapy. The 2 formulations were studied to investigate the effect of zinc on the clinical response to insulin glargine. The primary objective was to compare NPH insulin with the insulin glargine formulations with respect to fasting plasma glucose (FPG) in these patients.

RESEARCH DESIGN AND METHODS

Study design

This 4-week study was a multicenter partially double-blind randomized parallel group controlled trial of the safety and efficacy of 2 formulations of insulin glargine compared with NPH insulin in patients with type 1 diabetes.

A total of 315 patients with type 1 diabetes were assessed for eligibility during a 1-week screening phase. Eligible patients were between 18 and 70 years of age and had a BMI of 18–28 kg/m^2, HbA_{1c} of <10%, and postprandial serum C-peptide of <0.2 pmol/ml. All study patients had been on a basal-bolus multiple daily insulin regimen for at least 2 months. A total of 257 patients were randomly assigned to 1 of 3 treatment groups (256 received treatment): blinded treatment with insulin glargine[30] or insulin glargine[80] or unblinded treatment with NPH insulin for 4 weeks.

Insulin glargine[30] and insulin glargine[80] (Aventis Pharmaceuticals, Frankfurt, Germany) contained the recombinant human insulin analog equimolar to 100 U/ml human insulin. Insulin glargine was given by subcutaneous abdominal injection once daily at bedtime. The initial dose of either formulation of insulin glargine was to be equal to the total daily dose of NPH insulin the patient was using at the time of randomization to treatment. NPH insulin (Eli Lilly, Indianapolis, IN) was given as a subcutaneous abdominal injection either once daily (at bedtime) or twice daily (before breakfast and at bedtime) based on the patient's prestudy treatment regimen. NPH insulin contained 100 U/ml recombinant human insulin. Injections of regular insulin were administered 30 min before meals according to the patient's usual practice. Basal insulin doses were adjusted during the titration phase to maintain fasting blood glucose (FBG) values between 4 and 7 mmol/l (72–126 mg/dl). The dose was increased (or reduced) if higher (or lower) FPG values were obtained over a 2- to 4-day period in the absence (or presence) of nocturnal hypoglycemia. The dose of regular insulin was adjusted every 2–4 days if needed to achieve target ranges, on the basis of 1–4 U per meal. Target ranges for premeal and bedtime blood glucose values were 4–7 mmol/l (72–126 mg/dl) and 6–8 mmol/l (100–144 mg/dl), respectively.

Efficacy

Because of the relatively short duration of the treatment period, the primary efficacy variable was FPG at study end point, calculated as the mean of 3 FPG values measured on days 27, 28, and 29. Baseline FPG was the mean of the 3 FPG values measured on days −7, −3, and 1 (day 1 corresponds with the randomization visit). Secondary efficacy variables included serial overnight plasma glucose, mean FBG, blood glucose profile, nocturnal blood glucose, stability of fasting glucose, fasting serum insulin, and HbA_{1c}. Laboratory measurements of plasma glucose, HbA_{1c}, and lipids were determined by SmithKline Beecham Clinical Laboratories.

Blood glucose measurements were obtained by self-monitoring of blood glucose (SMBG) using the One-Touch II (LifeScan, Milpitas, CA) blood glucose meter. FBG was the mean of 7 consecutive values obtained during the screening phase and each week during treatment. Blood glucose profiles were derived from the mean of 7 SMBG values obtained at end point (premeal; 2 h after breakfast, lunch, and dinner; and bedtime) compared with the mean of 7 corresponding values obtained on day −1. Nocturnal blood glucose was measured twice weekly (at 3:00 A.M.) and at end point (mean of 3 values measured on days 27, 28, and 29). Baseline was the mean of 2 values measured on days −3 and −1.

HbA_{1c} was determined at baseline (day 1) and at end point (day 29). To determine the day-to-day variability in glycemic control, the stability of FPG was calculated as the mean of the absolute differences between the subject's FPG and median FPG on days 22, 27, 28, and 29. Insulin doses were recorded as daily doses of regular and basal treatment insulin.

The numbers and percentages of patients experiencing at least 1 episode of hypoglycemia were determined. Hypoglycemia was categorized as follows:

- Symptomatic: symptoms of hypoglycemia reported by the patient that may have been confirmed by a blood glucose level <2.8 mmol/l
- Severe: symptomatic hypoglycemia in which routine activities were curtailed or assistance was required; this may have been confirmed by a blood glucose level <2.8 mmol/l or the prompt recovery of the patient after administration of oral carbohydrate, intravenous glucose, or glucagon
- Nocturnal: occurring between bedtime basal insulin and FBG determination the next morning
- Asymptomatic: blood glucose or plasma glucose level <2.8 mmol/l, with no symptoms

A subset of patients at 9 selected investigative sites had hourly plasma glucose measurements taken overnight (11:00 P.M. to 8:00 A.M.) at baseline and end point.

Safety

Laboratory values, determined at baseline (day 1) and end point (day 29) for all 3 treatment groups, included standard hematology, clinical chemistry, lipid profiles, and measurement of antibodies to insulin glargine and human insulin and the *E. coli* protein component of the recombinant

Table 2—*Adjusted mean, mean difference, and 95% CIs for FPG (millimoles/liter) at end point (ANCOVA)*

Treatment	*n*	Adjusted mean	Mean difference	95% CI	*P*
Insulin glargine pooled	168	9.2	−2.2	(−3.0 to −1.3)	0.0001
NPH insulin	88	11.3	—	—	—
Insulin glargine[30]	82	8.6	−2.8	(−3.7 to −1.8)	0.0001
Insulin glargine[80]	86	9.7	−1.6	(−2.5 to −0.6)	0.0012
NPH insulin*	88	11.3	—	—	—

*Insulin glargine[30] and insulin glargine[80] were compared with NPH insulin.

insulin. Clinical examinations included physical examination, blood pressure, heart rate, and body weight data, determined at screening day −7, baseline, and end point.

Adverse events were considered treatment-emergent if they were reported during treatment and were not present before treatment or, if present before treatment, they had become more severe during treatment.

Statistical analysis

The required sample size was based on achieving a clinically meaningful difference in FPG, defined as a difference of 2.2 mmol/l. The analysis to determine treatment response was based on each patient's last treatment evaluation using an intention-to-treat analysis for all patients with both a pretreatment and during-treatment value. Centers with fewer than 3 completed patients per treatment group were pooled for all efficacy and clinical analyses. To assess the primary efficacy variable (FPG at end point), analysis of covariance (ANCOVA) was performed using study end point data, with baseline values as covariate and treatment and investigator pool as fixed effects. The analysis was carried out to determine whether insulin glargine (2 insulin glargine formulations pooled) was significantly different from NPH insulin at the $\alpha = 0.05$ level. If a significant difference was found, each of the insulin glargine groups was then compared with NPH insulin. ANCOVA was also performed for end point comparisons of all 3 treatment groups for all secondary efficacy variables. These tests were 2-tailed with a significance level of 0.05. The Cochran-Mantel-Haenszel test was used to analyze the percentages of patients with severe, nonsevere, and nocturnal hypoglycemia.

RESULTS — A total of 257 patients were randomly assigned to treatment with insulin glargine[30] (n = 82), insulin glargine[80] (n = 87), or NPH insulin (n = 88). Characteristics of the enrolled patients are shown in Table 1. One patient assigned to insulin glargine[80] never received treatment. Only 1 patient, who was assigned to the NPH treatment group and lost to follow-up, did not complete the study. The mean age of all patients was 37.5 years, the mean age at onset of diabetes was 21.9 years, and the mean duration of diabetes was 16.3 years. Of the subjects, 52% were male and 93.8% were white; the mean BMI was 24.3 kg/m^2 (Table 1). No significant between-treatment differences were found for these baseline characteristics.

Efficacy

At baseline, there was a comparable degree of glycemic control as assessed by FPG in insulin glargine patients and NPH insulin patients (Table 2). Insulin glargine demonstrated greater efficacy than NPH insulin in lowering FPG with an adjusted mean FPG at end point of 9.2 mmol/l for the pooled insulin glargine groups and 11.3 mmol/l for NPH (P = 0.0001). This clinically meaningful effect on FPG was seen as early as week 1 (Fig. 1).

The advantage of insulin glargine over NPH insulin was seen primarily in patients previously taking NPH insulin twice daily as part of their prestudy treatment regimen, despite the fact that those patients had lower baseline FPG values than patients taking NPH insulin once daily (Table 3). Of the 168 patients who received insulin glargine and 88 patients who received NPH insulin analyzed for FPG, 118 (70.2%) and 62 (70.5%), respectively, were previously on a twice-daily NPH dosage regimen. Insulin glargine and NPH insulin groups were well-matched for glycemic control at baseline (Table 3). Patients in the insulin glargine groups improved their FPG levels during the study. Patients in the NPH group improved their FPG levels only if they were using a once-daily regimen (Table 3).

The treatment effect on FPG is also supported by the results of FBG from daily SMBG measurements (Table 4). At the end of the study, the mean ± SD FBG was 7.6 ± 2.3 and 7.5 ± 1.9 mmol/l for the insulin glargine[30] and insulin glargine[80] groups, respectively, and 9.0 ± 2.4 mmol/l for the NPH group. However, the blood glucose profile determined from 7 SMBG values during the day was not different among the treatment groups (Table 4).

Overnight plasma glucose profiles were obtained in a subset of patients (n = 71) at 9 selected centers. These profiles show similar plasma glucose levels during most of the night but show an increase in plasma glucose levels after 5:00 A.M. in patients who received NPH insulin, whereas insulin glargine suppressed this early morning increase, suggesting that insulin glargine lasts for a longer duration (Fig. 2). Insulin glargine patients exhibited lower FPG levels after 5:00 A.M.; the difference was significant

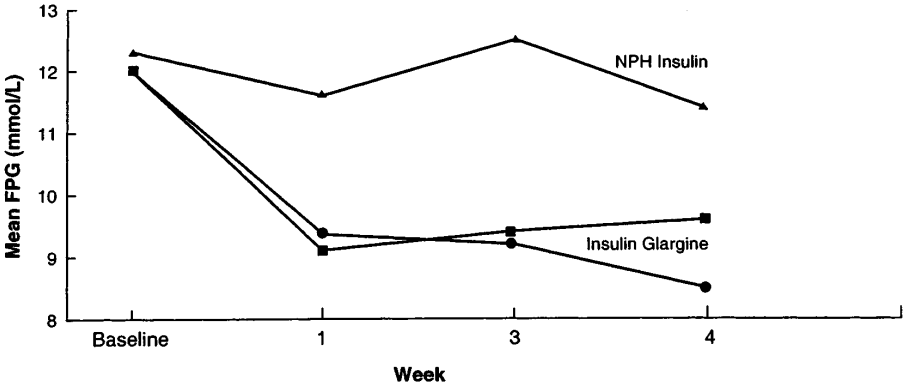

Figure 1—*Mean FPG (in millimoles per liter). A plot of mean plasma glucose levels for insulin glargine[30] (●), insulin glargine[80] (■), and NPH insulin (▲) is shown.*

Table 3—*Mean FPG by prestudy NPH insulin regimens: once or twice daily*

	Prestudy twice-daily NPH				Prestudy once-daily NPH			
	Insulin glargine		NPH insulin*		Insulin glargine		NPH insulin‡	
	n	FPG (mmol/l)	*n*	FPG (mmol/l)	*n*	FPG (mmol/l)	*n*	FPG (mmol/l)
Baseline	118	11.6	62	11.6	50	13.0	26	14.0
End point	118	8.4†	62	11.4	50	10.9†	26	11.2‡

*NPH insulin users continued their prestudy regimen of injections once or twice daily. †P = 0.0001, baseline to end point; ‡P = 0.0012, baseline to end point.

by 8:00 A.M. The adjusted mean for insulin glargine[30] was 7.8 mmol/l; for insulin glargine[80], 7.3 mmol/l; and for NPH, 10.7 mmol/l. Nocturnal blood glucose measured by SMBG at 3:00 A.M. was higher for insulin glargine than for NPH, with no evidence of increased severe nocturnal hypoglycemia (Table 4). FPG tended to be more stable at the end point for insulin glargine treatment groups than for NPH (Table 4).

Hypoglycemia

At least 1 episode of symptomatic hypoglycemia was reported by almost all patients during the 4-week dose titration and treatment period. Fewer patients receiving NPH insulin (93.2%) reported a hypoglycemic episode than patients receiving insulin glargine (97.6 and 100.0% for insulin glargine[30] and insulin glargine[80], respectively) (P = 0.030). This difference in frequency of reporting hypoglycemia, although statistically significant, is not clinically meaningful and appeared to extend across all types of hypoglycemia, with the exception of severe hypoglycemia. Over the course of the study, the occurrence of hypoglycemia, including nocturnal hypoglycemia, in patients treated with insulin glargine declined.

The proportion of episodes reported for the insulin glargine treatment groups is larger than that reported for NPH insulin between 3:00 and 9:00 A.M. and smaller during the remainder of the day. This finding is consistent with the study design that required the initial dose of insulin glargine to be calculated from the summation of the 2 doses of NPH for those patients who were on a prestudy regimen of twice-daily NPH.

Insulin dose

The dose of basal insulin was titrated to a target FBG level. Dose titration occurred during the first 3 weeks of the study; during the fourth week, the dose of insulin was to remain stable. The daily dose of basal insulin for the insulin glargine treatment group was titrated downward, whereas the dose of NPH insulin increased. Patients who had been using NPH once daily before the study were using median daily basal insulin doses of 11.5–14.0 U at baseline. Patients who had been using NPH twice daily before the study were using twice the basal insulin dose used by the once-daily group, i.e., 26.4–30.0 U at baseline. At end point, after completion of titration, median basal insulin doses of insulin glargine were similar to the NPH insulin dose in the once-daily NPH prestudy regimen cohort. However, the median basal insulin doses of insulin glargine were 6–7 U lower than the NPH total daily insulin dose in the twice-daily NPH prestudy regimen cohort. The median total daily doses of regular insulin were similar across treatment groups for both NPH prestudy regimen cohorts.

Safety

The most frequent adverse events that were considered by the investigator to be related to study medication were injection site reactions. All events were considered mild and none resulted in discontinuation from study treatment.

No clinically significant changes occurred in laboratory values. There was no evidence of increased antibody formation after treatment with insulin glargine or NPH insulin, and no clinically relevant changes in *E. coli* protein antibody formation were observed. No patients had clinically meaningful changes in systolic and diastolic blood pressure or weight.

CONCLUSIONS — This study compared the effects of once-daily insulin glargine and once- or twice-daily NPH insulin regimens as basal insulin treatment over 4 weeks in patients with type 1 diabetes previously receiving a multiple daily insulin regimen with NPH insulin and preprandial regular insulin. The primary finding of the study was the highly significant effect of insulin glargine on lowering FPG levels in these patients compared with NPH insulin. Overall, patients receiving insulin glargine exhibited a 2.2 mmol/l decrease in FPG compared with NPH insulin recipients by the end of the study; a significant difference between treatments was observed as early as the first week of treatment. No substantial differences between the 2 insulin glargine zinc formulations were observed in the study.

Among patients previously receiving NPH insulin twice daily, those randomized to continue the NPH twice-daily regimen

Table 4—*Summary of secondary variables of glycemic control*

	Insulin glargine[30]	Insulin glargine[80]	NPH insulin
Change from baseline			
FBG (mmol/l)	81 (−1.5 ± 2.45)	86 (−1.8 ± 2.19)	87 (−0.3 ± 2.53*)
Blood glucose profile (mmol/l)	77 (−0.1 ± 3.30)	81 (0.3 ± 3.05)	81 (−0.2 ± 2.56)
Nocturnal blood glucose (3:00 A.M.) (mmol/l)	80 (0.2 ± 3.80)	86 (0.4 ± 3.81)	82 (−0.3 ± 4.41†)
Stability of FPG (mmol/l)	81 (−0.4 ± 1.17)	84 (−0.3 ± 1.14)	84 (−0.2 ± 1.17†)
HbA_{1c} (%)	82 (−0.4 ± 0.48)	86 (−0.4 ± 0.49)	86 (−0.4 ± 0.48)
End point			
FBG (mmol/l)	81 (7.6 ± 2.3)	86 (7.5 ± 1.9)	87 (9.0 ± 2.4‡)

Data are *n* (means ± SD). *$P < 0.001$, pairwise comparisons with both insulin glargine[30] and insulin glargine[80]; †$P < 0.05$, pairwise comparison with insulin glargine[30]; ‡$P < 0.001$ for insulin glargine[30] and insulin glargine[80] compared to NPH insulin.

required increasing insulin doses from 26.4 to 30.0 U, with no significant changes in FPG levels, whereas those switched to bedtime insulin glargine treatment had a 3.2 mmol/l reduction from baseline (P = 0.0001) despite reductions in insulin dosages. To avoid nocturnal hypoglycemia, the evening dose of NPH insulin in patients injecting twice daily is often lower than the morning NPH dose, and because of the relatively short duration of action of NPH insulin, the effect wanes in the early morning, resulting in inadequate control of fasting glucose. Predictably, replacement of the total daily dose of twice-daily NPH with the longer-acting once-daily insulin glargine, as was done in this study, resulted in significantly better and more predictable control of fasting glucose levels and did not significantly increase the incidence of severe nocturnal hypoglycemia.

Patients who had been receiving NPH insulin once daily had poorer glycemic control at baseline than patients who had been receiving NPH insulin twice daily. Patients receiving NPH insulin once daily exhibited a significant decrease in FBG during the study, with the degree of reduction being comparable to that observed among insulin glargine recipients. However, this reduction in FPG in the once-daily NPH insulin group was observed in the context of an increase in median daily insulin dose from 11.5 to 14.5 U.

Most patients reported at least 1 episode of hypoglycemia during the study. The overall incidence was lower in patients receiving NPH insulin; however, differences in the occurrence of hypoglycemia among the treatment groups were not clinically relevant. The frequency of hypoglycemia decreased over time during the study, particularly in the insulin glargine treatment groups. This decreasing frequency of hypoglycemia is likely attributable to the ongoing dose titration during the study. The finding that many insulin glargine patients had their doses lowered without impairment of effectiveness in maintaining reduced FPG levels suggests that the initial doses were higher than necessary in many instances, which is likely to have contributed to the occurrence of hypoglycemia.

The beneficial effect of insulin glargine treatment on FPG control is also indicated by results of the overnight plasma glucose measurements. Patients receiving NPH insulin exhibited a characteristic increase in FPG between the 5:00 and 8:00 A.M. measurements, consistent with the short duration of action and the lack of suppression of the characteristic early morning hyperglycemia known as the "dawn phenomenon." Consistent with its expected protracted duration of action, insulin glargine treatment was associated with maintained suppression of glucose levels during these morning hours.

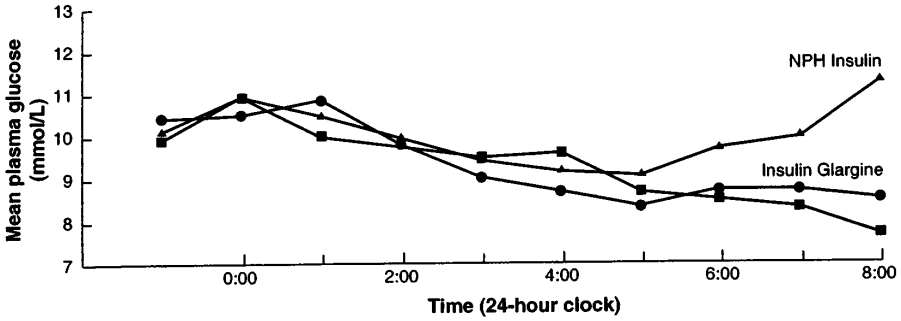

Figure 2—*Mean serial overnight plasma glucose (in millimoles per liter) at end point. A plot of mean serial overnight plasma glucose at study end point measured hourly in a subpopulation of patients receiving insulin glargine[30] (●, n = 23), insulin glargine[80] (■, n = 24), or NPH insulin (▲, n = 24) is shown.*

Insulin glargine was as safe as NPH insulin. No differences between treatments were observed with regard to the incidence of adverse effects, including the most frequent events—injection site reactions. No treatment effects on development of insulin antibodies or antibodies to the foreign protein component of insulin glargine were observed. No clinically relevant laboratory abnormalities or significant changes in vital signs were observed in either treatment group.

Of note, a recent European study comparing the efficacy and safety of insulin glargine versus NPH insulin in patients with type 1 diabetes showed a significant reduction in nocturnal hypoglycemia in patients taking glargine at bedtime compared with those taking NPH once daily at bedtime (14). However, patients taking insulin glargine were not analyzed by subsets according to prior once- versus twice-daily NPH administration before study entry, and overnight glucose profiles were not measured. These issues are addressed in the present study, which expands upon the European trial, showing that insulin glargine achieves robust reductions in FPG. Furthermore, the nocturnal blood glucose profiles show a significant difference between insulin glargine and NPH at 8:00 A.M., with glargine maintaining a persistent blood glucose–lowering effect and NPH showing hyperglycemic escape by early morning.

Interestingly, in the present study, the benefit of insulin glargine compared with NPH insulin in reducing FPG levels is primarily evident in patients who have received prior twice-daily NPH—a group comprising the majority of study patients. This result may reflect the fact that these patients tolerated overall higher total dosages of insulin glargine (from the addition of previous morning and bedtime doses at study entry) without experiencing severe hypoglycemia.

Intensive insulin therapy with multiple daily injections has become a more common treatment for type 1 diabetes and can be quite effective in maintaining glycemic control; however, both NPH and ultralente have limitations as basal insulins. A recent study by Zinman et al. (15) showed that these 2 insulins are similar in safety and efficacy and highlighted their inadequacy to provide 24-h coverage. The implications of this study support the idea that in the long-term, twice-daily injections of either of these 2 insulins are eventually needed to control blood glucose levels in patients with longer duration of disease and greater hyperglycemia.

In summary, results of the present study indicate that once-daily basal insulin glargine is associated with significantly better fasting glucose control, using lower insulin doses than NPH insulin in the short-term treatment of type 1 diabetes. Longer-term comparisons of basal insulin glargine and NPH insulin regimens will better define the overall effects of this novel insulin analog on measures of glycemic control in this patient population.

References

1. Volund A: Insulin therapy and its shortcomings: the need for new approaches. *Diabet Med* 14:S5–S8, 1997

2. Johnson NB, Owens DR: Insulin analogues. *Lancet* 349:47–51, 1997
3. Shannon AG, Bolli GB: Pharmacokinetics and pharmacodynamics of insulin: relevance to the therapy of diabetes mellitus. *Diabetes Nutr Metab* 10:24–34, 1997
4. Heinemann L, Richter L: Clinical pharmacology of human insulin. *Diabetes Care* 16 (Suppl. 3):90–100, 1993
5. Binder C, Lauritzen T, Faber O, Pramming S: Insulin pharmacokinetics. *Diabetes Care* 3:188–199, 1984
6. Hoffman A, Ziv E: Pharmacokinetic considerations of new insulin formulations and routes of absorption. *Clin Pharmacokinet* 33: 285–301, 1997
7. Brange J, Langkjaer L: Insulin formulation and delivery. *Pharm Biotechnol* 10:343–409, 1997
8. Brange J: The new era of biotech insulin analogues. *Diabetologia* 40 (Suppl. 2):S48–S53, 1997
9. deLeiva A: Frontiers of clinical research in type I diabetes. *Horm Res* 45 (Suppl. 1):32–35, 1996
10. Seipke G, Geisen K, Neubauer HP, Pittius C, Rosskamp R, Schwabe D: New insulin preparations with prolonged action profiles: A21-modified arginine insulins. *Diabetologia* 35 (Suppl. 1):A4, 1992
11. Hilgenfeld R, Dorschug M, Geisen K, Neubauer H, Oberneier R, Seipke G, Berchtold H: Controlling insulin bioavailability by crystal contract engineering. *Diabetologia* 35 (Suppl. 1):A4, 1992
12. Dreyer M, Pein M, Schmidt C, Heidtmann B, Schlunzen M, Rosskamp R: Comparison of the pharmacokinetics/dynamics of Gly(A21)-Arg(B31,B32)-human-insulin (HOE71GT) with NPH-insulin following subcutaneous injection by using euglycaemic clamp technique. *Diabetologia* 37 (Suppl. 1):A78, 1994
13. Taulaulicar M, Willms B, Rosskamp R: Efficacy of HOE 901 following subcutaneous injection for four days in type I diabetic subjects. *Diabetologia* 37 (Suppl. 1):A169, 1995
14. Pieber TA, Eugène-Jolchine I, Derobert E, for the European Study Group of HOE 901 in Type 1 Diabetes: Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. *Diabetes Care* 23:157–162, 2000
15. Zinman B, Ross S, Campos RV, Strack T, for the Canadian Lispro Study Group: Effectiveness of human ultralente versus NPH insulin in providing basal insulin replacement for an insulin lispro multiple daily injection regimen: a double-blind randomized prospective trial. *Diabetes Care* 22:603–608, 1999