A 16-Week Comparison of the Novel Insulin Analog Insulin Glargine (HOE 901) and NPH Human Insulin Used With Insulin Lispro in Patients With Type 1 Diabetes

PHILIP RASKIN, MD
LESLIE KLAFF, MD
RICHARD BERGENSTAL, MD
JEAN-PIERRE HALLÉ, MD
DAVID DONLEY, PHD
THOMAS MECCA, PHD

OBJECTIVE — To determine the safety and efficacy of the long-acting insulin analog, insulin glargine, as a component of basal bolus therapy in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Patients with type 1 diabetes receiving basal-bolus insulin treatment with NPH human insulin and insulin lispro were randomized to receive insulin glargine (HOE 901), a long-acting basal insulin analog, once a day (n = 310) or NPH human insulin (n = 309) as basal treatment with continued bolus insulin lispro for 16 weeks in an open-label study. NPH insulin patients maintained their prior schedule of administration once or twice a day, whereas insulin glargine patients received basal insulin once a day at bedtime.

RESULTS — Compared with all NPH insulin patients, insulin glargine patients had significant decreases in fasting blood glucose measured at home (means ± SEM, −42.0 ± 4.7 vs. −12.4 ± 4.7 mg/dl [–2.33 ± 0.26 vs. −0.69 ± 0.26 mmol/l]; P = 0.0001). These differences were evident early and persisted throughout the study. More patients in the insulin glargine group (29.6%) than in the NPH group (16.8%) reached a target fasting blood glucose of 119 mg/dl (<6.6 mmol/l). However, there were no differences between the groups with respect to change in GHb. Insulin glargine treatment was also associated with a significant decrease in the variability of fasting blood glucose values (P = 0.0124). No differences in the occurrence of symptomatic hypoglycemia, including nocturnal hypoglycemia, were observed. Overall, adverse events were similar in the two treatment groups with the exception of injection site pain, which was more common in the insulin glargine group (6.1%) than in the NPH group (0.3%). Weight gain was 0.12 kg in insulin glargine patients and 0.54 kg in NPH insulin patients (P = 0.034).

CONCLUSIONS — Basal insulin therapy with insulin glargine once a day appears to be as safe and at least as effective as using NPH insulin once or twice a day in maintaining glycemic control in patients with type 1 diabetes receiving basal-bolus insulin treatment with insulin lispro.

Diabetes Care 23:1666–1671, 2000

From the Department of Internal Medicine (P.R.), University of Texas Southwestern Medical Center, Dallas, Texas; Rainier Clinical Research Center (L.K.), Renton, Washington; International Diabetes Center (R.B.), Minneapolis, Minnesota; Quintiles (D.D., T.M.), Kansas City, Missouri; and Hospital Maisonneuve-Rosemont (J.-P.H.), Montreal, Quebec, Canada.

Address correspondence and reprint requests to Philip Raskin, MD, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75930-8853.

Received for publication 3 April 2000 and accepted in revised form 26 July 2000.

This study was supported by Hoechst Marion Roussel. P.R., L.K., and J.-P.H have received consulting fees from and given lectures sponsored by Aventis. R.M.B. has participated in symposia sponsored by and received honorium from Aventis. D.D. and T.M. were employed by Hoechst Marion Russell during this study.

Abbreviations: ANCOVA, analysis of covariance; DCCT, Diabetes Control and Complications Trial; ECG, electrocardiogram.

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

Currently available intermediately or long-acting insulin products used for basal insulin treatment are associated with either pronounced insulin peaks after injection, a duration of action that is too short to maintain glycemic control throughout the dosing period, or high day-to-day variability (1,2). Insulin analogs designed to more closely mimic endogenous basal insulin patterns have been produced through recombinant DNA technology (3–6). A novel insulin analog, 21^{A} -Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin (HOE 901 or insulin glargine), has been designed with a modified isoelectric point that results in precipitation at neutral tissue pH and thus delayed absorption from subcutaneous tissue (7–10). Early-phase short-term trials in patients with type 1 diabetes indicated that the use of insulin glargine once a day is associated with metabolic control equivalent or superior to NPH insulin once or twice a day (11–13). One study showed a reduction in the occurrence of nocturnal hypoglycemia with insulin glargine treatment (13).

In our study, we compared the effects of insulin glargine once a day at bedtime and NPH insulin once or twice a day as basal insulin treatment for 16 weeks in patients with type 1 diabetes who were currently receiving NPH insulin for basal treatment and preprandial insulin lispro for postprandial glycemic control. The effects of insulin glargine once a day were compared with those of NPH insulin once or twice a day on fasting plasma glucose, fasting plasma glucose variability, GHb, and occurrence of hypoglycemia.

RESEARCH DESIGN AND METHODS

Protocol

The study was a phase III multicenter randomized open-label comparison of insulin glargine and NPH insulin as basal insulin

treatment in patients with type 1 diabetes who had been receiving NPH and premeal insulin lispro. Patients were enrolled at 60 centers; the study was conducted between October 1997 and July 1998. Eligible patients had type 1 diabetes, were 18–80 years of age, and had been receiving treatment with NPH insulin for at least 1 year and insulin lispro for at least 3 months. Patients had to have a serum C-peptide level ≤9 mg/dl (0.5 mmol/l) in the presence of a blood glucose level ≥99.0 mg/dl (5.5 mmol/l) and a GHb value ≤12.0%. Patients with hepatic or renal impairment, those who were pregnant or breast feeding, and those who had received treatment with any glucose-lowering drug other than insulin within 4 weeks of the study were excluded. Written informed consent was obtained from all patients before study enrollment.

During a 1- to 4-week screening phase, patients continued their current NPH insulin and insulin lispro treatment and were instructed on the use of the glucose meter for at-home self-measured blood glucose assessment. Patients performed blood glucose measurements for 7 consecutive days before the baseline visit (week 0). After the screening phase, patients were stratified on the basis of their prior regimen of NPH insulin: once a day or more than once a day. Patients were then randomized via a telephone randomization center to receive open-label subcutaneous insulin glargine once a day at bedtime or subcutaneous NPH insulin once a day at bedtime or twice a day before breakfast and at bedtime for a 16-week treatment period. Because insulin glargine is a clear solution and can easily be distinguished from NPH insulin visually, an open-label design was required. All patients continued to administer individually titrated insulin lispro before meals.

Insulin glargine (Hoechst Marion Roussel, Frankfurt, Germany) was supplied in vials containing a 5-ml solution (1 ml containing 100 U insulin). NPH insulin (Eli Lilly, Indianapolis, IN) was supplied in vials containing a 10-ml suspension (1 ml containing 100 U insulin). Insulin lispro (Eli Lilly) was supplied in vials containing 10 ml solution (1 ml containing 100 U insulin). Starting dosages of insulin glargine and NPH insulin were based on prior NPH insulin dosage on a unit-for-unit basis but were left to the discretion of the investigator. Investigators were informed of results of phase II comparative studies, which suggested a 10% decrease in the insulin glargine dose compared with total dosage in patients receiving NPH insulin twice a day (12–14). Thereafter, insulin glargine and NPH insulin doses were to be individually titrated to obtain a target fasting blood glucose <120.6 mg/dl (6.7 mmol/l).

Study patients made seven clinic visits as follows: a screening phase visit, baseline visit (week 0), and visits at weeks 1, 4, 8, 12, and 16. Study end point was defined as the last available measurement on treatment. Efficacy variables included changes in GHb between baseline and study end point and at weeks 8 and 16, fasting plasma glucose at each study visit, fasting blood glucose assessed by patient self-monitoring for 7-day periods before baseline and before the week 8 and week 16 visits, and occurrence of hypoglycemia. GHb was measured in whole blood using affinity chromatographic methods by the Diabetes Diagnostic Laboratory (University of Missouri, Columbia, MO). The upper limit for nondiabetic individuals in this assay is 6.05%. The GHb test method is certified as traceable to the Diabetes Control and Complications Trial (DCCT) reference method and thus to results of this trial, in which relationships between mean blood glucose and risk of vascular complications have been established. The certification procedures have been established by the National Glycohemoglobin Standardization Program. Fasting plasma glucose was measured by standard laboratory methods at Covance Central Laboratories (Indianapolis, IN). Self-monitoring of blood glucose was performed with the One Touch Profile system (LifeScan, Milpitas, CA).

Hypoglycemic episodes were categorized as symptomatic, nocturnal symptomatic, and severe. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the subject required assistance from another person and which was accompanied by a blood glucose level <36.0 mg/dl (2.0 mmol/l) or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. Nocturnal hypoglycemia was defined as that occurring while the subject was asleep during the time between bedtime after the evening injection and before getting up in the morning (i.e., before morning determination of fasting blood glucose and morning injection). The incidence of each type of hypoglycemia, as well as the incidence of each type associated with a blood glucose level <36.0 mg/dl (2.0 mmol/l), was determined.

Safety assessments included monitoring for clinical adverse events; standard clinical chemistry and clinical hematology; assessment of insulin glargine, human insulin, and *Escherichia coli* protein antibodies; ophthalmologic examination for changes in diabetic retinopathy; evaluation of vital signs; and electrocardiography.

Differences in GHb between treatment groups were assessed by analysis of covariance (ANCOVA) using change from baseline to study end point as the dependent variable, with treatment and (pooled) center as fixed effects and the corresponding baseline value as covariate. The difference in mean change from baseline among treatment groups was estimated using adjusted mean values along with the associated SEM and 95% CI from the ANCOVA model. Variability of fasting blood glucose (variance among the seven daily values before study visit) was assessed by ANCOVA using ranked change from baseline in variability and ranked baseline values. Percentages of subjects with at least one episode of hypoglycemia were compared by ranked analysis of variance. Baseline variables were compared using analysis of variance and the Cochran-Mantel-Haenszel test. All statistical tests were two-sided and performed at a significance level of α = 5%, unless otherwise indicated.

RESULTS

Patients

A total of 619 patients were randomized to receive study treatment. Baseline characteristics of patients are shown in Table 1. Most patients (75.9%) and similar proportions in the treatment groups had previously received basal insulin treatment at least twice a day. A total of 31 patients, 15 in the insulin glargine group and 16 in the NPH insulin group, withdrew from the study before the end of the treatment phase; most of these patients either wanted to discontinue study participation or were lost to follow-up. None of the patients in the insulin glargine group and two in the NPH insulin group cited adverse events as a reason for discontinuation.

Insulin dose

Insulin doses were adjusted to achieve target fasting blood glucose levels of 79.2–120.6 mg/dl (4.4–6.7 mmol/l). Overall, the means ± SD dose of basal insulin at study end point decreased by 4.5 U from the prior NPH insulin dose in insulin glargine

Table 1—*Patient demographics and baseline characteristics*

	Insulin glargine	NPH human insulin
n	310	309
M/F	151 (48.7)/159 (49.4)	162 (52.4)/147 (47.6)
Age (years)	38.9 ± 12.2	39.5 ± 12.2
BMI (kg/m^2)	25.5 ± 3.4	25.7 ± 3.9
Ethnicity		
White	299 (96.5)	301 (97.4)
Black	10 (3.2)	6 (1.9)
Hispanic	3 (1.0)	6 (1.9)
Other	1 (0.3)	2 (0.6)
Reported prior basal insulin schedule		
Once a day	77 (24.8)	72 (23.3)
Twice a day	225 (72.5)	230 (74.4)
>Twice a day	8 (2.5)	7 (2.2)
Diabetic history		
Duration (years)	18.7 ± 11.5	18.4 ± 11.8
Age at onset (years)	20.9 ± 12.5	21.8 ± 12.7
Insulin treatment (years)	18.4 ± 11.6	17.9 ± 11.7
Metabolic control		
GHb (%)	7.6 ± 1.2	7.7 ± 1.2
Fasting plasma glucose (mg/dl [mmol/l])	214.4 ± 99.1 [11.9 ± 5.5]	218.0 ± 91.9 [12.1 ± 5.1]
Fasting blood glucose (mg/dl [mmol/l])	174.7 ± 59.4 [9.7 ± 3.3]	172.9 ± 46.8 [9.6 ± 2.6]
Symptomatic hypoglycemia during screening phase		
Total	211 (68.1)	200 (64.7)
Once-daily basal insulin	55 (75.3)	37 (53.6)*
>Once-daily basal insulin	156 (65.8)	163 (67.9)

Data are *n*, *n* (%), or means ± SD. *P = 0.0034.

patients (28.4 ± 13.3 to 23.9 ± 10.9 U), with a marked decrease evident after 1 week that was maintained throughout the treatment period (Fig. 1). Among NPH insulin patients, the dose increased by 0.9 U (28.3 ± 14.4 to 29.2 ± 15.0 U) from baseline to end point. The overall decrease in insulin glargine patients was due to a 6.2-U decrease in patients who had previously received NPH insulin at least twice a day (31.5 ± 13.2 to 25.3 ± 11.4 U), compared with a 1.8-U increase in those with a prior once-a-day basal regimen (19.6 ± 9.0 to 21.4 ± 9.9 U). Among NPH insulin patients, mean dose increased from baseline to end point by 1.8 U in those with a prior once-a-day regimen and by 0.7 U in those who had received a more-than-once-a-day regimen.

Overall, the mean daily insulin lispro dose increased by 1.5 U in insulin glargine patients, with a decrease in mean dose of 3.6 U in those with a prior once-a-day basal insulin schedule and an increase of 3.1 U in those with a more frequent schedule. In NPH insulin patients, mean daily insulin lispro dose decreased by 0.5 U, with a 1.0-U decrease in those with a prior once-a-day basal insulin schedule and a decrease of 0.3 U in patients receiving NPH twice a day. None of these changes were statistically significant.

GHb

Insulin glargine and NPH insulin had similar but minimal effects on GHb between baseline and study end point (P = 0.8409 by ANCOVA). The change from baseline to end point, expressed as means ± SD, was 7.59 ± 1.19 to 7.53 ± 1.19% in insulin glargine patients, and 7.71 ± 1.2 to 7.60 ± 1.14% in NPH insulin patients (Table 2). On average, patients with higher baseline GHb had a statistically greater reduction in GHb during treatment, but the relative effects of insulin glargine and NPH insulin on GHb did not vary significantly as a function of baseline.

Fasting blood glucose and fasting plasma glucose

Changes from baseline in self-monitored fasting blood glucose and fasting plasma glucose levels at specified study intervals are expressed as means ± SD values in Table 2. Insulin glargine was associated with significantly greater reductions in fasting blood glucose than NPH insulin. At end point, the target fasting blood glucose value of <120.7 mg/dl (6.7 mmol/l) was achieved by more insulin glargine patients (29.6%) than NPH patients (16.8%). Changes in fasting plasma glucose paralleled those of self-monitored fasting blood glucose. Changes from baseline in self-monitored fasting blood glucose and fasting plasma glucose levels at specified study intervals are expressed as means ± SD values in Table 2.

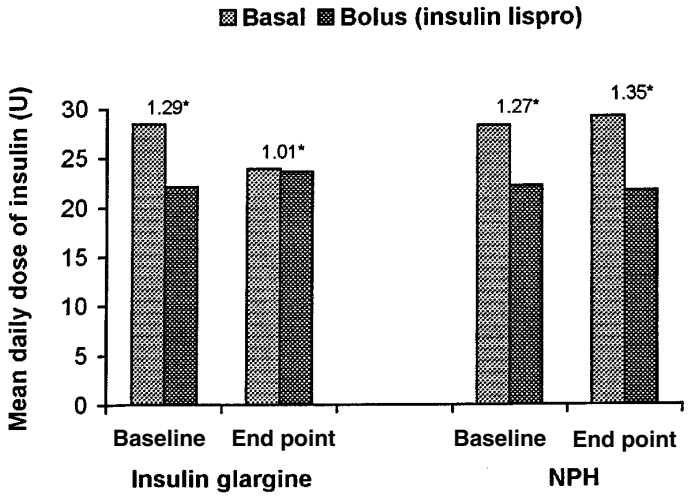

Figure 1—*Mean daily dose of basal and bolus insulin with basal-to-bolus ratios at baseline and end points for insulin glargine and NPH treatments arms. *Basal-to-bolus ratio.*

Table 2—*Baseline–to–end point changes in GHb, fasting plasma glucose, and fasting blood glucose*

	Insulin glargine	NPH insulin	*P* value for treatment effect (insulin glargine vs. NPH)
GHb (%)			
Baseline	7.6 ± 1.19	7.7 ± 1.2	
Week 8	7.4 ± 1.1	7.5 ± 1.03	NS
End point	7.5 ± 1.19	7.60 ± 1.14	NS
Fasting blood glucose (mg/dl [mmol/l])			
Baseline	174.7 ± 56.0 (9.7 ± 3.1)	172.9 ± 47.7 (9.6 ± 2.7)	
Week 8	147.7 ± 43.1 (8.2 ± 2.4)	163.9 ± 43.4 (9.1 ± 2.4)	0.0001
End point	144.1 ± 42.2 (8.0 ± 2.3)	162.1 ± 43.7 (9.0 ± 2.4)	0.0001
Fasting plasma glucose (mg/dl [mmol/l])			
Baseline	214.4 ± 99.4 (11.9 ± 5.5)	218.0 ± 99.4 (12.1 ± 5.5)	
Week 1	192.8 ± 97.2 (10.7 ± 5.4)	212.6 ± 90.4 (11.8 ± 5.0)	0.0165
Week 4	185.6 ± 79.1 (10.3 ± 4.4)	216.2 ± 88.6 (12.0 ± 4.9)	0.0001
Week 8	180.1 ± 82.1 (10.0 ± 4.6)	198.2 ± 76.6 (11.0 ± 4.3)	0.0019
Week 12	180.0 ± 81.1 (10.0 ± 4.5)	209.0 ± 88.3 (11.6 ± 4.7)	0.0001
End point	174.7 ± 74.9 (9.7 ± 4.16)	205.4 ± 87.3 (11.4 ± 4.9)	0.0001

Data are means ± SD and are based on the number of intention-to-treat subjects for whom data were available at each time point. *P* values are based on adjusted mean changes from the ANCOVA model. End point is defined as the last available value collected on study treatment.

The ranked change from baseline in variability of fasting blood glucose was analyzed by ANCOVA (see RESEARCH DESIGN AND METHODS). At baseline, the treatment groups showed comparable variability in fasting blood glucose ($P = 0.4591$). However, by week 16, the median decrease in variability between insulin glargine and NPH patients achieved statistical significance ($P = 0.0427$). This significance was maintained at study end point, with a median decrease in variability of 61.9 mg/dl (3.44 mmol/l) in insulin glargine patients and 14.2 mg/dl (0.79 mmol/l) in NPH insulin patients ($P = 0.0124$).

Hypoglycemia

Episodes of symptomatic hypoglycemia were reported and evaluated according to three primary subsets: symptomatic, nocturnal, and severe. Patients were asked to record self-monitored blood glucose values at the time of each episode (although it was understood that they may have required time to recover before they were able to take the measurements), and these values were reported as <50.4 mg/dl (2.8 mmol/l) and <36.0 mg/dl (2.0 mmol/l). The number of patients and hypoglycemic episodes for which blood glucose measurements were recorded is summarized in Table 3, with separate summaries of confirming glucose values <36.0 mg/dl (2.0 mmol/l) in each of the three subsets.

Similar incidences of both symptomatic and asymptomatic hypoglycemia were observed in the insulin glargine group and the NPH insulin group during the first month of treatment and from month 2 to the end of the study. During the dose titration period, the rate of nocturnal hypoglycemia approached statistical significance, with the rate in the insulin glargine group higher than that in the NPH insulin group (44.5 vs. 38.8%, $P = 0.09$). However, the rate from month 2 through the end of the study was not significantly different (59.3 vs. 59.0%, $P = 0.65$). Rates of nocturnal hypoglycemia in the insulin glargine versus NPH insulin groups, confirmed by blood glucose level <36.0 mg/dl (2.0 mmol/l), were similar during month 1 and during the entire treatment phase (12.3 vs. 12.0%). No differences between treatment groups, according to prior basal insulin schedule, were observed during study treatment.

No differences in rates of severe hypoglycemia were observed between the insulin glargine and NPH insulin groups during the first month of treatment (2.6 vs. 1.3%, $P = 0.23$) or during month 2 through the end of the study (5.2 vs. 4.6%, $P = 0.67$). Severe episodes confirmed by low blood glucose values (<36.0 mg/dl [2.0 mmol/l]) occurred in four patients (1.3%) in each group.

Safety

Overall, adverse events were similar in the treatment groups, with the exception of injection site pain. Treatment-emergent adverse events regardless of relationship to study medication occurred in 250 of 310 (80.6%) insulin glargine patients, compared with 236 of 309 (71.4%) NPH insulin patients. The most common adverse event considered by the investigator to be related to the study treatment was injection site events. Of these events, injection pain was reported more frequently by insulin glargine patients than by NPH insulin patients (6.1 vs. 0.3%). Adverse events considered treatment-related that occurred in ≥2% of patients are summarized in Table 4. No insulin glargine patients discontinued study treatment because of adverse events, whereas two NPH insulin patients did, including one who discontinued treatment because of cancer of the pancreas, which was unrelated to study treatment. The other patient discontinued treatment after a severe hypoglycemic reaction with coma. No deaths occurred during the study.

Use of radiolabeled tracers for insulin glargine and human insulin antibodies, expressed as adjusted means ± SEM percentage bound/total, showed no clinically relevant treatment-related effects on antibody levels. Because of the cross-reactivity of human insulin antibodies with insulin glargine tracer and of insulin glargine antibodies with human insulin tracer, all samples were assayed with both tracers. The insulin glargine group exhibited significant reductions (adjusted means ± SEM percentage bound/total) compared with the NPH insulin group in both insulin glargine antibodies (−1.35 ± 0.42 vs. 0.83 ± 0.42% bound/total, $P = 0.0002$) and human insulin antibodies (−2.56 ± 0.43 vs. −0.08 ± 0.43% bound/total, $P = 0.0001$).

The number of retinal events reported for each treatment group was similar: 2.9% in the insulin glargine arm compared with 2.3% in the NPH arm. The most commonly occurring of such an event was retinal vascular disorder, reported in 1.9 and 1.0% of patients treated with insulin glargine and NPH insulin, respectively. The types of retinal adverse events seen in this study are expected for this subject population (15).

No differences between groups were observed with regard to changes in labora-

Table 3—*Frequency of hypoglycemic episodes for which blood glucose values were obtained*

	Insulin glargine		NPH (all regimens)		
	n (%)	Number of episodes	*n* (%)	Number of episodes	*P**
Symptomatic hypoglycemia					
Month 1	257/310 (82.9)	1,768	244/309 (79.0)	1,557	0.15
Month 2 to end	254/305 (83.3)	3,719	263/307 (85.7)	3,788	0.60
Entire phase	281/310 (90.6)	5,487	280/309 (90.6)	5,345	0.84
Nocturnal hypoglycemia					
Month 1	138/310 (44.5)	340	120/309 (38.8)	289	0.09
Month 2 to end	181/305 (59.3)	774	181/307 (59.0)	703	0.65
Entire phase	214/310 (69.0)	1,114	195/309 (63.1)	992	0.06
Severe hypoglycemia					
Month 1	8/310 (2.6)	9	4/309 (1.3)	4	0.23
Month 2 to end	16/305 (5.2)	20	14/307 (4.6)	16	0.67
Entire phase	20/310 (6.5)	29	60/309 (5.2)	20	0.44

**P* values were determined from the Cochran-Mantel-Haenszel test, comparing insulin glargine with NPH.

tory values or vital signs. No clinically relevant treatment-related electrocardiogram (ECG) changes were observed. Mean increase in body weight from baseline to end point was statistically significantly less among insulin glargine patients than among NPH insulin patients (0.12 vs. 0.54 kg, $P = 0.034$). However, the clinical relevance of this difference over the 16-week treatment period is not clear.

CONCLUSIONS — The results of this 16-week randomized open-label study indicate comparable effectiveness of once-a-day insulin glargine and once- or twice-a-day NPH insulin in maintaining glycemic control as reflected by GHb levels in patients with type 1 diabetes receiving multiple daily injections of basal insulin and premeal insulin lispro. No significant difference between the two treatment groups in changes from baseline levels of GHb was observed, with average levels of ~7.6% in both groups at the end of study. That reductions in GHb were small in both treatment groups is not surprising given the fairly good metabolic control in both groups before study treatment, evidenced by an average GHb value of ~7.7%. In the DCCT which examined intensive versus conventional insulin treatment in patients with type 1 diabetes, average GHb at the start of treatment was ~8.9%, with the level in the intensive therapy group decreasing to ~7.2% after 6 months of treatment (16). In fact, the same assay for GHb used in the DCCT was used in this study.

Both self-monitored fasting blood glucose and fasting plasma glucose levels were significantly reduced with insulin glargine compared with NPH insulin. In addition, a greater percentage of insulin glargine than NPH patients achieved a target fasting blood glucose level of <120.6 mg/dl (6.7 mmol/l). In adjusted mean values, insulin glargine patients exhibited a decrease in fasting blood glucose of 29.3 mg/dl (1.63 mmol/l) by the end of study, compared with a 11.9 mg/dl (0.66 mmol/l) reduction in the NPH insulin group. A significant decrease in fasting plasma glucose levels was evident in the first week in insulin glargine patients, and an adjusted mean reduction of 41.9 mg/dl (2.33 mmol/l) was seen by the end of the study, compared with a 12.4 mg/dl (0.69 mmol/l) reduction in the NPH insulin group.

These results were obtained despite lower daily doses of basal and total insulin in the insulin glargine group. The failure of this improvement in fasting glucose to produce differences in GHb is most likely due to higher glucose levels at other times of the day. The results suggest that the use of lispro with insulin glargine may not have been optimized during the study, and premeal doses of insulin lispro may not have been increased appropriately in these patients. However, there was less day-to-day variability in fasting blood glucose levels in the insulin glargine patients than in the NPH patients.

Despite the findings of similar or better glycemic control with insulin glargine, no significant differences in the occurrence of hypoglycemia were observed in this study. In an earlier study in type 1 diabetes, in which bedtime insulin glargine was compared with NPH insulin taken once or twice a day, there was a significant reduction in the occurrence of severe and nocturnal hypoglycemia with insulin glargine (17). In this study, insulin glargine was also associated with significantly lower fasting blood glucose levels compared with NPH insulin, although there was no difference in GHb levels. Insulin glargine would thus seem to offer an advantage over NPH insulin, at least in terms of the development of hypoglycemia.

Insulin glargine appears to be as safe as NPH insulin. The only difference in the safety profile of insulin glargine and NPH insulin was a disproportionate number of insulin glargine patients reporting pain at the injection site (19 vs. 1). This effect, which has been noted in previous studies of insulin glargine, may be related to the more acidic pH of insulin glargine or to a reporting bias introduced by the open-label design of the study. All injection site pain was assessed as mild in intensity and did not lead to discontinuation of study medication in any patient. The overall incidence of injection site reactions was similar for insulin glargine and NPH patients (13.2 vs. 10.4%). None of the treatment-related adverse events in the study, apart from

Table 4—*Treatment-related adverse events occurring in ≥2% of patients*

	Insulin glargine	NPH insulin
n	310	309
Total with adverse events	68 (21.9)	35 (11.3)
Severe hypoglycemic reaction	19 (6.1)	14 (4.5)
Injection site reactions		
Pain	19 (6.1)	1 (0.3)
Hemorrhage	10 (3.2)	13 (4.2)
Mass	7 (2.3)	7 (2.3)
Headache	7 (2.3)	0 (0.0)

Data are *n* (%).

hypoglycemic reactions, were considered serious. Treatment-related adverse events resulted in study withdrawal in none of the insulin glargine patients and one of the NPH insulin patients. There was no evidence of increased immunogenicity or systemic hypersensitivity reactions with insulin glargine administration. In fact, there was a suggestion of less immunogenicity because significant reductions in insulin antibodies occurred in the insulin glargine patients.

The finding that there was less variability in both self-monitored fasting blood glucose measurements and clinic-measured fasting plasma glucose levels requires some comment. The daily variability in the hypoglycemic effect of insulin, a common clinical feature of its use, is probably caused by unpredictable absorption from subcutaneous sites after injection (18). The finding that the use of insulin glargine results in a less variable effect on fasting glucose levels suggests that its absorption is more predictable than that of NPH insulin.

In summary, insulin glargine taken once a day appears to be as safe as and at least as effective as NPH insulin taken once or twice a day in maintaining glycemic control in patients with type 1 diabetes receiving basal-bolus insulin treatment. In particular, the self-monitored fasting blood glucose and fasting plasma glucose findings of this study suggest that insulin glargine may have the potential to provide better metabolic control when used with appropriate premeal bolus insulin therapy, with a similar risk of hypoglycemia as NPH insulin.

APPENDIX

Investigators and locations for multicenter clinical trials

Stephen Bookin, Portland, OR; Nancy J. Bohannon and Ilyas Iliya, San Francisco, CA; Raymond Fink, San Diego, CA; Satish K. Garg, Denver, CO; Richard A. Guthrie and Belinda Childs, Wichita, KS; Kenneth Hershon, New Hyde Park, NY; Irl B. Hirsch and Timothy Evans, Seattle, WA; Lois Jovanovic and Nancy Rikalo, Santa Barbara, CA; David Kayne, Encino, CA; Leslie Klaff, Renton, WA; Philip Raskin and Dan Lender, Dallas, TX; Julio Rosenstock, Dallas, TX; Sherwyn Schwartz, San Antonio, TX; Paul Tung, Dover, NH; Thomas C. Blevins, Austin, TX; Richard M. Bergenstal, Minneapolis, MN; Marshall B. Block, Phoenix, AZ; Cynthia Clinkingbeard and R. Christenson, Boise, ID; Ehud Ur, Halifax, Nova Scotia; Irving S. Gottesman, Mississauga, Ontario; Vasti L. Broadstone, Louisville, KT; Ronald Goldberg and Luigi F. Meneghini, Miami, FL; John I. Malone, Tampa, FL; Charles Clark and S. Edwin Fineberg, Indianapolis, IN; Andrew J. Drexler, New York, NY; Hertzel C. Gerstein, Hamilton, Ontario; Sheldon Berger, Chicago, IL; Martin Conway, Albuquerque, NM; John Ch'ng, Nashville, TN; Sergio Mather, Fort Myers, FL; Ronald K. Mayfield and Angela Taylor, Charleston, SC; Leann Olansky, Oklahoma City, OK; John B. Buse and Joseph Largay, Chapel Hill, NC; John Sheehan, Westlake, OH; David S.H. Bell, Birmingham, AL; John Stokes, Palm Harbor, FL; Richard O. Kamrath and Richard L. Weinstein, Walnut Creek, CA; Jackie See and M. Arthur Charles, Tustin, CA; Peter A. Lodewick, Birmingham, AL; Andre Belanger, Laval, Quebec; and Steven Kulback, Birmingham, AL.

References

1. Barnett AH, Owens DR: Insulin analogues. *Lancet* 349:47–51, 1997
2. Galloway JA, Chance RB: Improving insulin therapy: achievements and challenges. *Horm Metab Res* 26:591–598, 1994
3. Grau U: Insulin-Arg2, a new retardation principle based on a natural proinsulin-derived processing intermediate (Abstract). *Diabetes Res Clin Pract* 1:204, 1985
4. Jorgensen S, Vaag A, Langkjaer L, Hougard P, Markussen J: NovoSol Basal: pharmacokinetics of a novel soluble long-acting insulin analogue. *BMJ* 299:415–419, 1989
5. Zeuzem S, Stahl E, Jungmann E, Zoltobrocki M, Schoffling K, Caspary WF: In vitro activity of biosynthetic human diarginylinsulin. *Diabetologia* 33:65–71, 1990
6. Monti LD, Poma R, Caumo A, Stefani I, Picardi A, Sandoli EP, Zoltobrocki M, Micossi P, Pozza G: Intravenous infusion of diarginylinsulin, an insulin analogue: effects on glucose turnover and lipid levels in insulin-treated type II diabetic patients. *Metabolism* 41:540–544, 1992
7. Hilgenfeld R, Dorschug M, Geisen K, Neubauer H, Obermeier R, Seipke G, Berchtold H: Controlling insulin bioavailability by crystal contact engineering (Abstract). *Diabetologia* 35 (Suppl. 1):A193, 1992
8. Seipke G, Geisen K, Neubauer H-P, Pittius C, Rosskamp R, Schwabe D: New insulin preparations with prolonged action profiles: A21-modified arginine insulins (Abstract). *Diabetologia* 35 (Suppl. 1):A4, 1992
9. Seipke G, Berchthold H, Geisen K, Hilgenfeld R, Rosskamp R: HOE 901: a new insulin with prolonged action (Abstract). *Eur J Endocrinol* 132 (Suppl. 1):25, 1995
10. Lepore M, Kurzhals R, Pamjpanelli S, Fanelli CG, Bolli GB: Pharmacokinetics and dynamics of s.c. injection of the long-acting insulin glargine (HOE 901) in T1DM (Abstract). *Diabetes* 48 (Suppl. 1):A97, 1999
11. Talaulicar M, Willms B, Rosskamp R: Efficacy of HOE 901 following subcutaneous injection for four days in type I diabetic subjects (Abstract). *Diabetologia* 37 (Suppl. 1):A169, 1995
12. Rosenstock J, Park G, Zimmeman J, the U.S. Study Group of HOE 901 in Type I DM: Efficacy and safety of HOE 901 in patients with type I DM: a four-week randomized, NPH insulin-controlled trial (Abstract). *Diabetes* 47 (Suppl. 1):A92, 1998
13. Pieber T, Eugene-Jolchine I, Derobert E: Efficacy and safety of HOE 901 in patients with type 1 diabetes: a four-week randomised, NPH insulin-controlled trial (Abstract). *Diabetes* 47 (Suppl. 1):A62, 1998
14. Raskin P, Park G, Zimmerman J, for the U.S. Study Group of HOE 901 in Type 2 Diabetes Mellitus: The effect of HOE 901 on glycemic control in Type 2 diabetes. *Diabetes* 47 (Suppl. 1):A103, 1998
15. Aiello LM, Cavallerano J: Diabetic retinopathy. *Curr Ther Endocrinol Metab* 5:436–446, 1994
16. Diabetes Control and Complications Trial (DCCT) Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
17. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA, the U.S. Study Group of Insulin Glargine in Type I Diabetes: Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care* 23:639–643, 2000
18. Binder C, Lauritzen T, Faber O, Pramming S: Insulin pharmacokinetics. *Diabetes Care* 7:188–199, 1984