Less Nocturnal Hypoglycemia and Better Post-Dinner Glucose Control With Bedtime Insulin Glargine Compared With Bedtime NPH Insulin During Insulin Combination Therapy in Type 2 Diabetes

HANNELE YKI-JÄRVINEN, MD
ANSGAR DRESSLER, PHD
MONIKA ZIEMEN, MD
THE HOE 901/3002 STUDY GROUP

OBJECTIVE — Available basal insulin formulations do not provide a constant and reliable 24-h insulin supply. We compared the efficacy and safety of glargine (a long-acting insulin analog) and NPH insulins in insulin-naive type 2 diabetic patients treated with oral antidiabetic agents.

RESEARCH DESIGN AND METHODS — There were 426 type 2 diabetic patients (age 59 ± 9 years, BMI 28.9 ± 4.3 kg/m^2, mean ± SD) with poor glycemic control on oral antidiabetic agents randomized to treatment for 1 year with bedtime insulin glargine or bedtime NPH insulin. Oral agents were continued unchanged. The fasting blood glucose (FBG) target was 6.7 mmol/l (120 mg/dl).

RESULTS — Average glycemic control improved similarly with both insulins (HbA_{1c} [reference range <6.5%] 8.3 ± 0.1 vs. 8.2 ± 0.1% at 1 year, glargine vs. NPH, mean ± SEM, $P < 0.001$ vs. baseline for both). However, there was less nocturnal hypoglycemia (9.9 vs. 24.0% of all patients, glargine vs. NPH, $P < 0.001$) and lower post-dinner glucose concentrations (9.9 ± 0.2 vs. 10.7 ± 0.3 mmol/l, $P < 0.02$) with insulin glargine than with NPH. Insulin doses and weight gain were comparable. In patients reaching target FBG, HbA_{1c} averaged 7.7 and 7.6% in the glargine and NPH groups at 1 year.

CONCLUSIONS — Use of insulin glargine compared with NPH is associated with less nocturnal hypoglycemia and lower post-dinner glucose levels. These data are consistent with peakless and longer duration of action of insulin glargine compared with NPH. Achievement of acceptable average glucose control requires titration of the insulin dose to an FBG target ≤6.7 mmol/l. These data support use of insulin glargine instead of NPH in insulin combination regimens in type 2 diabetes.

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Previous controlled trials comparing various insulin regimens in patients with type 2 diabetes poorly controlled with oral agents have shown that the simple addition of NPH insulin at bedtime (1–3) or of 70/30 premixed insulin (70% NPH insulin/30% regular insulin) before supper (4) to previous treatment with sulfonylureas alone (3,2), sulfonylureas and metformin (1,3,5), or metformin alone (3) gives as good overall glycemic control than the use of several insulin injections (1,3,4,6,7). However, use of NPH insulin creates 2 problems. If NPH insulin is injected at bedtime in patients with type 2 diabetes, the greatest decrease in blood glucose is observed during the early morning hours, which is consistent with a peak in the action profile of NPH (1). This peak increases the frequency of nocturnal hypoglycemia and prevents adequate titration of the insulin dose, particularly when NPH is combined with glyburide (3). The other recognized problem with NPH is that its duration of action is too short to adequately control glucose around dinner time after an injection at bedtime the previous day (1). Another currently available basal insulin formulation is the once-daily long-acting crystalline human zinc insulin. However, one injection of long-acting insulin per day seems inferior to twice-daily NPH with respect to the rate of hypoglycemia, glycemic control, and treatment satisfaction (8). Also, the variability of absorption from subcutaneous tissue is high with long-acting crystalline human zinc insulin (9).

Insulin glargine is a human insulin analog produced with recombinant DNA technology with the addition of 2 basic amino acids (arginine) to the B-chain and a substitution of asparagine with glycine in position A21 in the insulin molecule. These changes result in a shift of the isoelectric point from 5.4 in native insulin toward a pH of 7.0 in insulin glargine. As a result, insulin glargine precipitates at physiological pH in subcutaneous tissue after injection, which delays its absorption. Addition of zinc to stabilize interhexamer contacts further prolongs the activity of this analog. Studies in healthy volunteers have indicated that insulin glargine indeed has a smooth peakless profile of action that is required from a basal insulin injected once daily (10). However, the possible clinical benefits of insulin glargine compared with other currently

From the Department of Medicine (H.Y.-J.), Division of Diabetes, University of Helsinki, Helsinki, Finland; and Hoechst Marion Roussel Deutschland Clinical Development (A.D., M.Z.), Frankfurt, Germany.

Address correspondence and reprint requests to Hannele Yki-Järvinen, MD, University of Helsinki, Department of Medicine, Division of Diabetes, Haartmaninkatu 4, P.O. Box 340, 00029 HUCH, Helsinki, Finland. E-mail: ykijarvi@helsinki.fi.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCCT, Diabetes Control and Complications Trial; FBG, fasting blood glucose.

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

available basal insulins in the treatment of type 2 diabetic patients with insulin and oral antidiabetic agents are still lacking.

This phase III clinical trial was undertaken to evaluate the efficacy and safety of insulin glargine compared with NPH insulin—currently, the most widely used basal insulin—in patients with type 2 diabetes who had poor glycemic control when using oral antidiabetic agents.

RESEARCH DESIGN AND METHODS

Design

The study protocol consisted of a 4-week screening phase and a 52-week treatment phase. Inclusion criteria were as follows: men or women age 40–80 years with BMI <40 kg/m^2, HbA_{1c} between 7.5 and 12.0% (reference range $<6.5\%$), duration of diabetes of at least 3 years, previous oral therapy with either sulfonylureas alone or combined with acarbose, metformin, or metformin alone for at least 1 year. Another arm of the protocol randomized patients who had been previously treated with a combination regimen consisting of insulin once daily plus oral antidiabetic drugs, but data on these subjects (a total of 144 randomized and treated, i.e., 25% of the total study population) are not included in this article. Additional inclusion criteria were as follows: negative history of ketoacidosis was required, women of childbearing potential were to be using adequate contraceptive protection, and an ability and willingness to perform blood glucose profiles using a blood glucose meter at home was needed, as evidenced by a complete 8-point blood glucose profile obtained over a single 24-h period during the screening phase. Exclusion criteria were as follows: pregnancy; treatment with regular insulin in the last 4 weeks before the screening visit; diabetic retinopathy with surgical treatment in the 3 months before study entry or requiring treatment within 3 months of study entry; likelihood of requiring treatment during the study period with drugs not permitted by the clinical study protocol; being a night shift worker; treatment with any investigational drug in the last 2 months before study entry; clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic diseases that would make implementation of the clinical study protocol or interpretation of the study results difficult; history of drug or alcohol abuse; impaired hepatic function, as shown by but not limited to alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than twice the upper limit measured at visit 1; impaired renal function, as shown by but not limited to serum creatinine >133 μmol/l (>1.5 mg/dl) measured at visit 1; a mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study; evidence of an uncooperative attitude; or inability to attend follow-up visits. At each center, the patients gave written informed consent to participate in the study, which was approved by the respective ethical committees for human investigation.

Visit 1 and screening phase

At the visit 4 weeks before the start of the study, the patient's medical history was recorded, a physical examination was performed, entry criteria were reviewed, and blood was withdrawn to determine serum creatinine, AST, ALT, and HbA_{1c} concentrations. During the screening phase, the subjects continued their previous antidiabetic treatment. The subjects were familiarized with the use of an insulin pen (OptiPen; Hoechst Marion Roussel) and a blood glucose meter (OneTouch II; LifeScan, Milpitas, CA) for the determination of blood glucose at home. To practice self-monitoring of blood glucose, the subjects were asked to measure fasting blood glucose (FBG) on 7 consecutive days immediately preceding and on the day of the next visit (0 weeks) and to provide a 24-h blood glucose profile. The latter consisted of measurements of blood glucose before and 2 h after breakfast, lunch, and dinner, and at bedtime and 3:00 A.M. The patients were asked to record the occurrence of hypoglycemic symptoms daily. An ophthalmologic examination and fundus photography were performed during the screening phase.

Randomization

At the end of the screening phase, once it had been established that a subject met the inclusion criteria, the investigators telephoned an independent agency (CLINDATA [Clinical Data Management]) and supplied basic demographic details relating to the subject (subject number, birth date, sex, HbA_{1c}, and previous treatment). In accordance with the randomization schedule held by the agency, the investigator was informed about the study medication the subject was to receive and the randomization number of the subject.

Treatment phase (52 weeks)

During the treatment phase, the patients visited the treatment center at 8, 20, 36, and 52 weeks in the morning before eating breakfast. At these visits, fasting blood was withdrawn for measurement of fasting serum insulin and C-peptide, FPG, HbA_{1c}, full hematology and clinical chemistry (complete blood count, creatinine, AST, ALT, alkaline phosphatase, γ-GT, total bilirubin, sodium, potassium, total and HDL cholesterol, and triglycerides), antibodies against glargine, and human insulins. In addition, body weight and vital signs were recorded, results of home glucose monitoring were checked (vide infra), adverse events and injection site reactions (if any) were recorded, and study medication was dispensed. Before the treatment phase visits, the patients were asked to perform home glucose monitoring as described above for the 0-week visit (visit 2). Telephone visits were scheduled if needed at 1, 2, 4, 6, 12, 28, and 44 weeks.

During the treatment phase, either insulin glargine or NPH human insulin was administered in an individually titrated dose by subcutaneous injection once daily at bedtime. The insulin glargine formulation was a cartridge containing 3 ml of an insulin glargine solution at a concentration of 100 U/ml. The formulation contained 30 μg/ml zinc. The NPH human insulin formulation was a semisynthetic human insulin/biosynthetic human insulin in a cartridge containing 3 ml of a suspension with a concentration of 100 U/ml. Treatment was started at week 0. The dose of insulin glargine or NPH human insulin injected on the first treatment day was left to the discretion of the investigator. Insulin dose adjustments during the treatment phase were also left to the discretion of the investigator. However, if possible, the insulin dose was to be adjusted in such a way that an FBG target of ≤ 6.7 mmol/l (120 mg/dl) was achieved. Doses of oral agents were maintained unchanged. Subjects were instructed to return their study medication and the insulin pen, together with the cartridge in use and any empty cartridges, to the investigation site at every visit. Compliance was assessed by inspection and counting of the study medication cartridges.

Analytical methods

FBG and 24-h blood glucose were measured by home glucose monitoring using OneTouch II LifeScan blood glucose meter. HbA_{1c} was measured using boronate affin-

Table 1—*Percentage of subjects with end point data at 52 weeks*

Variable	Percentage of subjects	
	Insulin glargine	NPH
HbA_{1c}	89.2	83.3
Change in 24-h blood glucose profile	97.3	95.1
Change in nocturnal glucose	93.7	90.7
Symptomatic hypoglycemia	98.2	95.1

ity high-performance liquid chromatography (Primus CLC330; Primus, Kansas City, MO; reference range 5.1–6.4%). This method is certified by the National Glycohemoglobin Standardization Program and is similar to the Diabetes Control and Complications Trial (DCCT) HbA_{1c} results (www.web.missouri.edu/~diabetes/ngsp/). Fasting serum C-peptide and plasma glucose concentrations were measured using a commercially available radioimmunoassay (C-peptide RIA; BioChem ImmunoSystems, Freiburg, Germany) with slight modifications. Hematology, clinical chemistry analyses, and pregnancy tests were carried out according to standard laboratory procedures at the Covance Central Laboratory (Geneva, Switzerland). Insulin antibodies to glargine and human insulins were determined using a semiquantitative assay from binding of iodinated insulin tracers ^{125}I-labeled HOE 901 and ^{125}I-labeled human insulin to identical serum samples with an assay developed and validated by Hoechst Marion Roussel (document number 016593, addendum document number 017553). Because of cross-reactivity of human insulin antibodies with HOE 901 tracer and HOE 901 antibodies with the human insulin tracer, all samples were assayed with both tracers.

Data analysis

The primary efficacy assessment was HbA_{1c}. Secondary efficacy assessments were fasting blood or plasma glucose, 24-h blood glucose profile, incidence of hypoglycemia, and serum C-peptide concentrations. Hypoglycemia was categorized as symptomatic if clinical symptoms were confirmed by measurement of a blood glucose value <2.8 mmol/l (50 mg/dl) or as asymptomatic in the case of any event without symptoms but with a confirmed blood glucose level <2.8 mmol/l (50 mg/dl). Severe hypoglycemia was defined according to the DCCT (11) as an event with symptoms consistent with hypoglycemia for which the subject required assistance of another person and that was associated with a blood glucose level <2.8 mmol/l or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. Nocturnal hypoglycemia was defined as hypoglycemia occurring while the subject was asleep between the evening injection and getting up in the morning, i.e., before the morning determination of FBG. Safety was assessed on the basis of hematology and clinical chemistry findings (data not shown), an analysis of adverse events, determination of *Escherichia coli* antibodies (data not shown) and insulin antibodies, ophthalmologic examination, and 7-standard field fundus photography (data not shown).

Data review and analysis planning were performed independent of treatment assignments and before database closure. For the efficacy analyses listed above, the change in a given parameter from baseline to study end point was investigated. An analysis of covariance was performed using the change from baseline to end point as the dependent variable, with treatment and (pooled) center as fixed effects and corresponding baseline value as a covariate. End point was defined as the last measurement available during the treatment phase. Data in the text represent end point values. The end point value was essentially identical to the 52-week value for all data because complete data were available for a high proportion of the subjects (Table 1). In the figures, data available from each time point are shown. Rates of hypoglycemia were compared between treatment groups using rank analysis of variance. Assessment of the treatment effect was performed by comparing insulin glargine to NPH. The insulin-naive and previously insulin-treated (not included in the present article) groups were analyzed separately. Analysis was by intention-to-treat for all efficacy variables except for hypoglycemia and analysis of antibodies, lipids, and vital signs. All statistical tests were 2-sided and performed at a significance level of α = 5%, unless stated otherwise. All analyses

Table 2—*Baseline clinical and biochemical characteristics of the study groups*

	Insulin glargine plus OAD (all patients)	NPH plus OAD (all patients)	Insulin glargine plus OAD (FBG ≤6.7 mmol/l)	NPH plus OAD (FBG ≤6.7 mmol/l)
n	214	208	87	73
Age (years)	59 ± 1	59 ± 1	62 ± 1	61 ± 1
Duration of diabetes (years)	10 ± 1	10 ± 1	10 ± 1	10 ± 1
Sex (% male)	55	53	55	52
BMI (kg/m^2)	29.3 ± 0.3	28.5 ± 0.3	28.4 ± 0.5	27.6 ± 0.5
HbA_{1c} (%)	9.1 ± 0.1	8.9 ± 0.1	8.9 ± 0.1	8.6 ± 0.1
Fasting serum C-peptide (nmol/l)	0.98 ± 0.04	0.93 ± 0.03	0.94 ± 0.06	0.88 ± 0.05
Serum triglycerides (mmol/l)	2.4 ± 0.2	2.3 ± 0.2	2.1 ± 0.2	2.1 ± 0.2
Serum HDL cholesterol (mmol/l)	1.23 ± 0.02	1.22 ± 0.02	1.27 ± 0.03	1.25 ± 0.04
Serum total cholesterol (mmol/l)	5.6 ± 0.1	5.6 ± 0.1	5.4 ± 0.1	5.6 ± 0.1
Systolic/diastolic blood pressure (mmHg)	145 ± 1/84 ± 1	145 ± 1/85 ± 1	146 ± 2/83 ± 1	145 ± 3/83 ± 1

Data are *n* or means ± SEM. OAD, oral antidiabetic drugs.

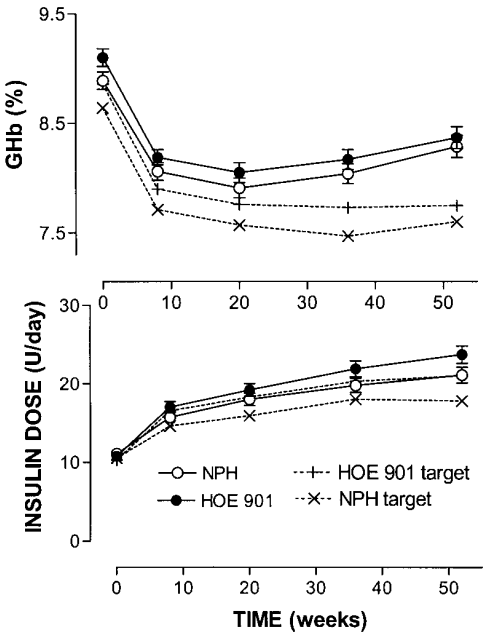

Figure 1—*HbA_{1c} concentrations and insulin doses in patients treated with insulin glargine (HOE 901) and NPH insulin (NPH). The patients who reached the target FBG (≤6.7 mmol/l [120 mg/dl]) are indicated with dotted lines.*

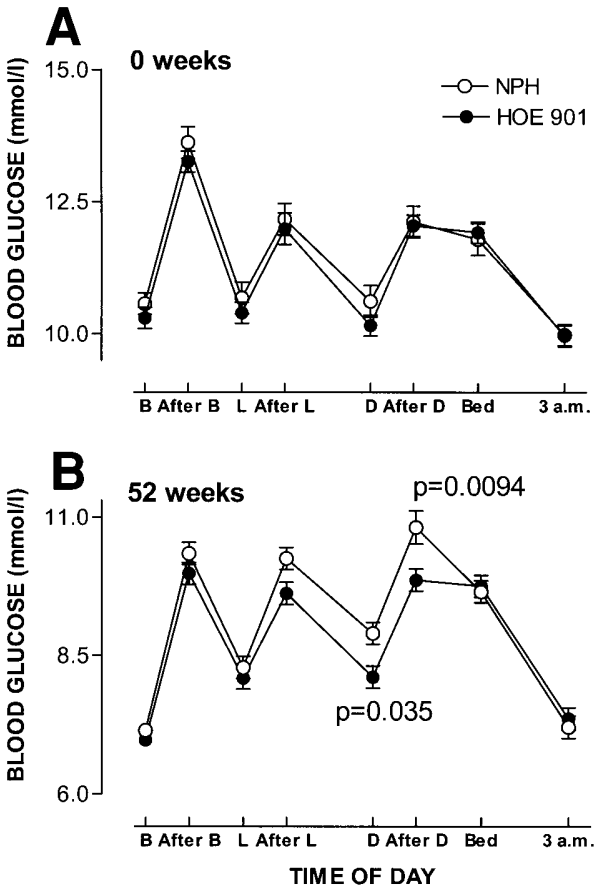

Figure 2—*Diurnal blood glucose profile measured at baseline (*A*, 0 weeks) and before the last visit (*B*, 52 weeks) in the insulin glargine (HOE 901) and NPH insulin (NPH) groups. B, breakfast; Bed, bedtime; D, dinner; L, lunch.*

were carried out using SAS version 6.12 run under the Unix operating system. Results are expressed as means ± SEM.

RESULTS

Baseline characteristics of study groups

Clinical and biochemical characteristics of the entire study group and of patients achieving the target FBG of 6.7 mmol/l are shown in Table 2.

Insulin doses and serum C-peptide concentrations

Initial doses of insulin were comparable in both groups (Fig. 1). At the end point, the average dose of insulin glargine was 23 ± 1 U/day (0.27 ± 0.01 U · kg^{-1} · day^{-1}), and the average dose of NPH was 21 ± 1 U/day (0.25 ± 0.01 U · kg^{-1} · day^{-1}) (NS) (Fig. 1). Serum C-peptide concentrations were comparable between the groups at baseline (Table 2) . During the treatment period, serum C-peptide concentrations decreased similarly in both groups ($P < 0.001$ for change at end point vs. baseline) and averaged 0.81 ± 0.03 nmol/l with insulin glargine and 0.78 ± 0.03 nmol/l with NPH (NS). Injection times were comparable for insulin glargine and NPH insulin, with 71 and 72% of the insulin glargine– and NPH-treated patients, respectively, injecting between 9:00 and 11:00 P.M. and the rest slightly before or after these times.

Glycemic control

HbA_{1c}. In the insulin glargine group, HbA_{1c} decreased to 8.34 ± 0.09% at end point ($P < 0.001$ vs. baseline) and in the NPH group to 8.24 ± 0.09% ($P < 0.001$ vs. baseline, Fig. 1). In patients achieving target FBG after 52 weeks in the insulin glargine group, HbA_{1c} decreased to 7.75 ± 0.14% and in the NPH group to 7.60 ± 0.12%, with no difference between the groups (Fig. 1).

Diurnal glucose profile. At baseline, diurnal glucose concentrations were comparable in the insulin glargine and NPH groups (Fig. 2*A*). At the end point, blood glucose concentrations were significantly lower in the insulin glargine group than the NPH group both before and after dinner (Fig. 2). This difference could be discerned in both patients who achieved the target and in those who didn't (Fig. 3). In the patients who achieved target FBG after 52 weeks, blood glucose at 3:00 A.M. was significantly lower in patients using NPH (5.6 ± 0.2 mmol/l, $n = 66$) than in those using insulin

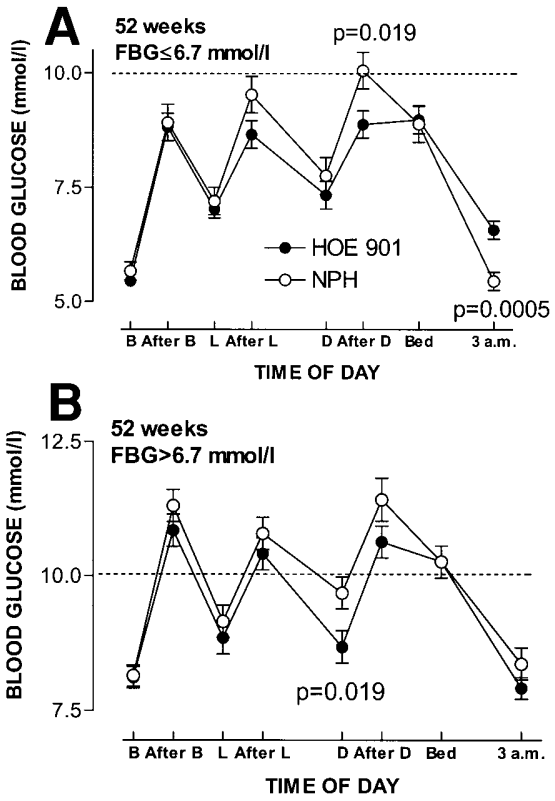

Figure 3—*Diurnal blood glucose profile in patients reaching the FBG target of ≤6.7 mmol/l (120 mg/dl) (*A*, 0 weeks) and in patients not reaching the FBG target (*B*) treated with insulin glargine (HOE 901) and NPH insulin (NPH). B, breakfast; Bed, bedtime; D, dinner; L, lunch.*

glargine (6.6 ± 0.2 mmol/l, $P = 0.0012$, n = 83, Fig. 3). In the entire group (Fig. 2), glucose at end point at 3:00 A.M. was similar in the insulin glargine (7.4 ± 0.2 mmol/l, n = 208) and NPH (7.3 ± 0.2 mmol/l, n = 185, Fig. 2) groups. In the patients not achieving target (Fig. 3), blood glucose averaged 8.0 ± 0.2 in the insulin glargine group (n = 104) and 8.4 ± 0.2 mmol/l (n = 96) in the NPH group at 3:00 A.M.

Hypoglycemia. In the entire group, the percentage of patients experiencing at least 1 symptomatic hypoglycemic episode (all hypoglycemia) was significantly lower in the insulin glargine group than the NPH group (Fig. 4). This difference was due to a significantly lower percentage of patients experiencing symptomatic hypoglycemia during the night in the insulin glargine group than in the NPH group (Fig. 4). In patients who achieved the FBG target, a lower percentage of insulin glargine patients (33.0%) experienced symptomatic hypoglycemia than NPH patients (50.7%, $P = 0.027$). The frequency of nocturnal hypoglycemia was significantly lower in the insulin glargine patients, both in patients reaching the FBG target (12.6% insulin glargine vs. 28.8% NPH, $P = 0.011$) and in those who didn't (9.0% insulin glargine vs. 21.4% NPH, $P = 0.012$).

Changes in body weight, blood pressure, and lipids

Weight gain during the entire treatment period was similar in both groups and averaged 2.57 ± 0.23 kg in the insulin glargine group and 2.34 ± 0.23 kg in the NPH group. Blood pressure remained unchanged compared with baseline (Table 2) in both groups and averaged 145 ± 1/83 ± 1 mmHg in the insulin glargine and 145 ± 1/82 ± 1 mmHg in the NPH group. At the end point, LDL cholesterol averaged 3.21 ± 0.06 mmol/l in the insulin glargine group and 3.27 ± 0.08 mmol/l in the NPH group. HDL cholesterol averaged 1.23 ± 0.02 mmol/l in the insulin glargine group and 1.25 ± 0.02 mmol/l in the NPH group, and serum triglycerides 2.18 ± 0.12 and 2.29 ± 0.14 mmol/l, respectively, with no difference between the groups.

Antibodies against insulin glargine, human insulin, and *E. coli* protein

Antibodies against insulin glargine and NPH insulin were determined in both groups. Antibodies against both insulins were less prevalent in patients treated with insulin glargine compared with NPH insulin (Fig. 5).

Side effects

There was no difference in the frequency of clinically noteworthy abnormal laboratory values between the insulin glargine and NPH groups (data not shown). During the treatment phase, there was no difference in treatment-emergent adverse events possibly related to study medication (data not shown), except for the frequency of hypoglycemia (vide supra).

CONCLUSIONS — We tested the potential clinical benefits of the long-acting insulin analog insulin glargine. This insulin was predicted, based on time-action studies

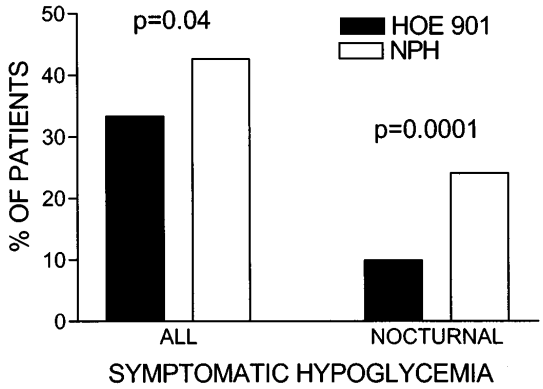

Figure 4—*The percentage of patients treated with insulin glargine (HOE 901) and NPH insulin (NPH) with symptomatic hypoglycemia during the entire treatment period. ALL, all symptomatic hypoglycemia; NOCTURNAL, nocturnal hypoglycemia.*

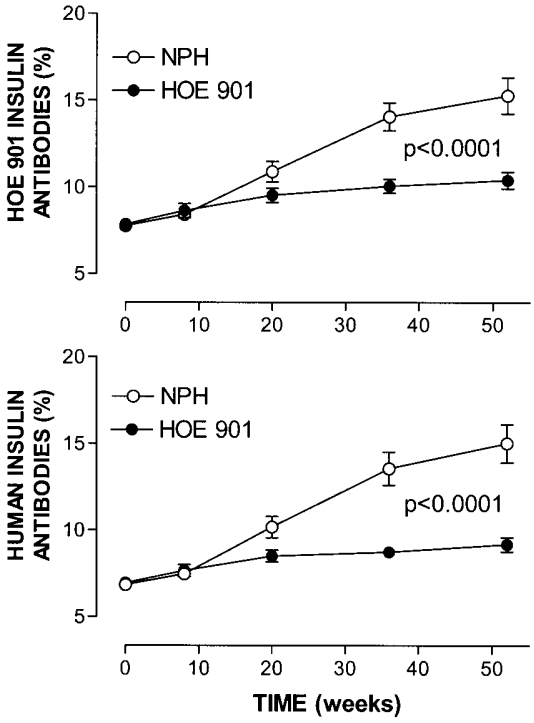

Figure 5—*Antibodies against insulin glargine (HOE 901) and human insulin in patients treated with HOE 901 and NPH insulin (NPH). The* P *values denote the significance of difference between the 2 treatment groups.*

performed using the euglycemic clamp technique in healthy subjects (10), to lack the typical peak of action observed during the early morning hours after injection of NPH insulin at bedtime and to act longer than NPH insulin. Both of these expectations were fulfilled. Patients treated with insulin glargine combination therapy had significantly less nocturnal hypoglycemia and lower post-dinner glucose levels than those treated with NPH insulin and oral agents in the face of similar overall glycemic control.

The FBG target was set at 6.7 mmol/l (120 mg/dl). This target was considered to be safe in a phase III study examining safety and efficacy of a new insulin preparation. In retrospect, this target was too conservative. It was higher than that which was recently found to be safe during comparison of combination therapy regimens using NPH insulin (6.0 mmol/l or 108 mg/dl) (3). The patients who achieved the target HbA_{1c} (FBG $\leq$6.7 mmol/l) averaged 7.7% in the insulin glargine and 7.6% in the NPH group (NS) and had FBG levels of 5.4 and 5.7 mmol/l (NS), respectively (Fig. 3*A*). No severe hypoglycemia occurred in any patient. Considering that less hypoglycemia was observed in the insulin glargine group than the NPH group, these data suggest that the target FBG can be lower for insulin glargine than for NPH.

A smaller percentage of patients experienced symptomatic hypoglycemia with insulin glargine than with NPH. This result is expected in light of the differences in the time-action profile of the 2 insulins. Thus, whereas NPH acts maximally during the early morning hours after a bedtime injection, insulin glargine has a peakless action profile (10). However, one would have also expected to observe a significantly lower nocturnal glucose concentration in the entire insulin glargine group compared with the NPH group, but such a difference was only observed in the patients who achieved target FBG after 52 weeks (Fig. 3). In these patients, the lack of difference in overall glycemia can logically be attributed to the combined effects of lower nocturnal glucose concentrations and higher post-dinner glucose concentrations in the NPH group compared with the insulin glargine group. In patients who did not achieve target FBG, glucose concentrations were significantly lower before dinner in the insulin glargine group compared with the NPH group, and there was no difference in the nocturnal values between the 2 groups. These data are discordant with the HbA_{1c} data. Possibly, the significant difference in the pre-dinner glucose concentrations was not sufficient to change overall glucose control, or the glucose measured at 3:00 A.M. in the NPH group did not represent the nadir in nocturnal glucose concentrations.

HOE 901 was less immunogenic than NPH insulin (Fig. 5). This difference did not, however, result in an insulin-sparing effect or in differences in glycemic control in the face of similar insulin doses. Whether the lack of a clinical sequela of insulin antibodies was due to the fact that an in vitro assay might not adequately reflect the impact of antibodies on insulin bioavailability in vivo or whether insulin antibodies do not limit insulin action cannot be determined based on the present data. The clinical significance of insulin antibodies thus remains controversial (12). One possibility would be that changes in endogenous insulin secretion might act to buffer insulin antibody-induced changes in insulin bioavailability. The similar decreases in serum C-peptide concentrations in both groups provides evidence against this possibility.

Both NPH and glargine insulins were injected at bedtime. Because variability of fasting glucose concentrations is less than that of post-meal glucose levels and because it is more convenient for most patients to monitor fasting rather than pre-dinner or post-dinner glucose concentrations, FBG could be recommended as an appropriate target according to which the basal insulin dose should be titrated. In the present study, the insulin dose titration was mostly done in the treatment center. In practice, unless visits to the treatment center are frequent, dose titration remains inadequate. The best alternative would be to teach the patient to not only self-monitor FBG concentrations but also to self-adjust the insulin dose, as was recently done successfully in another multicenter study (3).

In conclusion, use of insulin glargine during insulin combination therapy in patients with type 2 diabetes offers some advantages compared with NPH insulin. Its use is associated with less nocturnal hypoglycemia and better glycemic control after dinner. Given that 6.0 mmol/l is a safe FBG target for NPH insulin (3) and that insulin glargine induces less hypoglycemia than NPH insulin, the FBG target can be even lower than that for NPH. Because interindividual variation in insulin requirements is large, insulin dose titration is unlikely to be successful unless the patient is taught to

self-adjust the insulin dose. This result requires at least initially frequent contacts.

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APPENDIX

The European Study Group of Insulin Glargine in Type 2 Diabetes

The following individuals and their site personnel participated in the European study group of HOE 901 in type 1 diabetes. Austria: H. Drexel, G. Biesenbach, G. Kazerovsky-Bielesz, R. Prager, G. Schernthaner, F. Winkler, A. Luiskandl. Switzerland: R. Gaillard. Croatia: V. Profozic. Slovenia: F. Mrevlje. Czech Republic: A. Smahelova. Denmark: S.N. Holmegaard, K. Kolendorf, A. Prange, J. Rungby, K. Clemmensen. Finland: S. Bergkulla, J. Salmi, J. Saltevo, H. Yki-Järvinen. Germany: E. Austenat, V. Guentsch, M. Haslbeck, N. Lotz, K.O. Palitzsch, K.G. Petersen, C. Rosak, B. Schulze-Schleppinghoff, C. Jarusch-Hancke. Italy: R. Giorgino, M. Massi-Benedetti, I. Testa. Great Britain: J. Anderson, L.J. Borthwick, D. Owens, R.S. Gray. Norway: S. Vaaler, B. Mella. South Africa: L.A. Distiller, L.I. Robertson, J. Wing, R. Moore, W. Lourens, M. Seeber. Spain: R. Gomis, A. Sanmarti. Sweden: P. Arner, H. Arnqvist, K. Stenberg, A. Tenerz, A. Wajngot. The Netherlands: P. Biemond, E.J.K. Zweers, L.G. van Doorn, W. Bronsveld (principle investigator), W. Schouten (coinvestigator).

References

1. Yki-Järvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L, Rajala S, Ryysy L, Salo S, Seppälä P, Tulokas T, Viikari J, Karjalainen J, Taskinen M-R: Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 327:1426–1433, 1992
2. Wolffenbuttel BH, Sels JP, Rondas-Colbers GJ, Menheere PP, Nieuwenhuijzen KA: Comparison of different insulin regimens in elderly patients with NIDDM. *Diabetes Care* 19:1326–1332, 1996
3. Yki-Järvinen H, Ryysy L, Nikkilä K, Tulokas T, Vanamo R, Heikkilä M: Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 130:389–396, 1999
4. Riddle MC, Schneider J, the Glimepiride Combination Group: Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone. *Diabetes Care* 21:1052–1057, 1998
5. Chow C-C, Tsang LWW, Sorensen JP, Cockram CS: Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients. *Diabetes Care* 18:307–314, 1995
6. Peters AL, Davidson MB: Insulin plus a sulfonylurea agent for treating type 2 diabetes. *Ann Intern Med* 115:45–53, 1991
7. Pugh JA, Wagner ML, Sawyer J, Ramirez G, Tuley M, Friedberg SJ: Is combination sulfonylurea and insulin therapy useful in NIDDM patients? *Diabetes Care* 15:953–959, 1992
8. Taylor R, Davies R, Fox C, Sampson M, Weaver J, Wood L: Optimal insulin treatment for type 2 diabetes: a multicentre, randomized crossover study (Abstract). *Diabetes* 48 (Suppl. 1):A112, 1999
9. Binder C, Lauritzen T, Faber O, Pramming S: Insulin pharmacokinetics. *Diabetes Care* 7:188–199, 1984
10. Bolli GB, Di Marchi RD, Park GD, Pramming S, Koivisto VA: Insulin analogues and their potential in the management of diabetes mellitus. *Diabetologia* 42:1151–1167, 1999
11. The Diabetes Control and Complications Trial 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
12. Asplin CM, Hartog M, Goldie DJ: The relationship between circulating free and bound insulin, insulin antibodies, insulin dosage and diabetic control in insulin treated diabetics. *Acta Endocrinol (Copenh)* 87:330–338, 1978