DM

Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in Type 2 diabetic patients

HOE 901/2004 Study Investigators Group[1]

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Abstract

Aims A European, randomized, 29-centre, open-label study compared the safety and efficacy of two formulations of insulin glargine and neutral protamine Hagedorn (NPH) human insulin, in combination with oral agents, in patients with Type 2 diabetes mellitus (DM).

Methods Two-hundred-and-four patients with Type 2 DM, in whom oral treatment alone was inadequate, were randomized to insulin glargine with 30 μg/ml zinc [insulin glargine (30)], or insulin glargine with 80 μg/ml zinc [insulin glargine (80)] or NPH insulin subcutaneously once daily. Insulin was titrated to aim for fasting blood glucose (FBG) values between 4 and 7 mmol/l. All participants received oral therapy during the 3-week titration phase and 1-week maintenance phase of the trial.

Results No differences between treatment groups were observed in adjusted mean fasting plasma glucose; significant decreases of 3.4 mmol/l, 3.5 mmol/l and 3.1 mmol/l were observed within the insulin glargine (30), insulin glargine (80) and NPH insulin groups, respectively ($P < 0.0001$ in each case). No differences between groups, but significant changes within groups, were observed in self-monitored FBG, mean FBG, blood glucose profile, stability of FBG, nocturnal blood glucose, fasting serum C-peptide, non-esterified fatty acids, haemoglobin A_{1c}, fructosamine and fasting serum insulin. A significantly greater proportion of NPH insulin patients experienced symptomatic nocturnal hypoglycaemia (19.1 NPH group vs. 7.3% glargine groups; $P = 0.0123$). Both insulins were well tolerated; one patient in each group experienced an injection site reaction.

Conclusions Insulin glargine is as safe and effective as NPH insulin given once daily and in this study caused fewer episodes of nocturnal hypoglycaemia.

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Keywords HOE 901, insulin glargine, NPH insulin, recombinant insulin analogue, Type 2 diabetes mellitus

Abbreviations ANCOVA, analysis of covariance; ANOVA, analysis of variance; DM, diabetes mellitus; FBG, fasting blood glucose; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; NPH, Neutral Protamine Hagedorn; SC, subcutaneous

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Introduction

Effective glycaemic control plays an important role in preventing chronic complications of diabetes mellitus (DM) [1]. However, available insulin products are still sub-optimal [2,3]. Intermediate- and long-acting insulins have been developed for once-daily administration through complexing with protamine [Neutral Protamine Hagedorn (NPH) insulin] or zinc (lente and ultralente insulins) to delay absorption. However, these products are still associated with excessive rates of hypoglycaemia because of pronounced peaks after injection, a duration of action that is too short to maintain glycaemic control with once-daily injection, or high variability of absorption [4,5].

Recombinant DNA technology has permitted the design of insulin analogues intended to improve glycaemic control [2]. These have included long-acting analogues with delayed absorption characteristics and protracted duration of action, although restricted bioavailability of some of these agents has limited their clinical potential [6–9]. Insulin glargine (HOE 901, 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin) is a novel human insulin analogue that exhibits increased bioavailability and prolonged duration of action in association with a modified isoelectric point, resulting in precipitation at neutral tissue pH and consequent delayed absorption [10–12]. In crystallography studies, an increase was observed in the intramolecular bonding of the insulin hexamer [10]. When insulin glargine is injected as a clear solution of pH 4.0, it forms a microprecipitate in the physiological pH of the subcutaneous (SC) space. When the insulin hexamer and higher aggregates are stabilized, the nature of the precipitate and the rate of its dissolution and absorption from the injection site are affected. Insulin glargine therefore has a delayed and prolonged absorption from the SC injection site.

Studies of insulin glargine in animals have indicated a protracted action profile compared with NPH insulin [11,12]; studies in healthy human subjects have indicated a flat insulin profile with no peaks, in contrast to the early insulin peak and return to pre-injection values observed with NPH insulin [13]. Early clinical trials in patients with Type 1 DM indicated the suitability of insulin glargine for use as a basal insulin [14]. The addition of zinc as a hexamer-stabilizing agent was found to delay onset and further increase the duration of action of insulin glargine.

In the current study, we compared treatment with insulin glargine and NPH insulin. We assessed the effects of two formulations of insulin glargine, which differed only in their zinc content (30 or 80 μg/ml) vs. NPH insulin in patients with Type 2 DM in whom oral hypoglycaemic agents resulted in inadequate glycaemic control.

Patients and methods

The study was a 4-week, randomized, open-label, parallel group-controlled trial of the safety and efficacy of two insulin glargine formulations compared with NPH insulin in patients with Type 2 DM. All patients were receiving oral treatment (maximal doses of an oral sulphonylurea alone or in combination with metformin/acarbose for at least 3 months) that resulted in inadequate glycaemic control. The two insulin glargine formulations, insulin glargine (30) and insulin glargine (80), differed only in their zinc content: 30 and 80 μg/ml, respectively.

A total of 256 patients were enrolled at 29 centres in Europe and South Africa. All patients gave informed consent to participate in the trial, which conformed to the guidelines of the Declarations of Helsinki (1975 and 1983). All participants were 40–80 years of age and had a haemoglobin A_{1c} (HbA_{1c}) level of 7.0% or greater and a body mass index of 21–35 kg/m^2 at baseline. None of the patients had received prior insulin treatment. Thirty-seven per cent were on sulphonylurea monotherapy (predominantly glibenclamide), 55% on sulphonylurea plus biguanide, and 8% on acarbose with other therapy. After a 2-week screening period, the patients were randomized in a double-blind fashion to either insulin glargine (30) or insulin glargine (80) (Hoechst AG, Frankfurt, Germany) or in an open fashion to NPH insulin (Hoechst AG, Frankfurt, Germany) for 4 weeks. Randomization was performed centrally by telephone by an independent company (CLINDATA GmbH, Weilerswist, Germany) to prevent possible bias in assigning study medication to subjects by the investigators. Patients were allocated and data analysed on an intention-to-treat basis. The protocol included a 3-week titration phase and a 1-week maintenance phase. There were a total of five visits: screening, baseline and three visits during treatment. Patients continued to take their existing oral treatment regimen during the study, and were asked not to vary their usual diet.

All three insulin formulations were supplied in 3-ml cartridges, with an individually titrated single dose given by SC abdominal injection at bedtime using the OptiPen insulin injection device. One-millilitre solutions of insulin glargine (30) and insulin glargine (80) contain recombinant human insulin analogue equimolar to 100 U human insulin; a 1-ml suspension of NPH insulin contains 100 U semi-synthetic human insulin. During the titration phase, basal insulin doses were adjusted to achieve fasting blood glucose (FBG) values between 4 and 7 mmol/l; the dose was increased if higher values were obtained in the absence of nocturnal hypoglycaemia. Dose increases were at least 10% of the total daily basal insulin dose and were not implemented more frequently than every 2 days. Patients were asked to record changes, and these were verified and documented at clinic visits. During both the titration and the maintenance phases, the basal insulin dose was reduced if FBG was less than 4 mmol/l and/or if nocturnal hypoglycaemia occurred.

Efficacy

The primary efficacy variable was fasting plasma glucose (FPG). FPG levels were measured from samples collected at the beginning of the screening period, at the beginning of the dose-titration period, and at the final clinic visit after the maintenance period. Fasting blood glucose was measured daily, the 03.00 h value was assessed at least five times and the blood glucose profile five times. These values were used to assess

secondary variables: FBG level, blood glucose profile (mean values of pre-meal, 2 h after breakfast, lunch, and dinner, and bedtime), and nocturnal blood glucose level (03.00 h). FBG values and the blood glucose profile, including nocturnal blood glucose values, were determined by the patient via self–blood glucose monitoring using the One-Touch II blood glucose meter (Ortho Diagnostics Systems GmbH, Neckargemund, Germany). The values determined during the maintenance phase and at baseline, as well as the values from the screening phase, were analysed. From the FBG values, the 7-values measured during the maintenance phase were used to calculate the following variables: trimmed mean of seven daily values, i.e. the five central values of the seven measurements, during maintenance phase; mean FBG level; and stability of FBG (difference between FBG and median FBG during screening and maintenance phases). Insulin dose was recorded daily in the patient diaries. Additional secondary variables were fasting serum insulin, fasting serum C-peptide, insulin dose, hypoglycaemia, HbA_{1c}, fructosamine and non-esterified fatty acids. All variables were measured at the central laboratory. The reference ranges for insulin, C-peptide and non-esterified fatty acids were 2–25 μlU/ml, 0.6–4.4 ng/ml and 0.19–0.90 mmol/l, respectively.

Safety

Laboratory variables included standard haematology, clinical chemistry and lipid profiles, as well as measurement of insulin antibodies and antibody to the *Escherichia coli* protein component of the recombinant insulin (Antibody Capture Assay, specific Mock preparation pGTL II). Patients were monitored for adverse events, including serious symptomatic hypoglycaemia and local tolerance (monitored by inspection). Hypoglycaemia was defined as either symptomatic or asymptomatic in the context of a glucose level below 2.8 mmol/l. Severe hypoglycaemia was defined as a symptomatic event in which the patient required assistance to perform routine activities; this was confirmed by a glucose level of less than 2.8 mmol/l or by the patient's rapid recovery after the administration of oral carbohydrate, intravenous glucose or glucagon. Nocturnal hypoglycaemia was defined as an event that occurred between bedtime basal insulin administration and FBG determination the next morning. Clinical examination included physical examination, heart rate, blood pressure and body weight.

Statistics

Based on a 1 : 1 : 1 randomization, a total patient number of 159 (53 patients for each treatment group) was required to detect a difference of 1.39 mmol/l (25 mg/dl) between insulin glargine (30) and insulin glargine (80) with a type I error of $\alpha = 10\%$ and a statistical power of 80%. To assess the primary efficacy variable of FPG, analysis of covariance (ANCOVA) was performed with baseline values as covariate and treatment effect and (pooled) centre effect as fixed effects after 4 weeks and at study endpoint. The country effect was included in each statistical analyses, i.e. in the ANCOVA model as fixed effect. A one-sided comparison was performed to assess the two insulin glargine formulations (significance level of 0.10), and a two-sided comparison was performed for pooled insulin glargine analogue comparison with NPH insulin (significance level of 0.05). ANCOVA was also performed to compare all three treatment groups for levels of FBG, mean FBG, stability of FBG, nocturnal blood glucose, mean blood glucose profile, fasting serum C-peptide, fasting serum insulin, non-esterified fatty acids, HbA_{1c}, fructosamine, lipids, insulin antibodies and vital signs at study endpoint. Baseline characteristics were assessed by analysis of variance (ANOVA). Statistical evaluations were carried out using the SAS programme package (SAS Institute, Cary, NC, USA).

Results

A total of 256 patients were enrolled; 206 were randomized, and 204 were randomized and treated. Of the 50 who were withdrawn, 44 no longer met the criteria to remain in the study, four subjects did not wish to continue, and two withdrew for other reasons. Two subjects received no study treatment. Characteristics of the 204 patients in the treatment groups are shown in Table 1. The mean age of all participants was 59.4 years, with a mean age at onset of DM of 50.7 years and a mean duration of DM of 9.5 years. There were no major differences among the three treatment groups with regard to baseline variables, including measures of metabolic control. Two patients in the insulin glargine(30) group discontinued treatment early; one had a myocardial infarction, and the other was lost to follow-up.

Fasting plasma glucose

No significant differences in values of adjusted mean FPG at study endpoint were found in the pairwise comparison between the two formulations of insulin glargine (9.00 vs. 8.68 mmol/l; $P = 0.224$) or in the pairwise comparison of the pooled insulin glargine group and the NPH insulin group (8.74 vs. 8.62 mmol/l, respectively; $P = 0.741$). Each group, however, exhibited a clinically relevant and statistically significant decrease in FPG level over the 4 weeks (Fig. 1): mean values decreased from 12.57 to 9.15 mmol/l (–3.42 mmol/l; $P = 0.0001$) in the insulin glargine (30) group, from 12.22 to 8.73 mmol/l (–3.49 mmol/l; $P = 0.0001$) in the insulin glargine (80) group and from 11.70 to 8.60 mmol/l (–3.10 mmol/l; $P = 0.0001$) in the NPH insulin group.

Hypoglycaemia

Fifty-two patients each had at least one episode of hypoglycaemia (25.5%): 18.8% of insulin glargine (30) patients, 25.0% of insulin glargine (80) patients and 32.4% of NPH insulin patients (Table 2). No cases of severe hypoglycaemia were reported, and no episode was characterized as a serious adverse event. There was no significant difference among groups in overall incidence of hypoglycaemia. For comparison, all the insulin glargine patient data were combined and compared with the NPH data. A significantly greater proportion of NPH insulin patients experienced symptomatic nocturnal hypoglycaemia (19.1 NPH group vs. 7.3% glargine

Table 1 Baseline characteristics of study patients

	Insulin glargine (30) (n = 64)	Insulin glargine (80) (n = 72)	NPH insulin (n = 68)
Men/women (%)	37/27 (58/42)	46/26 (64/36)	39/29 (57/43)
Age (years), mean (range)	58.9 (29–75)	60.0 (38–78)	59.2 (30–78)
Body mass index (kg/m^2), mean (range)	26.84 (19.8–34.2)	27.62 (19.6–35.3)	27.69 (20.1–39.0)
Age at onset of DM (years), mean	50.3	50.8	50.9
Duration of DM (years), mean	9.5	9.9	9.1
Duration of oral anti-diabetic treatment (years), mean	7.5	7.7	7.1
Patients with diabetic late complications, n (%)*	22 (34.4)	28 (38.9)	25 (36.8)
Fasting plasma glucose (mmol/l), mean (SD)	12.4 (3.1)	12.2 (2.7)	11.7 (3.1)
HbA_{1c} level (%), mean (SD)	9.7 (1.5)	9.7 (1.2)	9.5 (1.4)
Patients with hypoglycaemia during year before study, n (%)	6 (9.4%)	4 (5.6%)	4 (5.9%)
Patients with hypoglycaemia during screening phase, n (%)	1 (1.6%)	1 (1.4%)	4 (5.9%)

NPH, Neutral Protamine Hagedorn; DM, diabetes mellitus; HbA_{1c}, haemoglobin A_{1c}.
*Complications assessed by enquiry with reference to a systematic list and free text at entry to trial.

Table 2 Occurrence of at least one episode of hypoglycaemia during study treatment

	Insulin glargine (30) (n = 64)	Insulin glargine (80) (n = 72)	Combined glargine group (n = 136)	NPH insulin (n = 68)	P-value (combined glargine vs. NPH)
Total number of patients with at least one episode	12 (18.8%)	18 (25.0%)	30 (22.1%)	22 (32.4%)	0.112*
Patients with individual types of hypoglycaemia:					
Symptomatic					
Daytime, non-severe	11 (17.2%)	16 (22.2%)	27 (19.9%)	20 (29.4%)	0.126*
Nocturnal, non-severe	4 (6.3%)	6 (8.3%)	10 (7.3%)	13 (19.1%)	0.0123*§
Asymptomatic					
Daytime	1 (1.6%)	3 (4.2%)	4 (2.9%)	5 (7.4%)	0.148*
Nocturnal	0 (0)	0 (0)	0 (0)	4 (5.9%)	0.0116†

*χ^2 test; †Fisher's exact test; §P = 0.0373 for glargine (30) vs. NPH.

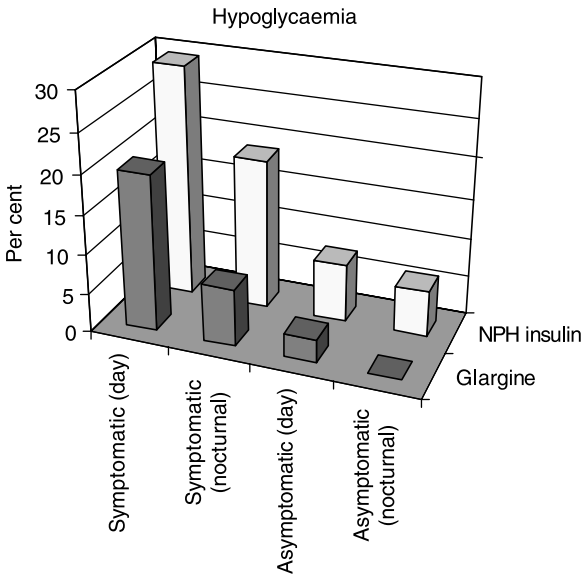

Figure 1 Hypoglycaemia rates in the study, expressed as per cent of patients studied.

groups; P = 0.0123, χ^2), and more NPH insulin patients experienced asymptomatic nocturnal hypoglycaemia (5.9 vs. 0%; P = 0.0116, Fisher's exact).

Of patients with symptomatic hypoglycaemia, two in the insulin glargine groups (1.4%) and three in the NPH insulin group (4.4%) had hypoglycaemia confirmed by blood glucose values below 2.8 mmol/l. The most frequently reported symptoms of hypoglycaemia were aesthenia, increased sweating and tremor: aesthenia occurred in seven (5.1%) of the insulin glargine patients and 10 (14.7%) of the NPH insulin patients; increased sweating occurred in 13 (9.6%), and 12 (17.6%) patients, respectively; and tremor occurred in three (7.4%), and 10 (14.7%), respectively.

Most patients with hypoglycaemia had single episodes. Six patients in each group experienced two or more episodes of symptomatic hypoglycaemia. Two patients in the insulin glargine (30) group, three in the insulin glargine (80) group and four in the NPH insulin group had at least two episodes of nocturnal hypoglycaemia. Two patients in the NPH insulin group had multiple episodes of asymptomatic hypoglycaemia compared with none of the patients in the insulin glargine groups.

Table 3 ANCOVA results for other secondary variables: adjusted means and pair-wise comparisons of insulin glargine (30), insulin glargine (80), and NPH insulin

	Mean FBG[a] (mmol/l)	Blood glucose profile[b] (mmol/l)	Stability of FBG level[c] (mmol/l) Estimate 1	Estimate 2	Nocturnal blood glucose (mmol/l)	Fasting C-peptide (ng/ml)	Fasting serum insulin (μlU/ml)	NEFA (mmol/l)
Adjusted means at endpoint:								
Insulin glargine (30)								
n	61	57	61	61	60	60	60	61
Adjusted mean	7.00	8.56	0.85	1.84	6.99	3.69	21.5	0.86
Insulin glargine (80)								
n	66	65	66	66	66	68	68	70
Adjusted mean	6.95	8.57	0.79	1.75	7.23	3.53	21.6	0.84
NPH insulin								
n	63	59	63	63	61	65	65	66
Adjusted mean	6.53	8.38	0.79	1.74	6.68	3.57	22.1	0.90
Differences of adjusted means:								
Insulin glargine (30)—NPH insulin								
P-value	0.0798	0.5549	0.5553	0.6970	0.4043	0.4805	0.7318	0.2723
Insulin glargine (80)—NPH insulin								
P-value	0.1042	0.5130	0.9838	0.9839	0.1318	0.8352	0.7874	0.1475
Insulin glargine (30)—insulin glargine (80)								
P-value	0.8645	0.9645	0.5391	0.7104	0.5156	0.3611	0.9353	0.7606

Note: all glucose measurements were determined by self-monitoring of blood glucose. [a]Calculated from the last seven consecutive blood glucose values from the treatment phase. [b]The mean blood glucose profile calculated per patient and profile day (pre-meal and 2 h after breakfast, lunch and dinner, and at bedtime). [c]Stability of FBG: estimate 1, calculated as the mean of the absolute differences between the patient's FBG and the patient's median FBG; estimate 2, calculated as the absolute difference between the 2nd and 6th of the ranked seven values of FBG.

Secondary efficacy variables

Findings for secondary efficacy variables closely reflected findings for FPG (Table 3). No significant differences in adjusted mean FBG values (calculated from the last seven consecutive values from the treatment phase) at study endpoint were observed between the insulin glargine (30) group and the insulin glargine (80) group (7.00 vs. 6.95 mmol/l; $P = 0.86$) or between the pooled insulin glargine groups and the NPH insulin group (6.92 vs. 6.49 mmol/l; $P = 0.056$). An identical pattern (i.e. significant decreases in values within each group but with no differences between treatments) was observed for mean FBG, blood glucose profile, stability of FBG, nocturnal blood glucose, fasting serum C-peptide, non-esterified fatty acids, HbA_{1c} and fructosamine; significant and similar increases in fasting serum insulin level were observed in each group. Decreases in levels of HbA_{1c} between baseline and study endpoint were 0.82% (9.79–8.98%) in the insulin glargine (30) group, 0.86% (9.71–8.84%) in the insulin glargine (80) group, and 0.79% (9.47–8.68%) in the NPH insulin group ($P = 0.0001$ in each case). Similar marked reductions in levels of fructosamine (decreases in mean values of 48.0, 47.6 and 44.9 mmol/l, respectively) were observed.

There were comparable increases in insulin dose in each group during the study. Between day 1 and study endpoint, median daily basal insulin dose increased from 8 to 12 U in the insulin glargine (30) group, from 10 to 14 U in the insulin glargine (80) group and from 8 to 12 U in the NPH insulin group. Median dose by U/kg body weight increased from 0.11 to 0.17 U/kg in the insulin glargine (30) group, from 0.13 to 0.17 U/kg in the insulin glargine (80) group and from 0.11 to 0.15 U/kg in the NPH insulin group.

Safety

Adverse events considered possibly related to study treatment occurred in three of 64 insulin glargine (30) patients (4.7%), three of 72 insulin glargine (80) patients (4.2%) and two of 68 NPH insulin patients (2.9%). Of the three insulin glargine (30) patients, one experienced tachycardia, one experienced tongue oedema and one experienced an injection site reaction with pruritus and rash. Of the three insulin glargine (80) patients, one experienced paraesthesia, one dyspepsia, and one increased appetite. Of the two NPH insulin patients with treatment-related adverse events, one had headache and one experienced nausea and asthenia. All treatment-related adverse events were mild, except for headache (moderate) in one NPH insulin patient. One patient in each group experienced an injection site reaction.

No deaths occurred during the study. The one serious adverse event, a myocardial infarction in a patient in the insulin glargine (30) group, was not considered treatment-related.

No significant treatment effects were observed for insulin glargine antibodies or human insulin antibodies. No patient had a change in insulin antibodies of more than 10% bound/total. The *E. coli* antibody status changed in one insulin

glargine (30) patient (positive to negative) and in two NPH insulin patients (borderline to negative in one and negative to positive in the other).

No differences in vital signs were observed among treatment groups. Mean body weight increased by 0.31 kg in the insulin glargine (30) group, by 0.64 kg in the insulin glargine (80) group and by 0.68 kg in the NPH insulin group. No clinically relevant alterations in laboratory variables were observed.

Discussion

One of the goals of insulin treatment is to attain normal glycaemia by maintaining appropriate insulin concentrations throughout each 24-h period. Intermediate- and long-acting insulins have been developed in the attempt to satisfy basal insulin requirements. Insulin glargine is a novel recombinant human insulin analogue with key amino-acid alterations that result in a prolonged duration of action and delayed absorption.

This study was carried out as a randomized multicentre trial; the patients were heterogeneous in that they came from 26 clinics in nine European and one African country. As a precaution against possible disparities between country groups, the randomization was stratified. The results are thus likely to be generalisable. The study was not blinded because of the difficulty of masking one cloudy insulin and one clear insulin. However the adjustment rules were the same for both groups, and were unlikely to be biased, in that all three groups increased their insulin during the trial by a mean of 4 U.

In the current study, no significant differences were found in FPG levels between the insulin glargine patients and the NPH insulin patients or between insulin glargine (30) patients and insulin glargine (80) patients, although each treatment group exhibited clinically relevant reductions over the course of 4 weeks. Other measures of glycaemic control, including blood glucose variables and HbA_{1c}, showed similar patterns of response; no between-group differences were observed, but marked reductions occurred within each group over the course of treatment.

The magnitude of reduction in FPG and in other glucose measures in each of the treatment groups is consistent with the expected response in patients with Type 2 DM, in whom oral hypoglycaemic treatment is inadequate and who receive insulin for the first time. The presence of residual insulin secretion in these patients is indicated by a baseline fasting serum C-peptide level of between 3.53 and 3.69 ng/ml and a baseline fasting serum insulin level of 17–20 μlU/ml. The decreases in C-peptide levels observed during treatment indicate that there was some degree of suppression of endogenous insulin secretion in the fasting state. Compensatory insulin secretion may have concealed differences in the absorption profiles of insulin glargine and NPH insulin.

Of particular note is the significant reduction in episodes of nocturnal hypoglycaemia in the insulin glargine patients in the short term, when assessed both as symptomatic or non-symptomatic. The occurrence of nocturnal hypoglycaemia is a primary concern in patients with diabetes who are receiving insulin because it limits the ability to increase basal insulin doses to improve glycaemic control. Although there was no difference in mean values of subject-measured nocturnal blood glucose between treatment groups, the mean values do not reflect the variability in response among the relatively small number of patients who experienced nocturnal hypoglycaemia. Of greater clinical relevance than the mean values is that asymptomatic nocturnal hypoglycaemia (confirmed by blood glucose values below 2.8 mmol/l) was detected in four of the NPH insulin patients and in none of the insulin glargine patients. These episodes were in different patients—their insulin dose was reduced after experiencing hypoglycaemia. Given that the fasting glucose achieved in the NPH insulin group demonstrated a tendancy towards being lower than that observed in the insulin glargine (30) and insulin glargine (80) groups, a slightly higher frequency of nocturnal hypoglycaemia might be expected in the NPH insulin group. Lowering the fasting glucose levels further may, therefore, result in an increase in nocturnal hypoglycaemia.

Other clinical evaluations of insulin glargine have involved patients with Type 1 DM. Talaulicar *et al.* [14] found that once-daily insulin glargine with 15 or 80 μg/ml zinc resulted in blood glucose profiles similar to those seen with four-times-daily NPH insulin in a 4-day trial in 12 patients. More recently, Pieber *et al.* [15] found that once-daily insulin glargine (30) and insulin glargine (80) were associated with significant reductions in levels of FPG, fasting self-monitored blood glucose and HbA_{1c} compared with once- or twice-daily NPH insulin in 333 patients treated for 4 weeks. These investigators also found insulin glargine to be associated with a significant reduction in the occurrence of nocturnal hypoglycaemia; this difference was attributable to occurrence of hypoglycaemia with the once-daily NPH insulin regimen. One large study in Type 2 diabetes [16], also using NPH insulin as a comparator, showed similar findings with nocturnal hypoglycaemia reduced in the glargine group. A single-centre phase III trial [17] over the course of 1 year titrated insulin up to a FPG target of ≤6.7 mmol/l. A significantly lower number of patients on insulin glargine than on NPH insulin experienced hypoglycaemia, but using this target the numbers in both groups were high (33.0% on insulin glargine and 50.7% of the patients on NPH insulin) experienced symptomatic hypoglycaemia. These patients' nocturnal rates of hypoglycemia were also lower in the insulin glargine group than NPH insulin, both in those who reached the glycaemic target and those who did not.

Insulin glargine appears to be as safe as NPH insulin. We detected no evidence of a treatment effect for development of insulin or *E. coli* protein antibodies and observed no unexpected adverse events or laboratory abnormalities with insulin glargine. As in the study by Pieber *et al.* [15], we detected no clinically relevant differences between the insulin glargine (30) formulation and the insulin glargine (80) formulation—the differing zinc concentrations that were compared to assess their possible influence on the *in vivo* profile. Insulin glargine (30) was selected for use in the phase III clinical trial programme

and also as the final product formulation, because it offered a good stability profile with the lowest suitable zinc concentration.

Overall, the results of this study suggest that insulin glargine may have a favourable risk–benefit profile compared with NPH insulin in patients with Type 2 DM when administered in combination with oral hypoglycaemic agents. Insulin glargine was as effective as NPH insulin in reducing FPG levels, was tolerated as well as NPH insulin and resulted in significantly fewer occurrences of nocturnal hypoglycaemia.

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