DOI: 10.1111/j.1464-5491.2004.01323.x

Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin

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Accepted 5 December 2003

Abstract

Background Glargine is a long-acting insulin analogue potentially more suitable than NPH insulin in intensive treatment of Type 1 diabetes mellitus (T1 DM), but no study has proven superiority. The aim of this study was to test superiority of glargine on long-term blood glucose (BG) as well as on responses to hypoglycaemia vs. NPH.

Methods One hundred and twenty-one patients with T1 DM on intensive therapy on four times/day NPH and lispro insulin at each meal, were randomized to either continuation of NPH four times/day ($n = 60$), or once daily glargine at dinner-time ($n = 61$) for 1 year. Lispro insulin at meal-time was continued in both groups. In 11 patients from each group, responses to stepped hyperinsulinaemic-hypoglycaemia were measured before and after 1 year's treatment.

Results Mean daily BG was lower with glargine [7.6 ± 0.11 mmol/l (137 ± 2 mg/dl)] vs. NPH [8.1 ± 0.22 mmol/l (146 ± 4 mg/dl)] ($P < 0.05$). HbA_{1c} at 4 months did not change with NPH, but decreased with glargine (from 7.1 ± 0.1 to 6.7 ± 0.1%), and remained lower than NPH at 12 months (6.6 ± 0.1%, $P < 0.05$ vs. NPH). Frequency of mild hypoglycaemia [self-assisted episodes, blood glucose ≤ 4.0 mmol/l (72 mg/dl)] was lower with glargine vs. NPH (7.2 ± 0.5 and 13.2 ± 0.6 episodes/patient-month, $P < 0.05$). After 1 year, NPH treatment resulted in no change of responses to hypoglycaemia, whereas with glargine plasma glucose, thresholds and maximal responses of plasma adrenaline and symptoms to hypoglycaemia improved ($P < 0.05$).

Conclusions The simpler glargine regimen decreases the percentage of HbA_{1c} and frequency of hypoglycaemia and improves responses to hypoglycaemia more than NPH. Thus, glargine appears more suitable than NPH as basal insulin for intensive treatment of T1 DM.

Diabet. Med. 21, 1213–1220 (2004)

Keywords basal insulin, glargine, insulin analogues, nocturnal hypoglycaemia, Type 1 diabetes mellitus

Introduction

Intensified insulin regimens designed to maintain near-normoglycaemia in Type 1 diabetes mellitus (T1 DM) are based on administration of rapid-acting insulin at meals and replacement of basal insulin in the interprandial periods [1]. Supplementation of meal-time insulin is best achieved with rapid-acting insulin analogues [2], whereas basal insulin is best replaced with continuous subcutaneous (s.c.) insulin infusion (CSII) by means of an external minipump [3–6]. However, in practice, s.c. injections of the intermediate-acting NPH insulin are used most commonly to replace basal insulin in T1 DM. Because

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rapid-acting insulin analogues have a duration of action shorter than human unmodified regular insulin, intensification of supplementation of basal insulin is required whenever insulin analogues are used at meal-time to improve long-term glycaemic control [1,2,7]. This is best achieved with CSII [4–6] or multiple daily NPH insulin administrations [8–11].

The long-acting insulin analogue glargine, which exhibits an action profile flatter and longer than NPH insulin [12], is now available for replacement of basal insulin in patients with T1 DM and tested in several studies [11–19]. The main advantage demonstrated in the studies so far conducted in T1 DM [13,14] has been less nocturnal hypoglycaemia with glargine as compared with NPH insulin. However, at present, with the exception of one short-term study [20], none has shown better long-term glycaemic control in terms of decrease in percentage of HbA_{1c} with insulin glargine as compared with NPH in T1 DM. Thus, at present, the role of insulin glargine as compared with NPH in intensive treatment of T1 DM is not fully established.

The aim of these studies was, first, to compare the long-term glycaemic control in T1 DM with two regimens of optimized replacement of basal insulin, i.e. NPH combined with lispro insulin at each meal (and a fourth NPH injection at bedtime) [7], and insulin glargine once daily. Second, to test the hypothesis that the less frequent hypoglycaemia expected to occur with insulin glargine as compared with NPH, resulted in better responses of counter-regulatory hormones, symptoms and onset of cognitive dysfunction to hypoglycaemia.

Materials and methods

Subjects

One hundred and twenty-one patients with T1 DM (Table 1) and fasting plasma C-peptide ≤ 0.15 nmol/l, on intensified treatment with multiple daily combinations of lispro and NPH insulin at each meal, and NPH at bedtime as previously described [9] for at least 2 years, participated in these studies after giving fully informed, written, consent (Fig. 1). Patients were free of any detectable microangiopathic complication and were negative at the screening for autonomic neuropathy, as judged on the basis of standard battery of cardiovascular tests [21]. The studies were approved by the local Ethics Study Committee.

Table 1 Baseline characteristics of the patients studied

	NPH	Glargine
n	60	61
Gender (M/F)	33/27	34/27
Age (years)	34 ± 1.0	36 ± 1.0
BMI (kg/m^2)	23.2 ± 0.15	22.9 ± 0.14
Diabetes duration (years)	15 ± 0.3	13 ± 0.3
HbA_{1c}	7.1 ± 0.2%	7.1 ± 0.1%
Insulin dose (U/kg/day)	0.64 ± 0.04	0.66 ± 0.05

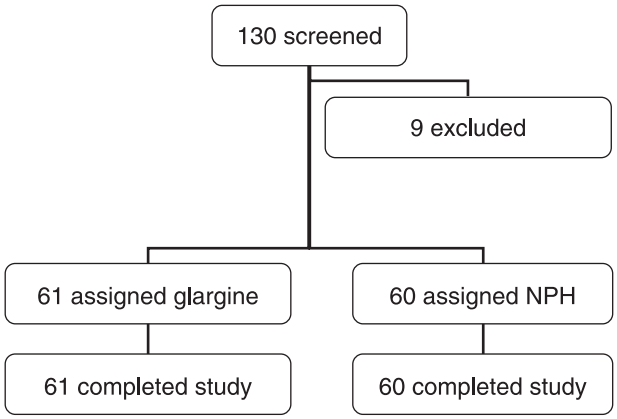

Figure 1 Trial profile.

Design of study

Patients who were eligible for the study (*n* = 121) continued their previous therapy during the 1-month run-in and had their baseline measurements taken. After the assessment of baseline measurements, the randomization procedure took place. Because the population was very homogeneous, a simple randomization was used based on computer-generated random numbers by a person who was not involved in establishing eligibility and entry of patients [22]. Concealment of the randomization was insured by having the allocation codes in a locked unreadable computer file handled by a person not involved in the recruitment of patients. Accordingly, patients were randomized to either (i) continuation of lispro and NPH insulin at each meal, and NPH at bedtime (*n* = 60), or (ii) administration of insulin glargine (Lantus®, Aventis Pharmaceutical, purchased from Hostato Apotheke, Frankfurt, Germany) at dinner-time (20.00 h, *n* = 61), for 1 year. Baseline characteristics of patients are given in Table 1, split by treatment type. Intention-to-treat analysis was conducted for all patients exposed to treatments.

The two groups were matched for age, gender, diabetes duration, insulin doses and percentage HbA_{1c} (*P* = NS). Mealtime lispro insulin was continued in both groups. The glycaemic targets in the two treatments were identical, i.e. blood glucose 6.4–7.2 mmol/l (115–130 mg/dl) in the fasting state, before meals and at bedtime, and blood glucose 8.0–9.2 mmol/l (145–165 mg/dl) 2 h after meals. Patients were advised to decrease or increase the dose of basal insulin if fasting blood glucose was repeatedly below 6.0 mmol/l (108 mg/dl) or above 7.8 mmol/l (140 mg/dl), and to decrease or increase the dose of rapid-acting insulin at meals if the 2-h post-prandial blood glucose was repeatedly below 7.0 mmol/l (126 mg/dl) or above 9.5 mmol/l (170 mg/dl). Adjustments of lispro dose was made according to carbohydrate content of meal. Insulin lispro was injected into the abdominal wall. Insulin glargine, or bedtime NPH insulin, was injected into the anterior part of one thigh. Either pens or syringes were used by patients. With syringes, lispro and NPH insulins were mixed and immediately injected. The rationale and relative percentages of lispro and NPH administered together at meals has previously been reported [9]. The ratio lispro/NPH was ~70/30 at breakfast, ~60/40 at lunch and

~90/10 at dinner. The bedtime NPH dose was ~0.2 U/kg. Insulin glargine was always injected alone without prior mixing with lispro. For the first 2 days of treatment, the daily glargine dose was assumed to be identical to the total daily NPH units of the run-in period. Afterwards, the dose of glargine was varied by 1–2 units every 2–3 days, if necessary, to meet the target fasting blood glucose. Similar adjustments were made with the NPH treatment. Mealtime doses of lispro were 0.04–0.08 U/kg at breakfast, and 0.10–0.17 U/kg at lunch and dinner. The lispro doses were adjusted daily on the basis of pre-prandial blood glucose, as well as 2 h after meal blood glucose of previous days, as well as composition and size of meal and physical activity. NPH doses at each meal were adjusted based on blood glucose values observed the previous days prior to meals. Weekly physical activity and calorie intake was similar between the two groups. All patients of the two groups had three meals/day with no snacks except for correction of hypoglycaemia. All patients were in daily telephone contact with the investigators, and were seen weekly in the outpatient unit. Patients were requested to measure capillary blood glucose before meals and bedtime every day, 2 hours after meals every other day, and at 03.00 h twice a week.

Frequency of hypoglycaemia

In these studies, hypoglycaemia was defined as any episode associated with measurement of blood glucose ≤ 4.0 mmol/l (72 mg/dl) irrespective of symptoms, as previously reported [23,24]. Hypoglycaemia was considered mild when the episodes were self-treated by the patients, and severe when the episode required external help (any kind). Nocturnal episodes of hypoglycaemia were calculated from values measured at 03.00 h or any time between 01.00 and 07.30 h when participants awoke with symptoms suggestive of hypoglycaemia.

Assessment of awareness of, counter-regulation to, and cognitive function during, hypoglycaemia after NPH and glargine treatment

To assess the effects of long-term treatment with NPH and glargine on awareness of, counter-regulation to, and cognitive function during, hypoglycaemia in relation to antecedent glycaemic control, 11 Type 1 diabetic patients of the NPH and glargine groups were randomly selected and studied at the end of the run-in period and again 12 months after treatment, with the stepped hyperinsulinaemic, hypoglycaemic clamp, as previously described [25], with minor modifications [26]. In brief, patients were maintained normoglycaemic [(5.0–5.5 mmol/l (90–100 mg/dl)] overnight by an intravenous infusion of insulin [27] and studied in the fasting state. An infusion of regular insulin was begun at the rate of 1 mU/kg/min for 270 min, followed by 2 mU/kg/min for additional 90 min. Arterialized-venous [28] plasma glucose was clamped by variable glucose infusion at sequential target glucose concentrations of 5.0, 4.3, 3.6, 3.0, 2.3 mmol/l (90, 78, 66, 54 and 42 mg/dl) based on plasma glucose concentrations measured every 5 min. Blood samples were drawn every 15–30 min for determination of plasma free insulin, growth hormone, glucagon, cortisol, adrenaline and noradrenaline, and non-glucose substrates [free fatty acids (FFA), β-OH-butyrate, and lactate]. A semiquantitative symptom questionnaire was given every 15 min [24]. In addition, at baseline and during each plateau the standard cognitive tests were given [24].

Analytical methods

Capillary blood glucose was measured by the One-Touch system (Lifescan, Johnson & Johnson, Milpitas, CA, USA). Plasma glucose was measured using a Beckman Glucose Analyser (Beckman Instruments, Palo Alto, CA, USA). Plasma insulin and glucagon were measured by means of commercially available kits (Linco Research, Inc., St Charles, MO, USA). To remove antibody-bound insulin, plasma was mixed with an equal volume of 30% polyethylene glycol immediately after drawing blood [29]. Plasma growth hormone, cortisol, adrenaline and noradrenaline, FFA, β-OH-butyrate, and lactate [30] were measured by previously described assays. HbA_{1c} was determined by a high performance liquid chromatography using a HI-Auto A_{1c} TM HA 8121 apparatus (DIC, Kyoto Daiichi, Kogaku Co. Ltd, Japan) (range in non-diabetic subjects 3.8–5.5%). At time of study, the HbA_{1c} values were not aligned with DCCT.

Statistical analysis

In this design, a total of 120 subjects were required to achieve 90% power to detect a difference of 0.3% among the means with group standard deviations of 0.4 at the significance level (alpha) of 5%. The primary endpoint of the study was the change in glycosylated haemoglobin (% HbA_{1c}) after 1 year of treatment. Changes in percentage of HbA_{1c} over the 1-year period were analysed using repeated measures ANCOVA with treatment as grouping factor and the baseline as co-variate [31]. Data from home monitoring over the last month of study were used to derive intrapatient variability (coefficient of variation of the blood glucose values) and blood glucose profiles. Glycaemic thresholds of responses to hypoglycaemia were calculated as previously reported [24]. Analyses were done using the two-tailed unpaired *t*-test. Data from cognitive tests were standardized to *Z* scores as previously reported [24] and analysed by repeated measures ANOVA. Differences between proportions were analysed using χ^2 test. Data in text and tables are given as mean ± SE and were considered to be significantly different at $P \leq 0.05$. We conducted the statistical analyses by using PASS/NCSS 2001 (Number Cruncher Statistical System, Kaysville, UT, USA) and Statistica 4.5 (Statsoft, Tulsa, OK, USA) softwares.

Results

Glycaemic control

Glycosylated haemoglobin (Fig. 2)

In the group randomised to continue on NPH insulin, the percentage of HbA_{1c} did not change over time and was 7.1 ± 0.1% by end of study (P = NS vs. baseline 7.1 ± 0.2%). In contrast, in the group randomised to insulin glargine, HbA_{1c} at 4 months decreased from 7.1 ± 0.1 to 6.7 ± 0.1% ($P < 0.05$) and remained lower as compared with NPH for entire duration of study ($P < 0.05$).

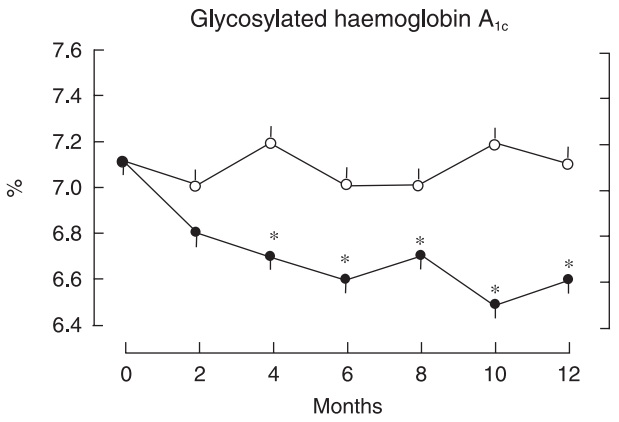

Figure 2 Percentage of glycosylated haemoglobin A_{1c} in the two groups of patients with Type 1 diabetes mellitus treated with either NPH (○, $n = 60$) or glargine (●, $n = 61$) as basal insulin for 1 year. Mean ± SEM. *$P < 0.05$.

Blood glucose profile (home blood glucose monitoring) [Fig. 3]

With insulin glargine, blood glucose was lower as compared with NPH in the fasting state and before meals, whereas it was similar after meals. However, the 03.00 h blood glucose was lower with NPH [7.5 ± 0.16 mmol/l (136 ± 3 mg/dL)] as compared with glargine [8.4 ± 0.27 mmol/l (152 ± 5 mg/dl)] ($P < 0.05$). The mean daily blood glucose was lower with glargine [7.6 ± 0.11 mmol/l (137 ± 2 mg/dl)] than NPH [8.1 ± 0.22 mmol/l (146 ± 4 mg/dl)] ($P < 0.05$).

Percentage of blood glucose measurements at target

The percentage of measurements of blood glucose in the target range was greater with glargine as compared with NPH in the fasting state, before meals and bedtime (Table 2).

Table 2 Proportions of blood glucose values at target values in the two groups of patients with T1 DM treated with either NPH or glargine (data from home blood glucose monitoring during last month of study)

	NPH	Glargine	Difference estimate (95% CI)
Fasting	0.22	0.45	–0.23 (–0.26 to –0.20)*
After breakfast	0.29	0.31	–0.03 (–0.07 to 0.01)
Before lunch	0.22	0.37	–0.15 (–0.18 to –0.12)*
After lunch	0.28	0.32	–0.04 (–0.08 to 0.01)
Before dinner	0.21	0.35	–0.14 (–0.17 to –0.11)*
After dinner	0.33	0.36	–0.03 (–0.07 to 0.02)
Bedtime	0.21	0.42	–0.21 (–0.24 to –0.18)*

*$P < 0.05$.

Blood glucose variability

The intrapatient variability of blood glucose with insulin glargine was no different as compared with NPH either during day or evening time, but at 03.00 h was lower with glargine (24 ± 2.1%), as compared with NPH (31 ± 2.5%) ($P < 0.05$).

Frequency and timing of hypoglycaemia

No episodes of severe hypoglycaemia occurred in these studies. The frequency of mild hypoglycaemia (last month of treatment) was lower with glargine (7.2 ± 0.5 episodes/patient-month) as compared with NPH (13.2 ± 0.6 episodes/patient-month). As compared with NPH, glargine resulted in lower frequency of hypoglycaemia both during day hours (6.0 ± 0.6 vs. 10 ± 0.8 episodes/patient-month, glargine and NPH, respectively, $P < 0.05$) as well as during night hours (1.2 ± 0.2 vs. 3.2 ± 0.3 episodes/patient-month, glargine and NPH, respectively, $P < 0.05$). Hypoglycaemia occurred at an earlier time at night with NPH as compared with glargine insulin [01.00–04.59 h, 2.1 ± 0.2 and 0.3 ± 0.02 of episodes/patient-month, NPH and

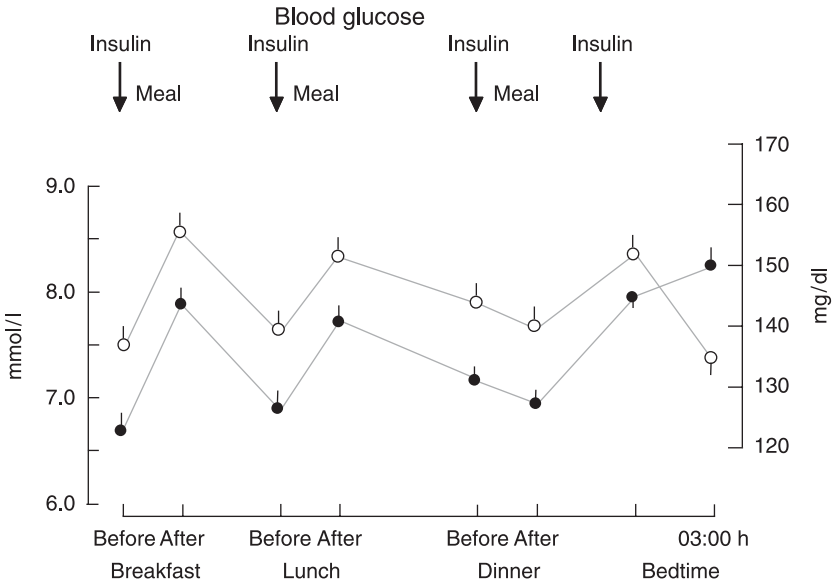

Figure 3 Daily blood glucose (data from blood glucose monitoring of the last month of the study) in the two groups of patients with Type 1 diabetes mellitus treated with either NPH (○, $n = 60$) or glargine (●, $n = 61$) as basal insulin for 1 year. Insulin glargine was given at dinner time (20:00 h). The fourth NPH injection was given at bedtime. Mean ± SEM.

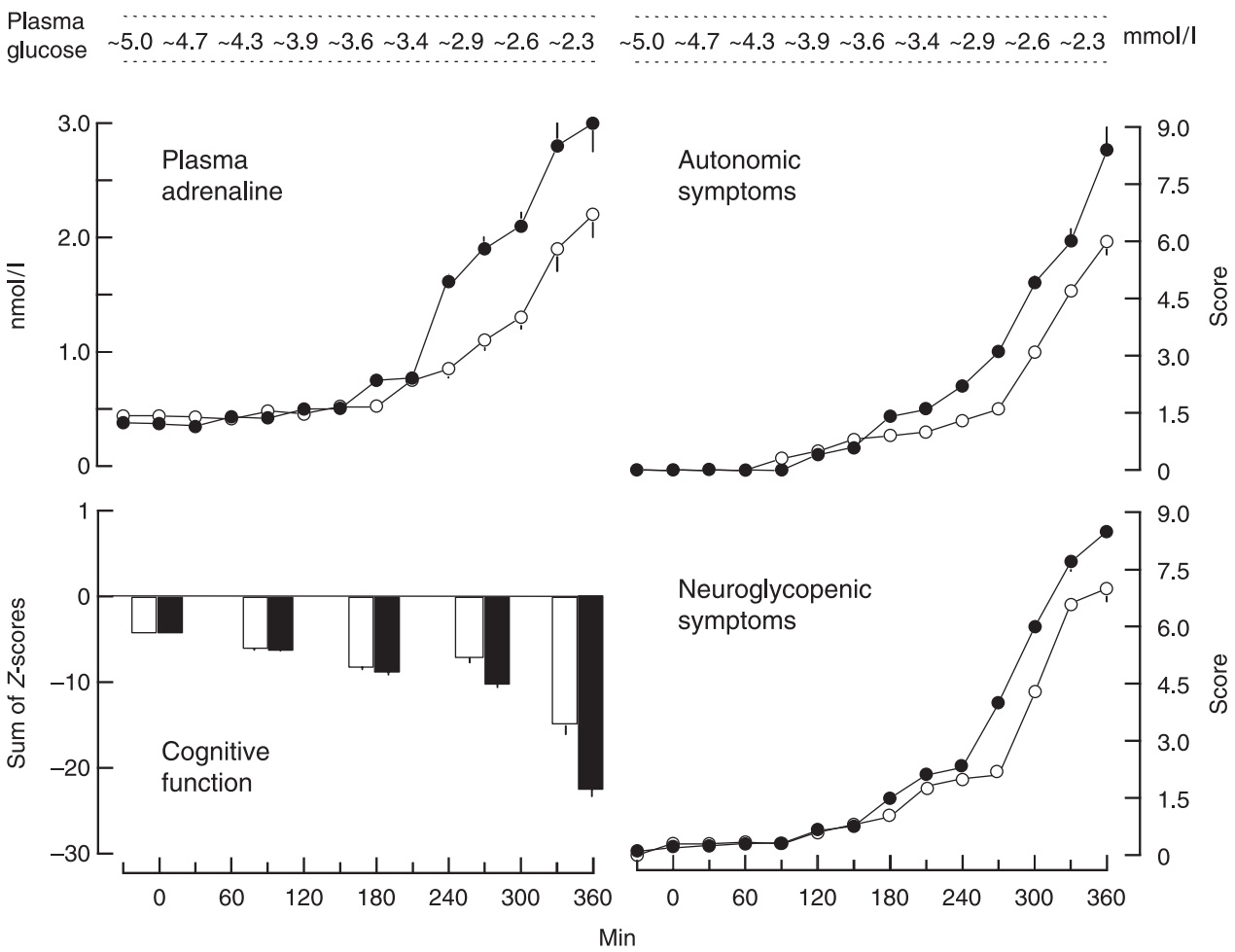

Figure 4 Responses to stepwise, insulin-induced, clamped hypoglycaemia in patients with Type 1 diabetes after 1 year treatment with insulin glargine (●, $n = 11$) and NPH (○, $n = 11$). Mean ± SEM.

glargine; 05.00–07.30 h, 1.11 ± 0.1 and 0.86 ± 0.08 episodes/patient-month, NPH and glargine ($P < 0.05$)].

Insulin doses

Total daily insulin doses were no different at the end of the two treatments (glargine 0.67 ± 0.04 U/kg/day, NPH 0.63 ± 0.04 U/kg/day, P = NS). With NPH treatment, there was no change in either meal-time or basal insulin dose. With glargine treatment, there was a decrease in dose of meal-time insulin lispro (from 0.36 ± 0.02 to 0.31 ± 0.02 U/kg/day, $P < 0.05$), and increase in basal insulin requirements (from 0.31 ± 0.03 to 0.36 ± 0.02 U/kg/day) ($P < 0.05$). The decrease in lispro insulin requirements was primarily accounted for by the decrease at breakfast (from 0.07 ± 0.01 to 0.04 ± 0.006 U/kg/day) ($P < 0.05$).

Body weight

There were no changes in body weight after treatment with either NPH or glargine insulin (P = NS, data not shown).

Awareness of, counter-regulation to, and cognitive function during, hypoglycaemia (Fig. 4, Table 3)

There were no differences in plasma insulin and glucose concentrations in the hypoglycaemic clamp study between the patients randomised to NPH and glargine treatments. At randomization, there were no differences in responses of symptoms, counter-regulatory hormones, substrates and cognitive function in the two groups of patients (data not shown).

After 1 year's treatment, the responses of the NPH-treated patients were no different as compared with those at randomization. In contrast, the plasma adrenaline and symptom responses in the glargine group improved both in terms of glycaemic thresholds (Table 3) and magnitude (Fig. 4). Cognitive function deteriorated to a greater extent in the glargine as compared with NPH group (sum of z score –22 ± 2 vs. –14 ± 3.3, $P < 0.05$). The responses of plasma noradrenaline, growth hormone and cortisol also improved in the glargine group as compared with NPH group ($P < 0.05$, data not shown). The

Table 3 Glycaemic thresholds [plasma glucose mmol/l (mg/dl)] of responses to hypoglycaemia in the glargine and NPH-treated patients after 1 year

	NPH	Glargine	Difference estimate (95% CI)
Adrenaline	3.1 ± 0.05 (56 ± 0.9)	3.4 ± 0.06 (61 ± 1.1)	−5 (−2.2 to −7.8)*
Autonomic symptoms	2.7 ± 0.07 (48 ± 1.2)	3.0 ± 0.08 (54 ± 1.4)	−6 (−2.3 to −9.6)*
Neuroglycopenic symptoms	2.6 ± 0.06 (47 ± 1.0)	2.9 ± 0.07 (52 ± 1.2)	−5 (−1.9 to −8.1)*
Cognitive dysfunction	2.5 ± 0.04 (45 ± 0.7)	2.8 ± 0.06 (50 ± 1.0)	−5 (−2.6 to −7.4)*

*$P < 0.05$.

responses of plasma glucagon, FFA, β-OH-butyrate, and lactate were no different (data not shown).

Discussion

The present studies were designed to compare the long-term effects of two optimized regimens of replacement of basal insulin, i.e. multiple daily NPH injections and a once-daily glargine injection at dinner-time, of patients with T1 DM intensively treated with the rapid-acting insulin analogue lispro at meal-time. The results indicate that both regimens resulted in fair to good glycaemic control, as suggested by the percentage of HbA_{1c}, absence of severe hypoglycaemia, and low frequency of mild hypoglycaemia. However, the regimen with glargine as basal insulin resulted in lower fasting, pre- and post-meal blood glucose as compared with NPH; in a greater reduction in percentage HbA_{1c}; in lower frequency of hypoglycaemia, primarily at night; in a greater percentage of blood glucose measurements at the target values primarily in the fasting state, before meals and at night, and in lower variability of blood glucose at night. Most important, the present studies indicate that the lower long-term frequency of hypoglycaemia with glargine as compared with NPH insulin, results in better counter-regulatory hormone responses to hypoglycaemia as well as better awareness of hypoglycaemia. Taken together, these results indicate the superiority of insulin glargine over NPH in the replacement of basal insulin in intensively treated T1 DM patients given rapid-acting insulin analogue at meal-time. In a broader sense, these studies indicate that optimal combinations of long-acting and rapid-acting insulin analogues in T1 DM control blood glucose better than the combination of human regular insulin at meals and evening NPH insulin, as recently also reported by Ashwell *et al*. [32]. Interestingly, the decrease in HbA_{1c} and frequency of hypoglycaemia observed in that study using both analogues [32] was similar to that reported in studies in which meal-time lispro was compared with unmodified human regular insulin [9] and glargine with NPH insulin (present study).

Notably, in these studies glargine insulin has been administered at dinner, not bedtime, because it has been shown that its effects are independent of time of administration [20,33]. This is an advantage as compared with NPH which should be given at bedtime, not dinner-time, to reduce the risk of nocturnal hypoglycaemia [24].

The differing blood glucose control throughout the day observed in the present studies with NPH and glargine as basal insulins, may be explained by the different pharmacokinetics of the two insulin preparations. In contrast to NPH, glargine plasma insulin does not peak in the early part of the night [12]. This explains the lower frequency of hypoglycaemia with insulin glargine as compared with NPH. In addition, with insulin glargine, plasma insulin does not decrease either in the second part of the night [20], or before lunch and dinner, thus restraining endogenous glucose production [33,34] and preventing increase in pre-prandial blood glucose.

In theory, a more aggressive titration of NPH would have resulted in lower mean daily blood glucose and HbA_{1c}. However, this was not possible in the present study because of more frequent hypoglycaemia.

We believe important factors in achieving the results of the present studies were the patients' long-term experience with intensive therapy at the time they entered the study; their consistency in complying with blood glucose monitoring and adaptation of insulin dose; and their generally generous co-operative efforts with the medical team. These factors were present in the people randomised to NPH as well as in those randomised to glargine insulin.

One well-taken criticism to this study as well as to a previous study [20] is that the study was not blind. However, in contrast to a previous study [20], the present study lasted 12 months, and the improved blood glucose control at the beginning of the study was confirmed at the end of this long observation period. This makes it unlikely that the bias of an open study could explain the results observed with insulin glargine.

In the present studies, the once-daily glargine insulin regimen was compared with the multiple daily NPH administration regimen [7], and resulted in lower percentage of HbA_{1c}. Although modest in absolute terms (~0.4%), the decrease in HbA_{1c} observed with glargine insulin is conceptually important because it was obtained in patients in already good glycaemic control, and because at the same time the frequency of hypoglycaemia decreased. In previous studies comparing NPH and glargine insulin in T1 DM [14–16,19], the percentage of HbA_{1c} did not differ between treatments. Previous studies

[13–19] were multicentre, and designed before the pharmacokinetics and -dynamics of insulin glargine were understood [12]. In contrast, the present study was unicentre, and allowed close contact with patients, homogeneity in the conduct of the study and greater efforts in titration of insulin dose to target.

Because glargine is a soluble insulin, it is expected that its pharmacodynamic effects are less variable within patients with T1 DM as compared with those of insulin in suspension such as NPH [2], as suggested by a recent meta-analysis [34]. In the present studies in which NPH insulin was administered four times daily, only the 03.00 h blood glucose value was less variable with glargine as compared with NPH insulin. Had NPH insulin been given only once daily, as is commonly the case in T1 DM, then the variability of insulin glargine may have been consistently lower than that of NPH insulin.

Of note, in the present studies, the less frequent hypoglycaemia with insulin glargine resulted in improved responses to hypoglycaemia, both in terms of glycaemic thresholds (i.e. responses begun earlier for a lower decrease in blood glucose) and maximal responses of counter-regulatory hormones and symptoms to hypoglycaemia. This is not a specific effect of insulin glargine over NPH, but the consequence of lower frequency of antecedent hypoglycaemia, as previously demonstrated [9,24]. Thus, long-term treatment with insulin glargine confers greater awareness of hypoglycaemia and greater defences against hypoglycaemia to patients with T1 DM.

In conclusion, both the long-acting insulin analogue glargine once daily at dinner-time and multiple daily NPH administrations maintain good long-term glycaemic control in patients intensively treated with insulin lispro at meals. However, with insulin glargine blood glucose control improves more, hypoglycaemia is less frequent and defenses against, as well as awareness of, hypoglycaemia, are better than with NPH. Therefore, insulin glargine appears a more suitable basal insulin than NPH for safely maintaining long-term near-normoglycaemia in the regimen of multiple injections when a meal-time rapid-acting insulin analogue is used.

Acknowledgements

This is an investigator-initiated trial with financial support obtained from National Ministery of Scientific Research and University of Perugia. No financial support for this study was obtained from any pharmaceutical company. This study is dedicated to the patients with T1 DM under the care of our outpatient unit.

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