

Intensive Replacement of Basal Insulin in Patients With Type 1 Diabetes Given Rapid-Acting Insulin Analog at Mealtime

A 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime

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OBJECTIVE — To establish differences in blood glucose between different regimens of optimized basal insulin substitution in type 1 diabetic patients given lispro insulin at meals, i.e., NPH injected four times a day versus glargine insulin once daily at dinner or at bedtime.

RESEARCH DESIGN AND METHODS — A total of 51 patients with type 1 diabetes on intensive therapy (NPH four times/day and lispro insulin at each meal) were randomized to three different regimens of basal insulin substitution while continuing lispro insulin at meals: continuation of NPH four times/day ($n = 17$), once daily glargine at dinnertime ($n = 17$), and once daily glargine at bedtime ($n = 17$) for 3 months. Blood glucose targets were fasting, preprandial, and bedtime concentrations at 6.4–7.2 mmol/l and 2 h after meals at 8.0–9.2 mmol/l. The primary end point was HbA_{1c}.

RESULTS — Mean daily blood glucose was lower with dinnertime glargine (7.5 ± 0.2 mmol/l) or bedtime glargine (7.4 ± 0.2 mmol/l) versus NPH (8.3 ± 0.2 mmol/l) ($P < 0.05$). A greater percentage of blood glucose values were at the target value with glargine at dinner and bedtime versus those with NPH ($P < 0.05$). HbA_{1c} at 3 months did not change with NPH but decreased with glargine at dinnertime (from 6.8 ± 0.2 to $6.4 \pm 0.1\%$) and glargine at bedtime (from 7.0 ± 0.2 to $6.6 \pm 0.1\%$) ($P < 0.04$ vs. NPH). Total daily insulin doses were similar with the three treatments, but with glargine there was an increase in basal and a decrease in mealtime insulin requirements ($P < 0.05$). Frequency of mild hypoglycemia (self-assisted episodes, blood glucose ≤ 4.0 mmol/l) was lower with glargine (dinnertime 8.1 ± 0.8 mmol/l, bedtime 7.7 ± 0.9 mmol/l) than with NPH (12.2 ± 1.3 mmol/l) (episodes/patient-month, $P < 0.04$). In-hospital profiles confirmed outpatient blood glucose data and indicated more steady plasma insulin concentrations at night and before meals with glargine versus NPH ($P < 0.05$). There were no differences between glargine given at dinnertime and at bedtime.

CONCLUSIONS — Regimens of basal insulin with either NPH four times/day or glargine once/day in type 1 diabetic patients both result in good glycemic control. However, the simpler glargine regimen decreases the HbA_{1c} level and frequency of hypoglycemia versus NPH. In contrast to NPH, which should be given at bedtime, insulin glargine can be administered at dinnertime without deteriorating blood glucose control.

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When rapid-acting insulin analogs are used in type 1 diabetic patients as mealtime insulin in place of human regular insulin, intensification of replacement of basal insulin is needed to improve long-term blood glucose control (1,2). This is best achieved with either continuous subcutaneous insulin infusion (3–5) or multiple daily administrations of NPH in addition to the rapid-acting insulin analog (6–12).

The long-acting insulin analog glargine exhibits an action profile flatter and longer than that of NPH insulin (1,13,14). Therefore, it is expected that use of glargine translates into benefits for insulin-requiring patients, especially those with type 1 diabetes. In previous studies (15–21), compared with NPH injected once (15–18) or twice daily (19), administration of glargine insulin at bedtime has reduced fasting blood glucose and decreased the risk for nocturnal hypoglycemia, but the HbA_{1c} level has not decreased (15–20). Currently, with the exception of one acute study (22), no observation has compared the regimen of intensive basal insulin supplementation with multiple daily NPH injections with glargine insulin administration once daily over a period of several months.

A second question is the optimal time of the evening administration of insulin glargine compared with NPH in type 1 diabetes. With the exception of a recent study (23), there are no observations comparing the effects of administration of insulin glargine at dinnertime with those at bedtime. Because of its peak action profile, NPH insulin should be injected in type 1 diabetic patients at bedtime, not at dinnertime, to decrease the risk of nocturnal hypoglycemia (24). In contrast, it is expected that the administration of the nearly peak-less insulin glargine at the more convenient dinnertime does not increase the risk of nocturnal hypoglyce-

mia as compared with bedtime administration.

The aim of these studies was, first, to establish glycemic control over a 3-month period in type 1 diabetic patients comparing two regimens of replacement of basal insulin, i.e., optimized NPH administration (NPH combined with lispro insulin at each meal and a fourth NPH injection at bedtime) (12), and glargine once daily. The second aim was to compare the effects of dinnertime versus bedtime administration of insulin glargine.

RESEARCH DESIGN AND METHODS

Subjects

A total of 51 patients with type 1 diabetes (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), participated in these studies after giving fully informed, written consent. The studies were approved by the local ethic study committee. After a 15-day run-in period during which previous insulin treatment was continued, the patients were randomized to either continuation of the lispro and NPH combinations at each meal and NPH at bedtime ($n = 17$), administration of insulin glargine (Lantus; Aventis Pharmaceutical, purchased from Hostato Apotheke, Frankfurt, Germany) at dinnertime (~ 2000 , $n = 17$), and administration of insulin glargine at bedtime (~ 2300 , $n = 17$) for 3 months. The three groups were matched for age, sex, diabetes duration, insulin doses, and HbA_{1c} level ($P = NS$ between groups). Mealtime lispro insulin was continued in all treatments. The glycemic targets in the three treatments were identical, i.e., blood glucose at 6.4–7.2 mmol/l in the fasting state, before meals, and at bedtime and blood glucose at 8.0–9.2 mmol/l 90 min after meals.

Patients were suggested to decrease or increase the dose of basal insulin if fasting blood glucose was repeatedly < 6.0 or > 7.8 mmol/l and to decrease or increase the dose of rapid-acting insulin at meals if the 2-h postprandial blood glucose was repeatedly < 7.0 or > 9.5 mmol/l. 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

Table 1—Clinical characteristics of the patients studied

| | NPH | Glargine | |
|--|-----------------|-----------------|-----------------|
| | | Dinnertime | Bedtime |
| <i>n</i> | 17 | 17 | 17 |
| Age (years) | 32 \pm 3 | 31.3 \pm 3.4 | 34 \pm 3.1 |
| Sex (M/F) | 9/8 | 8/9 | 10/7 |
| Diabetes duration (years) | 13.1 \pm 1.9 | 12.9 \pm 2.3 | 14.8 \pm 2.3 |
| BMI (kg/m ²) | 23.1 \pm 0.8 | 22.9 \pm 1.0 | 23.2 \pm 0.9 |
| HbA _{1c} (%) | 6.9 \pm 0.1 | 6.8 \pm 0.2 | 7.0 \pm 0.2 |
| Total insulin dose (U \cdot kg ⁻¹ \cdot day ⁻¹) | 0.63 \pm 0.04 | 0.63 \pm 0.04 | 0.68 \pm 0.04 |

Data are means \pm SE.

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 (9,12). The ratio of lispro to NPH was $\sim 70/30$ at breakfast, $\sim 60/40$ at lunch, and $\sim 90/10$ at dinner. The bedtime NPH dose was ~ 0.2 units/kg. Insulin glargine was always injected alone without previous 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. Afterward, 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 units/kg at breakfast and 0.10–0.17 units/kg at lunch and dinner. The lispro doses were adjusted daily on the basis of preprandial blood glucose, blood glucose 2 h after meals of previous days, as well as composition and size of meals and physical activity. NPH doses at each meal were adjusted based on preprandial blood glucose values. 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 at bedtime every day, 2 h after meals every other day, and at 0300 twice a week. In these studies, hypoglycemia was defined as any episode associated with measurement of blood glucose ≤ 4.0 mmol/l irrespective of symptoms, as previously reported (25). Hypoglycemia was considered mild when the episodes were self-treated by the patients and severe when the episode required any kind of external help.

During the last month of each treat-

ment period, eight patients from each of the three groups were randomly selected and admitted to the General Clinical Study Unit of the Department of Internal Medicine on one occasion for a 24-h monitoring study. Patients were admitted in the morning between 0700 and 0730 in the fasting state and initially put to bed. Two intravenous lines were started and kept patent with infusion of 0.9% NaCl solution. One line (superficial, antecubital vein) was prepared for infusion of glucose, if needed, to prevent decrease in plasma glucose concentration < 3.3 mmol/l. The second line was started from a superficial vein of the ipsilateral hand cannulated retrogradely for intermittent blood sampling. Thereafter patients were free to move and walk in the room and corridors. Patients followed a diet as similar as possible to that from home and decided the doses of insulin themselves. Breakfast, lunch, and dinner were served at 0730, 1300, and 1930, respectively. In all patients, samples for plasma glucose determination were obtained every 10–30 min and samples for plasma insulin every 30 min. Patients slept overnight from 2400 until after 0700.

Methods

Capillary blood glucose was measured by the One Touch System (Lifescan, Johnson & Johnson, Milpitas, CA). Plasma glucose was measured using a Beckman Glucose Analyzer (Beckman Instruments, Palo Alto, CA). Plasma insulin was measured by means of a commercially available kit (Linco Research, St. Charles, MO). To remove antibody-bound insulin, plasma was mixed with an equal volume of 30% polyethylene glycol immediately after drawing blood (26). HbA_{1c} was determined by a high-performance liquid chromatography using a HI-Auto A_{1c} TM

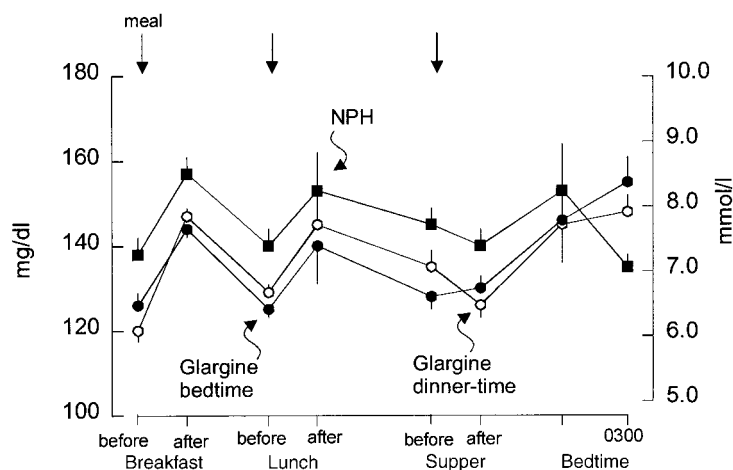


Figure 1—Daily blood glucose (data from blood glucose monitoring of the last month of the 3-month study) in three groups of patients with type 1 diabetes on intensive insulin treatment and lispro insulin at mealtime, given basal insulin either as NPH four times/day or insulin glargine once daily at dinnertime or bedtime.

HA 8121 apparatus (DIC; Kyoto Daiichi, Kogaku, Japan) (range in nondiabetic subjects 3.8–5.5%).

Statistical analysis

The primary end point of the study was the HbA_{1c} level. In this design, a total of 51 subjects were required to achieve 90% power to detect a difference of 0.3% among the means with a common standard deviation within a group assumed to be 0.4 at the significance level (α) of 5%. Statistical analysis was carried out using patients' data of the last month of treatment period using ANOVA (27). Data in text and tables are given as means \pm SE and were considered to be significantly different at $P < 0.05$.

RESULTS

Glycemic control

Glycosylated hemoglobin. With NPH, HbA_{1c} increased slightly, but the difference was not statistically significant. With glargine, HbA_{1c} decreased both with the dinnertime as well as the bedtime treatment ($P < 0.04$). The decreases in HbA_{1c} with dinnertime and bedtime glargine were no different ($P = NS$) (Fig. 1, Tables 2–4).

Blood glucose profile from home blood glucose monitoring. Glargine resulted in lower blood glucose concentration in the fasting state, after breakfast, before lunch, and after lunch ($P < 0.05$). The before-dinner blood glucose with NPH and glargine at dinnertime was similar

($P = NS$) but lower with glargine at bedtime ($P < 0.05$). The after-dinner blood glucose was lower with glargine at dinnertime and bedtime than with NPH ($P < 0.05$), whereas the bedtime blood glucose level was no different with the three treatments ($P = NS$). Finally, the 0300 blood glucose was lower with NPH than with glargine at dinnertime and bedtime ($P < 0.05$). The mean daily blood glucose was lower with glargine (dinnertime 7.6 ± 0.1 mmol/l, bedtime 7.6 ± 0.2 mmol/l) than with NPH (8.1 ± 0.2 mmol/l) ($P < 0.03$). There were no differences between dinnertime and bedtime glargine administration ($P = NS$) (Fig. 1).

Percentage of blood glucose measurements at target. When the percentage of measurements of blood glucose in the target values was calculated in the three treatments, glargine resulted in a greater percentage of blood glucose targets in the fasting state, before meals, and at bedtime (Table 3).

Blood glucose variability. The inpatient variability of blood glucose, calculated as the coefficient of variation of the

blood glucose values over the last month of study with glargine, either at dinner- or bedtime, was no different compared with NPH before meals, 2 h after meals, and at bedtime. Blood glucose variability in the fasting state tended to be lower with glargine at dinnertime ($31 \pm 4\%$) and bedtime ($30 \pm 5\%$) compared with NPH ($34 \pm 4\%$), but the difference did not reach statistical significance. However, blood glucose variability at 0300 was lower with glargine (dinnertime $27 \pm 1\%$, bedtime $25 \pm 1\%$) than with NPH ($32 \pm 1.5\%$) ($P < 0.03$).

Frequency of hypoglycemia. No episodes of severe hypoglycemia occurred in these studies. The frequency of mild hypoglycemia (last month of treatment) was lower with glargine than with NPH ($P < 0.005$), with no differences between glargine at dinnertime and bedtime ($P = NS$). There was no difference in the frequency of diurnal episodes of mild hypoglycemia between treatments ($P = NS$), but glargine resulted in lower frequency of nocturnal episodes (dinnertime 1.7 ± 0.2 , bedtime 2.0 ± 0.19 episodes/patient-month) than NPH (3.6 ± 0.4 episodes/patient-month) ($P < 0.05$), with no differences between glargine at dinnertime and bedtime ($P = NS$) (Table 4).

Insulin doses. Total daily insulin doses were no different at the end of any of the three treatments. With NPH there was no change in mealtime or basal insulin dose. In contrast, with glargine there was a decrease in mealtime insulin lispro and an increase in basal insulin requirements. The decrease in lispro insulin requirements was primarily accounted for by the decrease at breakfast (from 0.08 ± 0.01 to 0.05 ± 0.006 units \cdot kg⁻¹ \cdot day⁻¹ with glargine at dinnertime (from 0.08 ± 0.007 to 0.06 ± 0.007 units \cdot kg⁻¹ \cdot day⁻¹ glargine bedtime). With glargine, both at dinnertime and bedtime, the dose of basal insulin was greater than that for the total NPH daily dose (Table 5).

Table 2—Percentage of HbA_{1c} before and after 3 months of intensive insulin treatment for type 1 diabetes using either NPH (four times/day) or glargine insulin (one time/day) at dinnertime or bedtime, as basal insulin

| | NPH | Glargine at dinnertime | Glargine at bedtime |
|----------------|---------------|------------------------|---------------------|
| Baseline | 6.9 \pm 0.1 | 6.8 \pm 0.2 | 7.0 \pm 0.2 |
| After 3 months | 7.0 \pm 0.1 | 6.4 \pm 0.1* | 6.6 \pm 0.1* |

Data are means \pm SE. * $P < 0.04$ vs. baseline and NPH at 3 months.

Table 3—Mean \pm SE of the percentages of blood glucose values at target values in the treatments with NPH, glargine at dinnertime, and glargine at bedtime (data from home blood glucose monitoring during last month of study)

| | NPH | Glargine at dinnertime | Glargine at bedtime |
|-----------------|------------|------------------------|---------------------|
| Fasting | 20 \pm 3 | 49 \pm 4* | 47 \pm 4* |
| After breakfast | 31 \pm 3 | 35 \pm 3 | 37 \pm 4 |
| Before lunch | 22 \pm 4 | 40 \pm 3* | 45 \pm 4* |
| After lunch | 25 \pm 5 | 33 \pm 6 | 35 \pm 7 |
| Before dinner | 19 \pm 4 | 38 \pm 3* | 42 \pm 2* |
| After dinner | 27 \pm 3 | 35 \pm 5 | 36 \pm 6 |
| Bedtime | 23 \pm 3 | 41 \pm 3* | 42 \pm 3* |

* $P < 0.05$ vs. NPH.

Daily plasma insulin and glucose profile

In the subgroup of patients in whom a plasma glucose and insulin profile was obtained, the pattern of plasma glucose confirmed the observations of blood glucose monitoring of Fig. 1. Mean daily plasma glucose was lower with glargine (dinnertime 7.6 ± 0.2 mmol/l, bedtime 7.7 ± 0.1 mmol/l) than with NPH (8.2 ± 0.2 mmol/l) ($P < 0.05$). Only at 0300 was plasma glucose greater with glargine than with NPH ($P < 0.05$). There were no differences in daily plasma glucose between glargine at dinnertime and bedtime. Plasma insulin concentrations were greater with glargine before breakfast, lunch, dinner, and between 0400 and 0730 ($P < 0.05$). However, with NPH, plasma insulin was greater between 0100 and 0200 ($P < 0.05$). Plasma insulin concentrations with dinnertime and bedtime glargine insulin were similar ($P = NS$) (Fig. 2).

CONCLUSIONS— The present studies were designed to compare two regimens of replacement of basal insulin in type 1 diabetic patients intensively treated with lispro insulin at mealtime, i.e., multiple daily NPH injections and once daily glargine injection, over a period of 3 months. In addition, the present studies examined the effects of the bedtime as compared with dinnertime administration of insulin glargine. The results indicate that both the NPH four times/day and glargine once/day regimens result in good glycemic control, as suggested by the percentage of HbA_{1c} and absence of severe hypoglycemia, as well as relatively low frequency of mild hypoglycemia. However, insulin glargine resulted in lower fasting, premeal, and postmeal

blood glucose compared with NPH; in a greater reduction in HbA_{1c} level; in a lower frequency of hypoglycemia, primarily at night; in 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. Finally, the present studies indicate that the time of evening glargine administration, i.e., dinnertime versus bedtime, does not make a difference in terms of glycemic control. Thus, in contrast to NPH, which should be given preferentially at bedtime to limit the frequency of nocturnal hypoglycemia (24), glargine can be injected at the more convenient dinnertime without compromising nocturnal and day-long glycemic control.

The results of different 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, with glargine plasma insulin did not peak in the early part of the night. This explains the lower frequency of hypoglycemia with insulin glargine compared with NPH. In addition, with insulin glargine, plasma insulin did not decrease

in the second part of the night or before lunch and dinner, thus restraining endogenous glucose production (28,29). Plasma insulin tended to be higher 1–2 h after meals in the glargine compared with the NPH regimens, despite similar (or reduced at breakfast) doses of insulin lispro, most likely because of the greater premeal plasma insulin concentration. Notably, there were no differences in plasma insulin concentrations between glargine given at dinner and at bedtime.

The plasma insulin concentration data after administration of glargine insulin should be interpreted with caution. As of yet, a specific assay for insulin glargine is not available. Because the antibody against human insulin has only 56% cross-reactivity for glargine (internal report, Aventis ex HMR, document no. 016996, 25 September 1997), the results of plasma insulin concentration after subcutaneous glargine injection should be multiplied by a factor of 1.8. The hyperinsulinemia after glargine administration does not translate into greater pharmacodynamic activity compared with human insulin, because it is due to lower clearance by insulin receptors because of lower receptor affinity (14). In the present studies, where patients received subcutaneous insulin lispro in addition to glargine, it was not possible to distinguish between the contribution of the individual insulin analogs to final plasma insulin concentration. Therefore, the plasma insulin data presented are those originally generated by the laboratory without modifications. Due to the rapid disappearance of rapid-acting insulin analogs from plasma after subcutaneous injection (30), it is reasonable to assume that 4–5 h after lispro injection, plasma insulin concentration reflected primarily, if not exclusively, the contribution of glargine insulin. Therefore, the present study underestimates the plasma insulin concentration during

Table 4—Frequency of mild hypoglycemia (defined as any blood glucose reading < 4.0 mmol/l by the reflectometer irrespective of symptoms) before and after a 3-month intensive insulin treatment for type 1 diabetes using either NPH (four times/day) or glargine insulin (one time/day) at dinnertime or bedtime, as basal insulin

| | NPH | Glargine at dinnertime | Glargine at bedtime |
|----------------|----------------|------------------------|---------------------|
| Baseline | 13.9 \pm 0.1 | 12.8 \pm 0.2 | 13.6 \pm 0.2 |
| After 3 months | 12.2 \pm 1.3 | 8.1 \pm 0.8* | 7.7 \pm 0.9* |

Data are means \pm SE. Frequency of hypoglycemia is expressed as episodes/patient-month. * $P < 0.04$ vs. baseline and NPH at 3 months.

Table 5—Insulin doses before and after a 3-month intensive insulin treatment for type 1 diabetes using either NPH (four times/day) or glargine insulin (one time/day) at dinnertime or bedtime, as basal insulin

| | NPH | Glargine at dinnertime | Glargine at bedtime |
|----------------------------|-------------|------------------------|---------------------|
| Baseline | | | |
| Total insulin dose | 0.63 ± 0.04 | 0.63 ± 0.04 | 0.68 ± 0.04 |
| Lispro insulin dose | 0.33 ± 0.02 | 0.33 ± 0.03 | 0.38 ± 0.02 |
| Basal insulin dose | 0.30 ± 0.02 | 0.31 ± 0.03 | 0.31 ± 0.02 |
| After 3 months | | | |
| Total daily units | 0.63 ± 0.04 | 0.65 ± 0.05 | 0.64 ± 0.07 |
| Lispro insulin daily units | 0.33 ± 0.01 | 0.29 ± 0.01* | 0.30 ± 0.02* |
| Basal insulin daily units | 0.30 ± 0.01 | 0.36 ± 0.02* | 0.34 ± 0.01* |

Data are means ± SE. *P < 0.04 vs. baseline and NPH at 3 months.

glargine treatments between midnight and 0730, as well as before lunch and dinner. Although the plasma insulin concentrations of Fig. 2 are more qualitative than quantitative, the present study truly indicates in qualitative terms the difference in plasma insulin after subcutaneous administration of glargine compared with NPH, primarily at night and before meals. In addition, the present study provides evidence that plasma insulin concentrations after glargine administration either at dinner- or bedtime are superimposable.

In the present studies, the once daily glargine insulin regimen was compared with the four times daily NPH administration regimen (6–12) and resulted in lower percentages 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 already in good glycemic control, and because at the same time the frequency of hypoglycemia did not increase but rather decreased. In previous studies comparing NPH and glargine insulin in type 1 diabetes (15–20), the percentage of HbA_{1c} did not differ between treatments. The reasons for such a discrepancy are not entirely clear. However, of note, the previous studies (15–20) were multicenter and designed at a time at which the pharmacokinetics and dynamics of insulin glargine were not known. In contrast, the present study was unicenter and allowed close contact with patients, homogeneity in study conduction, and a greater guarantee of efforts in titration of insulin dose to target. In addition, in former studies, human regular insulin, not rapid-acting analog insulin, was used. A more recent study has reported a greater improvement in percentage of

HbA_{1c} with glargine compared with NPH insulin in markedly hyperglycemic patients with type 1 diabetes, but interpretation of the results is difficult because patients remained in poor control after treatment (21).

The present study offers a guide in terms of insulin doses for transferring patients on intensive therapy from NPH to glargine insulin. The total daily insulin doses of the NPH and glargine regimens were superimposable, but the latter resulted in a greater need for basal and a lower need for doses at mealtime, espe-

cially at breakfast. Specifically, with glargine there was an increase in daily units of basal insulin of ~10% compared with NPH and a specular decrease of lispro requirements primarily at breakfast. As mentioned earlier, the increase in basal insulin dose of glargine did not increase the risk for nocturnal hypoglycemia. In contrast, attempts to increase the bedtime NPH dose during the first 4–6 weeks of study resulted in greater frequency of nocturnal hypoglycemia. Therefore, the NPH insulin dose of the last month of study was ultimately no different from baseline (Table 5).

Because glargine is a soluble insulin, it is expected that its pharmacodynamic effects are less variable within patients with type 1 diabetes compared with those of insulin in suspension, such as NPH (1). The results of the present studies only marginally support such an expectation, because only the blood glucose value at 0300 was less variable with glargine than with NPH insulin. Of note, in the present studies, insulin NPH was given four times daily, and it is likely that this itself reduces the pharmacodynamic variability of NPH. It is possible that had NPH insulin been given only once daily, the variability of blood glucose with insulin glargine re-

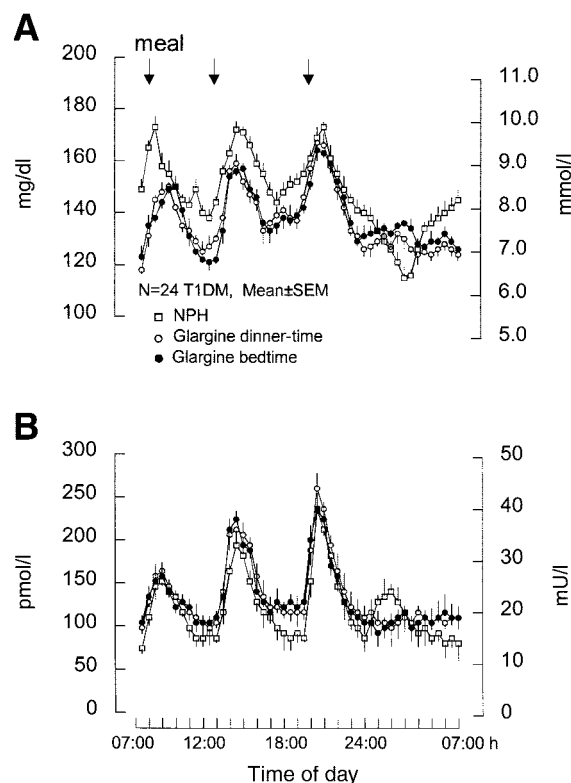


Figure 2—Plasma glucose (A) and insulin (B) concentrations during a 24-h in-hospital monitoring of 24 patients with type 1 diabetes (8 patients on NPH, 8 on glargine at dinnertime, and 8 on glargine at bedtime).

sulted lower than that of NPH, as observed in a previous study (18).

In the present studies, NPH given up to four times daily maintained good glycemic control in type 1 diabetic patients, as indicated by HbA_{1c} level, the absence of severe hypoglycemia, and the relative low frequency of measured (mild) hypoglycemia. However, the present study also indicates that once daily injection of glargine insulin results in several advantages over such an optimized use of NPH. We believe that the most important advantage of insulin glargine over NPH is protection against the risk for hypoglycemia, primarily at night. This finding is consistent with previous studies (15,16, 22). In addition, the present study demonstrates that glargine at the same time decreases the percentage of HbA_{1c}. The latter finding is of note because in the control treatment with NPH both at baseline and at end of study, the percentage of HbA_{1c} indicated good glycemic control of patients. Additional advantages of insulin glargine over NPH are its simpler administration (once compared with four times/day) and also the possibility of its injection in the early (dinnertime) rather than late evening, in contrast to NPH, which should always be administered at bedtime (24).

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This study is dedicated to the patients with type 1 diabetes under the care of our outpatient unit.

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