Pharmacokinetics and Pharmacodynamics of Subcutaneous Injection of Long-Acting Human Insulin Analog Glargine, NPH Insulin, and Ultralente Human Insulin and Continuous Subcutaneous Infusion of Insulin Lispro

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To compare the pharmacokinetics/dynamics of the long-acting insulin analog glargine with NPH, ultralente, and continuous subcutaneous (SC) infusion of insulin lispro (continuous subcutaneous insulin infusion [CSII]), 20 C-peptide–negative type 1 diabetic patients were studied on four occasions during an isoglycemic 24-h clamp. Patients received SC injection of either 0.3 U/kg glargine or NPH insulin (random sequence, crossover design). On two subsequent occasions, they received either an SC injection of ultralente (0.3 U/kg) or CSII (0.3 U · kg^{-1} · 24 h^{-1}) (random sequence, crossover design). After SC insulin injection or CSII, intravenous (IV) insulin was tapered, and glucose was infused to clamp plasma glucose at 130 mg/dl for 24 h. Onset of action (defined as reduction of IV insulin >50%) was earlier with NPH (0.8 ± 0.2 h), CSII (0.5 ± 0.1 h), and ultralente (1 ± 0.2 h) versus glargine (1.5 ± 0.3 h) (P < 0.05) (mean ± SE). End of action (defined as an increase in plasma glucose >150 mg/dl) occurred later with glargine (22 ± 4 h) than with NPH (14 ± 3 h) (P < 0.05) but was similar with ultralente (20 ± 6 h). NPH and ultralente exhibited a peak concentration and action (at 4.5 ± 0.5 and 10.1 ± 1 h, respectively) followed by waning, whereas glargine had no peak but had a flat concentration/action profile mimicking CSII. Interindividual variability (calculated as differences in SD of plasma insulin concentrations and glucose infusion rates in different treatments) was lower with glargine than with NPH and ultralente (P < 0.05) but was similar with glargine and CSII (NS). In conclusion, NPH and ultralente are both peak insulins. Duration of action of ultralente is greater, but intersubject variability is also greater than that of NPH. Glargine is a peakless insulin, it lasts nearly 24 h, it has lower intersubject variability than NPH and ultralente, and it closely mimics CSII, the gold standard of basal insulin replacement.
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ANOVA, analysis of variance; CSII, continuous subcutaneous insulin infusion; Di.M.I., Department of Internal Medicine; IV, intravenous; SC, subcutaneous.

The goal of treatment of type 1 diabetes is maintenance of long-term near-normoglycemia to prevent the onset and/or progression of long-term complications (1,2). At present, this goal is feasible with physiological models of insulin replacement (3), provided that patients are appropriately educated about the strategy of intensive insulin therapy (4,5). However, several obstacles, such as day-to-day variability in insulin requirements and slow (6) and variable absorption (7) of insulin from the subcutaneous (SC) site of injection, make it difficult for type 1 diabetic patients to maintain long-term near-normoglycemia.

The DNA-recombinant technique has led to synthesis of the short-acting human insulin analogs lispro and aspart, which are absorbed faster than human regular insulin and improve 1- and 2-h postprandial blood glucose levels (8). However, better postprandial blood glucose control with short-acting insulin analogs results in improvement in glycemic control in the long term only by the extent to which replacement of basal insulin is optimized at the same time, either by continuous subcutaneous insulin infusion (CSII) or multiple daily administrations of NPH (8). The latter regimen results in lower HbA_{1c} (9), with no increase (9) or a decrease in the frequency of hypoglycemia compared with the regimen based on mealtime administration of human regular insulin and bedtime NPH (8). In turn, less frequent hypoglycemia results in better awareness of and counterregulation to hypoglycemia in the long term (10). However, the approach of multiple daily injections of NPH or CSII may be too demanding for the majority of patients worldwide who use mealtime administration of short-acting insulin analogs.

An ideal basal insulin candidate is a peakless long-lasting preparation that mimics the flat interprandial insulin secretion of nondiabetic subjects, with reproducible SC absorption. The presently available intermediate-acting (NPH) or long-acting (ultralente) insulin preparations are poor surrogates for the ideal basal insulin, primarily because of their peak-action profile (11,12) and day-to-day variability in SC absorption (7). These factors contribute to instability of blood glucose with wide fluctuations from hypoglycemic (especially at night) to hyperglycemic values (particularly in the fasting

state). Clearly, it is important for type 1 diabetic patients who appreciate the advantages of mealtime administration of short-acting insulin analogs to have an SC injectable long-acting insulin preparation that closely mimics the effects of the gold standard of basal insulin replacement (i.e., CSII) (7).

Insulin glargine is a new long-acting human insulin analog soluble at acid pH but less soluble at neutral pH because its isoelectric point is at a pH level of ~6.4–6.6 (8). After SC injection, glargine results in a slow but sustained release of insulin into circulation (8). The aim of the present study was to establish the pharmacokinetic and pharmacodynamic effects of an SC injection of a therapeutic dose of glargine (compared with NPH and ultralente) and CSII in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS

Patients. Institutional Review Board approval was obtained for these studies. A total of 20 type 1 diabetic patients undergoing long-term intensive treatment (12 men, aged 32 ± 2 years, diabetes duration 15 ± 2 years, BMI 22.2 ± 0.4 kg/m^2, fasting plasma C-peptide 0.025 ± 0.01 nmol/l [normal range 1.5–3.0], HbA_{1c} 6.9 ± 0.1%) (4) were recruited among those attending the outpatient Diabetes Clinic of the Department of Internal Medicine (Di.M.I.), University of Perugia. At the time of the study, all type 1 diabetic patients were free of any detectable microangiopathic complication and tested negative at the screening for autonomic neuropathy, as determined by a standard battery of cardiovascular tests (13).

Design of studies. During the 2-week run-in period, patients continued their previously described model of insulin therapy (4), i.e., human regular insulin (or the short-acting insulin analog lispro) at breakfast, lunch, and dinner, and NPH insulin at bedtime. The 11 patients who used lispro at mealtime added NPH to lispro insulin at breakfast, lunch, and dinner, as previously reported (9,10). Afterward, to establish pharmacokinetics and pharmacodynamics of insulin glargine, NPH, ultralente, and CSII of lispro, the patients were studied on four different occasions. The patients were initially studied on two occasions after SC injection of glargine or NPH (random sequence, crossover design). Then, 6–9 months later, the patients were restudied on two additional occasions after SC injection of ultralente or CSII of lispro (random sequence, crossover design).

Comparison between SC glargine and NPH injection. These studies were performed at 2- to 10-week intervals and were double-blinded (a registered nurse gave the SC injection of either glargine or NPH). Patients had the last SC NPH injection the night before the studies at ~2300 and the last SC human regular (or lispro) injection the day of the studies at breakfast. Between 0900 and 1000, patients were admitted to the General Clinical Research Center of Di.M.I. and put to bed. A hand vein in one arm was cannulated retrogradely and maintained in a hot pad (~55°C) for sampling of arterialized venous blood (14). A superficial vein of the contralateral arm was cannulated for intravenous (IV) infusion of insulin and/or glucose. At 1125, an IV infusion of human regular insulin (diluted to 1 U/ml in 2 ml of the subject's blood and 0.9% NaCl to a final volume of 100 ml) was begun using a syringe pump (Harvard Apparatus, Ealing, South Natick, MA) to maintain plasma glucose at 130 mg/dl according to a previously described algorithm (15) and was continued during and after lunch until shortly after 1700. A light lunch (mixed meal of 344 kcal, 54% carbohydrate, 30% protein, and 16% lipids) was served at 1200 and eaten in 15–20 min. Thereafter, patients remained fasted until the end of study. At 1700 (time 0), an SC injection of 0.3 U/kg body wt of either NPH or glargine U-100 insulin was made into the internal part of one thigh by means of a syringe pen device (Optipen; Hoechst Marion Roussel). Before injection, the pen containing the NPH cartridge was adequately tipped until complete suspension was obtained, as recently recommended (16). Afterward, the rate of IV insulin infusion was gradually decreased and ultimately withdrawn when plasma glucose decreased to <125 mg/dl. At this time, IV glucose (10% solution) was started by means of a second syringe pump (Harvard Apparatus) and continued at a variable rate to maintain plasma glucose at the target value of 130 mg/dl (17). IV glucose was withdrawn when plasma glucose increased to >135 mg/dl. The study was terminated 24 h after the SC injection of NPH or glargine or earlier if plasma glucose increased to >200 mg/dl in the absence of glucose infusion. The plasma glucose value of 130 mg/dl was chosen as a realistic goal of intensive therapy, i.e., a compromise between normoglycemia and need to avoid hypoglycemia (18).

Comparison between CSII of lispro and SC ultralente injection. These studies were always performed after the above-described studies with glargine and NPH and were similar to the above-described studies, except that at 1700, either CSII of lispro (Eli Lilly, Indianapolis, IN) was begun at the rate of 0.3 U · kg^{-1} · 24 h^{-1} or 0.3 U/kg ultralente insulin (Eli Lilly) was injected into the internal part of one thigh. In contrast to the glargine and NPH studies, ultralente and CSII studies were not blind. CSII was performed by means of a separate Harvard pump equipped with a 2.5-ml syringe delivering U-40 lispro insulin through a 29-gauge butterfly needle inserted in the SC tissue of the abdomen 2 cm to the left or right of the umbilicus. Ultralente insulin (U-40) was injected by means of a syringe. Before injection, care was taken to resuspend the ultralente insulin in the vial by adequate tipping.

Analytical methods. Plasma glucose was measured using a Beckman Glucose Analyzer (Beckman Instruments, Palo Alto, CA). Plasma C-peptide (19) and free insulin (20) were measured by previously described radioimmunoassay methods. In all studies, plasma insulin was measured after extraction of antibodies with 30% polyethylene glycol (21). As yet, a specific assay for insulin glargine is not available. Therefore, the results of plasma insulin concentration after SC injection of glargine were calculated as reported below. HbA_{1c} was determined by high-performance liquid chromatography using an HI-Auto A_{1c} TM HA 8121 apparatus (DIC, Daaichi, Kogaku Co., Kyoto, Japan) (range in nondiabetic subjects 3.8–5.5%). The intra-assay coefficient of variation in the 5.0–8.0% range in our laboratory was 1.2%.

Calculations

Plasma insulin concentration after SC glargine injection. Because antibody against human insulin has only a 56% cross-reactivity for glargine (internal report, Aventis ex Hoechst Marion Roussel, document no. 016996, 25 September 1997), the results of the plasma insulin concentration after SC glargine injection should be multiplied by a factor of 1.8. This step would result in an accurate estimate of plasma insulin concentration in the absence of other sources of insulin delivery. Therefore, in the glargine study, the values were multiplied by 1.8 from 3 h onward when the rate of IV insulin infusion was nearly nil. In all four studies, but not in the glargine study, the values of plasma insulin concentrations at 1 and 2 h were calculated, subtracting the contribution of the IV insulin infusion rate (as the percentage reduction compared with time 0) from the measured plasma insulin and assuming that the difference would reflect the plasma insulin concentration derived from SC absorption of insulin. In the glargine study, these two values are indeterminate because of the uncertainty of the source of insulin in plasma (IV regular insulin vs. SC glargine).

Pharmacodynamics after SC injection of insulin or CSII. Because the meal was light and 5 h had elapsed between meal administration and SC injection of insulin, it was assumed that at time 0 (1700), type 1 diabetic patients were in the postabsorptive state. The parameters of pharmacokinetics were calculated as follows. Onset of action was defined as the time after SC injection of insulin or CSII, at which the rate of IV insulin consistently decreased by 50% compared with the 20-min preinjection time period. End of action was defined as the time at which plasma glucose consistently increased to >150 mg/dl. If plasma glucose was ≤150 mg/dl by the end of study at 24 h, then 24 h was assumed as the end of action. Such an assumption underestimates the end of action. Duration of action was defined as the time period between the end and onset of action.

Statistical methods. Data are expressed as means ± SE. All end points derived from the comparison of glargine and NPH were analyzed by analysis of variance (ANOVA) for crossover design with sequence (subjects and treatment included in the model). The same analysis was carried out on data obtained from ultralente and CSII studies. In addition, to compare the results of both crossover studies, data were subjected to ANOVA with subjects as a random effect and treatment condition as a fixed effect, followed by multiple comparison tests (Bonferroni's procedure) (22). P values <0.05 were considered statistically significant. One important factor when injecting insulin formulations subcutaneously is reproducibility of absorption (7). The present studies were not specifically designed to assess intrasubject variability. However, it was possible to calculate intersubject variability of effects of SC glargine and NPH, and ultralente and CSII were calculated by comparing the SDs of plasma insulin concentration and rates of glucose infusion obtained in the 24 h of the studies.

RESULTS

Preinjection and preinfusion period (1200–1700)

Plasma glucose concentration, rates of IV insulin infusion, and plasma insulin concentrations were superimposable in the glargine and NPH studies as well as in the ultralente and CSII (NS, data not shown).

Postinjection and postinfusion period (0–24 h)

Insulin infusion rate. After SC insulin injections or CSII, the rate of IV insulin decreased in all studies. The withdrawal of IV insulin infusion was faster with NPH (1.65 ± 0.15 h) than

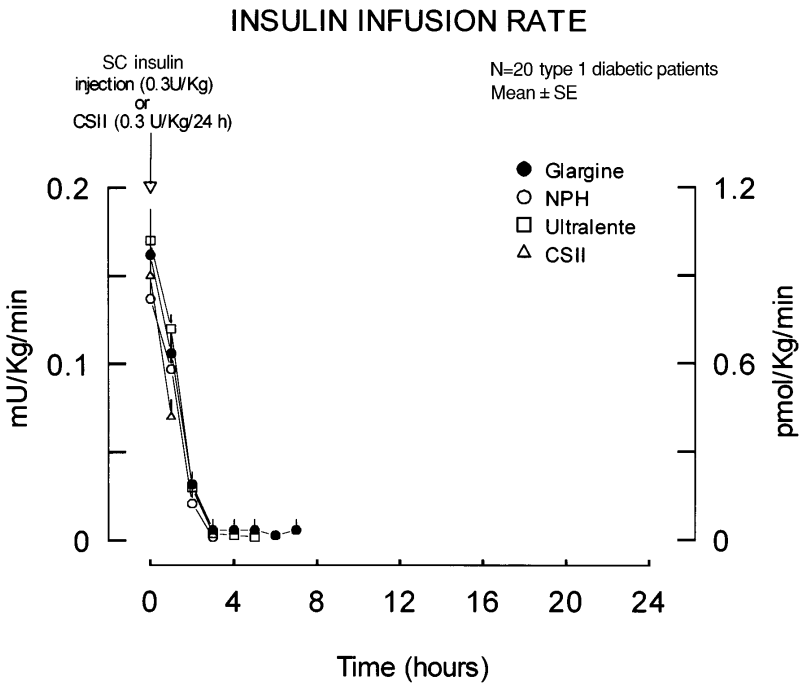

FIG. 1. Rates of IV insulin infusion needed to maintain plasma glucose at the target value of 130 mg/dl after SC injection of glargine, NPH, and ultralente and after CSII of lispro.

with glargine (2.1 ± 0.32 h) ($P < 0.05$). As expected, the withdrawal was faster with CSII (0.9 ± 0.08 h) than with ultralente (1.9 ± 0.18 h) ($P < 0.001$) (Fig. 1).

Plasma insulin concentration. After SC injection of NPH, plasma insulin increased rapidly to a peak of 22.8 ± 2.2 µU/ml at 4 h and thereafter decreased to below baseline by 13 h. This result was associated with an increase in plasma glucose to >200 mg/dl in two patients after 12 h. Because the study was terminated whenever plasma glucose increased to >200 mg/dl, the number of patients in the NPH study decreased from 20 at 12 h to 18 at 13 h, 16 at 14 h, 15 at 15 h, 7 at 17 h, 4 at 18 h, and 2 at 19 h. No patient was in the study after 20 h. After SC injection of glargine, plasma insulin increased to a plateau concentration of 18.9 ± 0.3 µU/ml between 3 and 24 h, with no peaks. All patients continued the glargine study until 24 h (Fig. 2).

With CSII, plasma insulin concentration reached a plateau between 4 and 24 h (20.6 ± 0.2 µU/ml). In contrast, after SC injection of ultralente, plasma insulin increased to a peak of 25.9 ± 2.1 µU/ml at 10 h and was below baseline after 19 h. All patients continued the ultralente and CSII studies until 24 h.

Glucose infusion rate. Glucose infusion started earlier after NPH (at 1.95 ± 0.2 h) than after glargine (at 6.25 ± 1.7 h) ($P < 0.05$). With NPH, the glucose infusion rate reached a peak of 3.4 ± 0.6 mg · kg^{-1} · min^{-1} at 5.4 ± 0.3 h and then decreased to 0 by 20 h. In contrast, with glargine, the glucose infusion

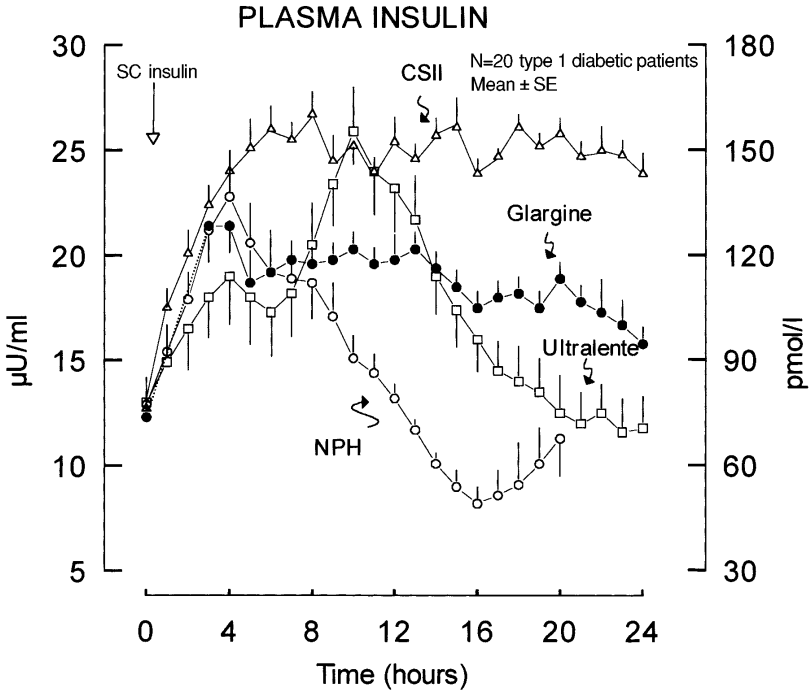

FIG. 2. Plasma (free) insulin concentrations after SC injection of glargine, NPH, and ultralente and after CSII of lispro. Because it was decided to terminate the study when the plasma glucose level was consistently increased to >200 mg/dl, in the NPH study there were 20 patients until 12 h, 18 until 13 h, 16 until 14 h, 15 until 15 h, 7 until 17 h, 4 until 18 h, and 2 until 19 h. Because a specific assay for measurement of glargine insulin in plasma is not available (see RESEARCH DESIGN AND METHODS), the estimated plasma insulin concentration after SC injection of glargine cannot be calculated in the presence of a significant rate of IV insulin infusion (····, 1 and 2 h).

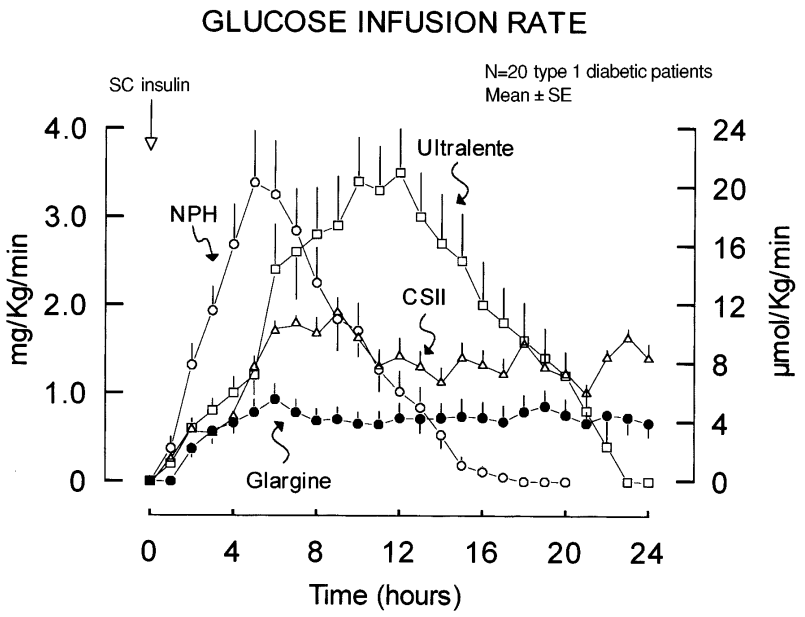

FIG. 3. Rates of glucose infusion needed to maintain plasma glucose at the target value of 130 mg/dl after SC injection of glargine, NPH, and ultralente and after CSII of lispro. In the NPH study, the number of patients decreased after 12 h (see legend to Fig. 2).

rate was nearly constant between 3 and 24 h (0.78 ± 0.6 mg · kg^{-1} · min^{-1}) (Fig. 3).

With CSII, the glucose infusion rate reached a plateau between 5 and 24 h (1.4 ± 0.4 mg · kg^{-1} · min^{-1}). In contrast, with ultralente, the glucose infusion rate increased to a peak of 3.5 ± 0.7 mg · kg^{-1} · min^{-1} at 12 h and then decreased to 0 by 23 h.

Plasma glucose. With NPH, plasma glucose concentration was maintained at the target of 130 mg/dl until 11 h, and then it increased progressively to a peak of 178 ± 17 mg/dl at 20 h. In contrast, with glargine, plasma glucose was at the target value until 15 h and then increased slightly to 141 ± 5 mg/dl between 16 and 24 h (Fig. 4).

With CSII, plasma glucose remained at the target value of 130 ± 2 mg/dl until 24 h. In contrast, with ultralente, plasma glucose increased progressively after 15 h to a peak of 166 ± 7 mg/dl at 24 h ($P < 0.05$ vs. CSII).

Pharmacodynamic parameters. NPH had an earlier onset of action, earlier end of action, and a shorter duration of action than glargine. As expected, CSII had an earlier onset of action and a greater end of action and duration of action than ultralente (Table 1).

Intersubject variability. Intersubject variability of the rate of glucose infusion was lower with glargine (0.64 ± 0.05 mg · kg^{-1} · min^{-1} [mean ± SE of SD]) than with NPH (1.05 ± 0.18 mg · kg^{-1} · min^{-1}, $P < 0.05$). As expected, intersubject variability was greater with ultralente than with CSII for the plasma insulin concentration (8.3 ± 0.28 vs. 4.1 ± 0.24 µU/ml) as well as for the rates of glucose infusion (1.5 ± 0.2 vs. 0.65 ± 0.04 mg · kg^{-1} · min^{-1}) (ultralente vs. CSII, respectively, $P < 0.001$) (Fig. 5).

DISCUSSION

The present studies were undertaken to directly compare the pharmacokinetics and pharmacodynamics of the new long-acting human insulin analog glargine with the intermediate-acting insulin NPH, most commonly used in type 1 diabetic patients to replace the need for basal insulin. In a sec-

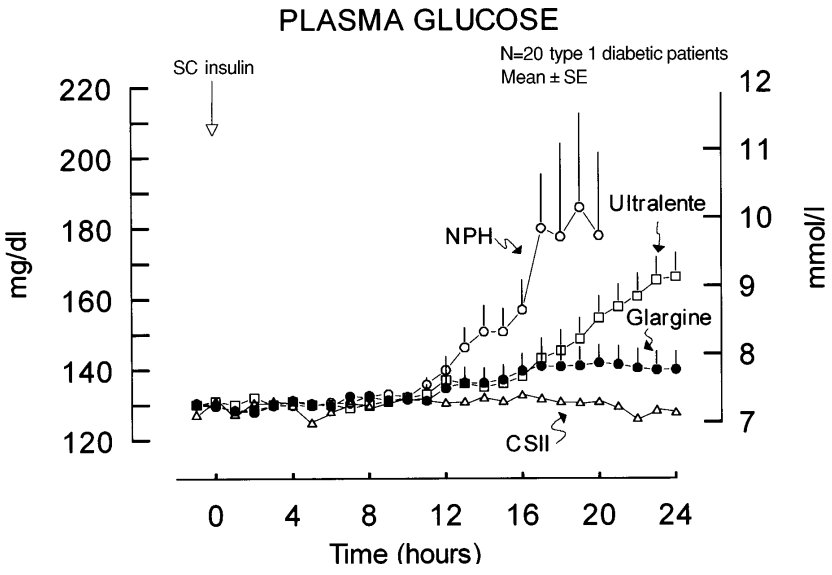

FIG. 4. Plasma glucose concentration after SC injection of glargine, NPH, and ultralente and after CSII of lispro. In the NPH study, the number of patients decreased after 12 h (see legend to Fig. 2).

TABLE 1
Pharmacodynamics of SC injection of glargine and NPH (0.3 U/kg), SC injection of ultralente (0.3 U/kg), and CSII of lispro (0.3 U · kg^{-1} · 24 h^{-1})

	Glargine	NPH	CSII	Ultralente
Onset of action (h)	1.5 ± 0.3	0.8 ± 0.2*	0.5 ± 0.1*	1.0 ± 0.2*
End of action (h)	22 ± 4	14 ± 3*	24 ± 0*	20 ± 6
Duration of action (h)	20.5 ± 3.7	13.2 ± 2.8*	23.5 ± 0*	19 ± 5.8

Data are means ± SE. Onset of action is defined as the time after SC injection of insulin or CSII at which the rate of IV insulin consistently decreased by 50% compared with the 20-min preinjection time period. End of action is defined as the time at which plasma glucose consistently increased to >150 mg/dl. Duration of action is defined as the difference between onset and end of action. *P < 0.05 vs. glargine.

ond set of experiments, the same type 1 diabetic patients were restudied after SC injection of the long-acting insulin ultralente as well as after treatment with the gold standard of basal insulin replacement, CSII. Although the latter two studies were performed after the first two studies, and therefore the results of the four studies cannot be immediately compared, it is still possible to indirectly compare the four treatments and draw meaningful conclusions for treatment of patients with type 1 diabetes.

The present studies demonstrate that in C-peptide–negative patients with type 1 diabetes, the SC injection of the long-acting insulin analog glargine has a peakless, nearly 24-h duration of action. This is strikingly different from the peak of NPH, which exhibits a considerably shorter duration of action and greater intersubject pharmacodynamic variability than glargine. Ultralente has a long duration, but it exhibits a peak similar to that of NPH. Because of the long duration of action, ultralente exhibits high variability of its pharmacokinetic and pharmacodynamic effects, as expected for insoluble retarded-action insulin preparations (7), and therefore its peak of action appears broader than that of NPH. With the notable limitation of the design of studies mentioned above, the activity of an SC injection of glargine qualitatively mimics closely the action profile of an identical dose of lispro insulin given over 24 h as CSII while exhibiting similar intersubject pharmacodynamic variability. Thus, this study suggests that an SC injection of the long-acting insulin analog glargine meets the criteria of a suitable candidate to replace basal insulin in type 1 diabetes (8).

The results of the present study have been obtained with the isoglycemic glucose clamp technique. Some aspects of this methodology should be discussed.

First, in the present clamp studies, the plasma glucose target was set at a slight hyperglycemic level (130 mg/dl) (not strictly at euglycemia) to better approach the clinical situation of intensive therapy of type 1 diabetes, aiming at realistic, not ideal, glycemic goals (18).

Second, to better mimic the real-life conditions of type 1 diabetic patients who need basal insulin especially at night, glargine or NPH insulin was injected subcutaneously in the late afternoon, and the evening meal was omitted to maintain the postabsorptive state.

Third, the definition of onset and end of action of the SC injection and CSII deserves a comment. In the present studies, onset of action was defined as the time at which the IV insulin requirements consistently decreased to <50%. This is a conservative estimate of onset of action. In fact, one might assume that action of SC insulin began earlier. However, the choice was made in view of the potential difficulty of the manual feedback insulin infusion during the initial phase of SC absorption of long-acting insulin preparations such as glargine and ultralente. End of action was defined as an increase in plasma glucose >150 mg/dl. This is an underestimation of the end of action because the effect of SC insulin clearly extends beyond the increase in plasma glucose concentration from 130 to 150 mg/dl. However, the choice of the criterion was based on the consideration that during intensive therapy, a good basal insulin level should maintain a given

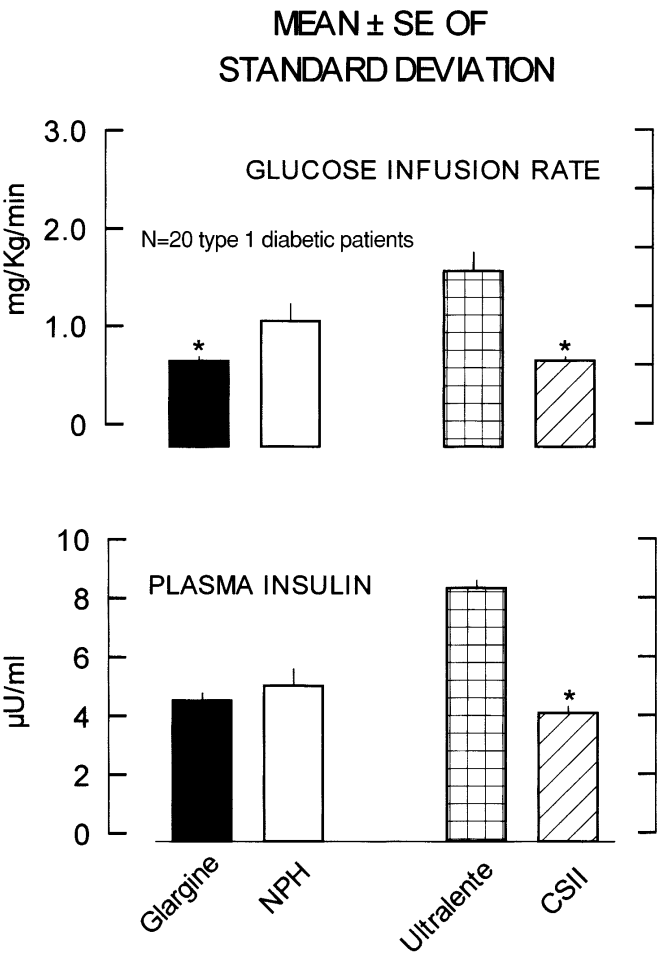

FIG. 5. Intersubject variability of plasma glucose and insulin concentrations and rates of glucose infusion calculated from the SDs of the 24 time points of the studies after SC injection of glargine, NPH, and ultralente and after CSII. *P < 0.05.

baseline plasma glucose constant over time. Certainly, end of action of SC glargine was underestimated in 16 type 1 diabetic patients in the present studies, whose plasma glucose concentration was still <150 mg/dl at 24 h. Theoretically, it would have been necessary to prolong the studies over 24 h, but this was not acceptable to the patients.

Fourth, the dose injected subcutaneously in the present studies (0.3 U/kg) is well within the range of the evening dose of intermediate- or long-acting insulin used in type 1 diabetes; the rate of CSII, which in the present studies was ~0.8 U/h (18), is also within the usual therapeutic range. Interestingly, in the present study, the therapeutic NPH dose resulted in peak activity and subsequent waning, as previously reported, similar to an SC injection of 0.2 U/kg lente insulin in type 1 diabetic patients (23). This observation confirms that an evening administration of intermediate-acting insulin NPH or lente cannot maintain fasting normoglycemia 10–12 h after SC injection without carrying over considerable risk for nocturnal hypoglycemia, as reported in cross-sectional (24) and prospective studies (25). On the other hand, if the dose of evening NPH or lente is titrated down to prevent nocturnal hypoglycemia, insulin waning will occur in the early part of the night, and hyperglycemia will develop the next morning (24).

As for any new insulin preparation, for glargine it is important to determine the variability compared with presently available NPH and ultralente. In the present studies, it was not possible to examine intrasubject variability because the type 1 diabetic patients were studied only once with each SC insulin injection. However, the present studies offer some indication regarding intersubject variability. The intersubject variability after glargine and NPH and after ultralente and CSII in the 24-h clamp studies was examined by analyzing the SD values of the 24 hourly time points (Fig. 5). The greater variability of ultralente compared with CSII was well expected (7). However, it was interesting to see that glargine had lower intersubject variability than NPH and that it was indeed similar to that of CSII. Although intersubject variability does not necessarily predict intrasubject variability in type 1 diabetes, it is nevertheless interesting to see that glargine, which has a longer duration of action than ultralente, has at the same time lower intersubject variability than NPH, which has a shorter duration of action. Likely, this is the result of the fact that glargine is a soluble insulin, whereas NPH and ultralente are insoluble insulin preparations (7). A recent study in normal nondiabetic subjects examined the intrasubject variability of SC glargine, NPH, and ultralente and found that glargine is less variable than ultralente but is similar to NPH (26).

In this study, the pharmacokinetics and pharmacodynamics of ultralente insulin have been assessed in type 1 diabetic patients. To the best of our knowledge, there are no studies in which ultralente insulin has been studied with the glucose clamp technique in type 1 diabetes. Starke et al. (12) studied normal nondiabetic subjects after SC injection of ultralente during combined continuous IV infusion of insulin to suppress endogenous insulin secretion. As for clamp studies in general done in nondiabetic individuals, duration of action appears longer in nondiabetic subjects than in type 1 diabetic patients either with short-acting analogs (27,28), human regular insulin (27,28), NPH (29), or glargine (30,31). The reason is probably the ongoing endogenous insulin secretion that amplifies the small "tail" of action of the subcutaneously injected insulin and also the technical approach of maintaining plasma glucose at 90 mg/dl during a prolonged fast. Because plasma glucose decreases during a prolonged fast (32), the artificial maintenance of euglycemia may stimulate endogenous insulin secretion and exaggerate the rate of glucose infusion. Regardless of the explanation, it is important to note that pharmacokinetics and pharmacodynamics are defined in the real users, i.e., C-peptide–negative patients with type 1 diabetes.

The present studies indicate that nearly 50 years after Hagedorn introduced NPH, insulin glargine, a more suitable insulin preparation to replace the need for basal insulin in type 1 diabetes, appears to be available. However, some questions need to be answered before insulin glargine can be considered the basal insulin of choice in type 1 diabetes. First, studies are needed to establish the pharmacokinetics and pharmacodynamics after several days of glargine administration to assess whether there is an accumulation of its effect over time. Second, prospective studies are needed to prove that glargine once daily may be optimally combined with short-acting insulin analogs (lispro or aspart insulin) at each meal and that glargine decreases the risk for nocturnal hypoglycemia, reduces postabsorptive plasma glucose, and decreases HbA_{1c} when compared with NPH.

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