Randomized Controlled Clinical Trial of Glargine Versus Ultralente Insulin in the Treatment of Type 1 Diabetes

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OBJECTIVE — Multiple daily insulin injection programs are commonly accompanied by considerable glycemic variation and hypoglycemia. We conducted a randomized crossover design clinical trial to compare glargine with ultralente insulin as a basal insulin in type 1 diabetes.

RESEARCH DESIGN AND METHODS — To determine whether the use of glargine insulin as a basal insulin would result in a comparable HbA_{1c} and less glycemic variation and hypoglycemia than ultralente insulin, 22 individuals (aged 44 ± 14 years [±SD], 55% men) with type 1 diabetes who were experienced with multiple daily insulin injections and had an HbA_{1c} of <7.8% were randomized in a crossover design to receive either glargine or ultralente as the basal insulin for 4 months. Aspart insulin was used as the prandial insulin. Physicians providing insulin dose adjustment advice were masked to the type of basal insulin.

RESULTS — Treatment with glargine resulted in lower mean HbA_{1c} (6.82 ± 0.13 vs. 7.02 ± 0.13, difference: 0.2 ± 0.08, $P = 0.026$), less nocturnal variability (plasma glucose 49.06 ± 4.74 vs. 62.36 ± 5.21 mg/dl, $P = 0.04$), and less hypoglycemia (24.5 ± 2.99 vs. 31.3 ± 4.04 events, $P = 0.05$), primarily due to less daytime hypoglycemia ($P = 0.002$). On the other hand, serious hypoglycemia and average glucose concentration measured with continuous subcutaneous glucose monitoring did not differ.

CONCLUSIONS — We conclude that while use of either ultralente or glargine as a basal insulin can result in excellent glycemic control, treatment with glargine is associated with slightly but significantly lower HbA_{1c} and less nocturnal glycemic variability and hypoglycemia.

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Type 1 diabetes is characterized by severe insulin deficiency. Injection of rapidly absorbed insulin before each meal and intraprandial and nocturnal coverage with a continuous subcutaneous insulin infusion or injection of a slowly absorbed "basal" insulin preparation can lower HbA_{1c} to values that are close to those observed in nondiabetic individuals. However, near normalization of HbA_{1c} is accompanied by a substantial increase in the prevalence of serious hypoglycemia (1). In the past, ultralente or NPH insulin were commonly used to provide basal insulin concentrations (2).

More recently, glargine has been shown to be an effective basal insulin preparation. Several studies have shown that when compared with NPH insulin, use of glargine as a basal insulin preparation results in comparable or lower HbA_{1c} concentrations and lower frequency of nocturnal hypoglycemia (3). However, the observation that nocturnal hypoglycemia was lower with glargine than NPH insulin is not particularly surprising since insulin concentrations peak 6–8 h after injection (i.e., in the middle of the night) when NPH insulin is injected at bedtime.

Ultralente has also been used as a basal insulin preparation (4). While beef-pork ultralente is essentially peakless and lasts at least 24 h, (5), human ultralente peaks at 12–16 h (6) and has been reported to be more variable than glargine (7). Therefore, use of glargine as a basal insulin for people with type 1 diabetes may result in better glycemic control, less glycemic variability, and a lower frequency of hypoglycemia. If so, glargine is a better basal insulin than ultralente. If not, since ultralente is considerably less expensive than glargine, its continued use to treat type 1 diabetes may be a reasonable option. The present experiments addressed these questions.

RESEARCH DESIGN AND METHODS

— The Mayo Institutional Review Board approved all procedures. Twenty-four subjects with type 1 diabetes participated in the study. Subjects were aged 18 years or older, with HbA_{1c} <7.8% and fasting C-peptide concentration <200 pmol/l. All subjects were using a multiple daily injection insulin program, with glargine or ultralente as the basal insulin preparation and a rapid-acting insulin at the time of enrollment. All were in good health and had been previously instructed in the principles of insulin dose adjustment.

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Abbreviations: CGMS, continuous subcutaneous glucose monitoring.

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

Table 1—*Demographics and disease variables at baseline of patients enrolled in trial*

Variables	Values
Demographics	
Men	10% (45.5)
Women	12% (54.6)
Age (years)	43 (24–72)
BMI (kg/m^2)	25.9 (21.0–36.5)
Diabetes history	
Duration of diabetes (years)	16 (3–54)
Age at onset (years)	24 ± 2.8
Metabolic control at baseline	
HbA_{1c} (%)	6.94 ± 0.14

Data are means ± SE, *n* (%), or median (range).

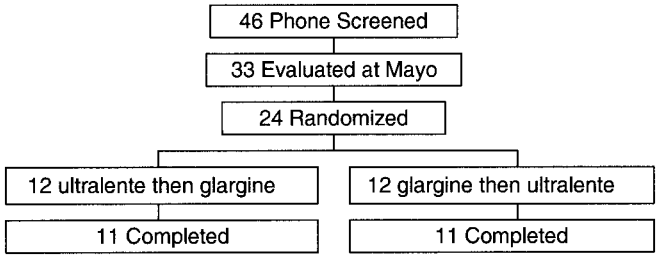

Figure 1—*Flow of patients through the trial.*

Blinding

The study was designed as a randomized, partially blind, crossover clinical trial. The primary end point was end-of-treatment-period HbA_{1c}. At enrollment, all patients started on aspart insulin as the prandial insulin. All enrolled subjects were randomized at a central location to treatment with glargine or ultralente as the basal insulin. Subjects were given the insulin preparations by a trial coordinator. Investigators involved in insulin dose adjustment were blinded to patient allocation to the treatment arms. Conversion from the prior basal insulin was made on a unit-by-unit basis. Basal insulin was given at bedtime. Before randomization, subjects underwent 3 days of continuous subcutaneous glucose monitoring (CGMS; Medtronic, MiniMed, Northridge, CA). A certified diabetes educator reviewed the principles of self-monitoring of blood glucose and provided guidelines for dose adjustments of short-acting and basal insulin preparations and supplementation of short-acting insulin.

Following randomization, endocrinologists, blinded to the patients' treatment allocation, assisted patients in titrating the dose of the basal insulin to achieve fasting, premeal, and bedtime glucose values of 80–120 mg/dl. The titration period was continued until adequate (in the investigator's judgment) glycemic control had been achieved. Subjects continued on the same basal insulin for a total of 16 weeks in each arm. Then patients crossed over, followed the same titration procedure, and used the other basal insulin agent for 16 weeks.

Data analyses

Glycemic control and variability. HbA_{1c} was measured in a central reference laboratory by high-performance liquid chromatography (Biorad, Hercules, CA) by personnel blinded to allocation. Fasting and preprandial meal glucose measurements were downloaded from memory glucometers. Variability in glucose measurements was assessed by two different techniques. We used the method that Service et al. (8) described to quantify glycemic variability termed mean amplitude glycemic variation using glucose concentrations on seven occasions in a 24-h period at the end of every month. In addition, CGMS was used to measure glucose concentrations every 5 min over a 72-h period at the start of the study and at the end of each 4-month period. The accuracy of CGMS was confirmed by independently measuring plasma glucose using the patient's meter every 6 h. Using the software MiniMed Solutions version 2.0B, all measurements analyzed had a correlation between the meter and sensor readings of ≥0.79, with absolute differences ≤28%. The time interval from 11:00 P.M. to 6:00 A.M. constituted the nocturnal period.

Hypoglycemia. Hypoglycemia was defined as symptoms suggestive of hypoglycemia with simultaneous capillary blood glucose <60 mg/dl during self-monitoring of blood glucose. Serious hypoglycemia was defined as symptoms consistent with severe hypoglycemia requiring third-party assistance with capillary blood glucose <50 mg/dl. Hypoglycemia-related quality of life was assessed using the Fear of Hypoglycemia Questionnaire at the start and end of the study (9). This questionnaire quantifies fear of hypoglycemia in type 1 diabetes.

Table 2—*Glycemic end points during trial*

	On glargine	On ultralente	Glargine-ultralente	*P*
Mean glycemia*	154.11 ± 9.97	145.54 ± 8.24	8.57 ± 6.76	0.2309
Fasting glucose*	155.28 ± 13.99	190.99 ± 23.25	−35.70 ± 15.97	0.0471
Preevening meal glucose*	167.56 ± 16.82	146.28 ± 11.83	21.28 ± 10.88	0.0763
The mean amplitude glycemic variation (7-point glucose readings)	110.49 ± 7.26	113.02 ± 9.19	−2.53 ± 9.31	0.7885
CGMS mean values	138.36 ± 5.84	148.21 ± 6.07	−9.85 ± 6.64	0.1530
CGMS (±SD)	59.05 ± 3.66	66.07 ± 3.99	−7.02 ± 3.67	0.0695
CGMS nocturnal values (±SD)	49.06 ± 4.74	62.36 ± 5.21	−13.29 ± 5.91	0.0360

Data are means ± SE, unless otherwise indicated. *Includes 12 participants. Self-monitoring of blood glucose data for everyday of the trial were available for 12 of 22 patients in the trial. Mean glycemia, fasting glucose, and pre-evening meal glucose are calculated for only these 12 participants.

Statistical methods

The primary end point was end-of-treatment-period HbA_{1c}. Equivalence of HbA_{1c} was defined a priori as an absolute difference of <0.5% in mean HbA_{1c} between the two treatments (2). To compare continuous outcomes, paired *t* tests on untransformed or log-transformed response or Wilcoxon's signed ranks tests were used, where appropriate. Descriptive statistics in the text are means ± SE. When data are skewed, we have reported median with range in tables such as Tables 1 and 3. For nonordinal categorical responses, sign tests were used. Linear mixed-effects models or general estimating equations, where appropriate, were used to determine period effects; however, none were found (data not shown).

RESULTS — Twenty-four patients with type 1 diabetes gave informed consent and participated. Table 1 shows baseline characteristics of the patients. The flow of patients is shown in Fig. 1. Two patients were unable to adhere to the study protocol and did not complete the study; therefore, 22 patients contributed comparative data (glargine vs. ultralente) to the analysis.

Insulin dose adjustment

Neither the dose (24 ± 2.1 vs. 23 ± 2.0 units) nor the time (31 ± 3.9 vs. 26 ± 1.6 days) required to titrate to a stable basal dose differed during treatment with ultralente or glargine. However, the number of contacts required to achieve an adequate basal dose was greater during treatment with ultralente than glargine (8.5 ± 1.06 vs. 6.3 ± 0.52, $P = 0.04$). Both the number of changes in the prandial insulin dose (2.3 ± 0.54 vs. 1.1 ± 0.29, $P = 0.05$) and the amount of prandial insulin (28 ± 3.1 vs. 26 ± 2.5 units, $P = 0.02$) was greater on ultralente than on glargine.

Glycemic control. HbA_{1c} was 6.94 ± 0.14% at baseline. HbA_{1c} (Fig. 2) following glargine was lower than following ultralente (6.82 ± 0.13% vs. 7.02 ± 0.13%, difference: 0.2 ± 0.08%, $P = 0.03$). Thirteen subjects on ultralente (59.1%) had an HbA_{1c} <7.0%, whereas 15 (68.2%) had an HbA_{1c} <7.0% with glargine. Therefore, our study showed that the two insulin preparations were equivalent according to criteria set a priori. However, HbA_{1c} at the end of the glargine phase was slightly but significantly lower than ultralente. The order in which the two basal insulin preparations were used in the trial did not influence A1c glargine or ultralente. Self-monitoring of blood glucose data daily throughout the trial was available for 12 patients (Table 2). Fasting plasma glucose was lower with glargine (155 vs. 191 mg/dl, $P = 0.047$) than with ultralente. Neither the mean amplitude glycemic variation based on a 7-point glycemic profile (110.49 ± 7.26 vs. 113.02 ± 9.19 mg/dl) nor mean 24-h CGMS glucose (138.36 ± 5.84 vs. 148.21 ± 6.07 mg/dl) differed on glargine and ultralente (Table 2). On the other hand, the mean SD of the 24-h blood CGMS glucose measurements tended to be lower following treatment with glargine than ultralente (59.05 ± 3.66 vs. 66.07 ± 3.99, $P = 0.07$).

Frequency of hypoglycemia. As shown in Table 3, patients reported more hypoglycemic events during treatment with ultralente than with glargine (31.3 ± 4.04 vs. 24.5 ± 2.99 events, $P = 0.05$); this difference was particularly marked for daytime hypoglycemia (28.6 ± 3.89 vs. 19.9 ± 2.48, $P = 0.001$). On the other hand, the number of episodes of nocturnal hypoglycemia tended to be fewer on ultralente than glargine (2.7 ± 0.59 vs. 4.6 ± 1.18, $P = 0.07$). The number of episodes of severe hypoglycemia did not differ during treatment with ultralente or glargine (0.1 ± 0.07 vs. 0.1 ± 0.07, $P = 1.00$).

Fear of Hypoglycemia Questionnaire. The Fear of Hypoglycemia Questionnaire consists of two scales: the Behavior and the Worry scales. Whereas the Behavioral scale score did not differ during treatment with ultralente or glargine (1.8 ± 0.13 vs. 1.7 ± 0.13, $P = 0.44$), the Worry scale score was lower with glargine than ultralente (1.2 ± 0.12 vs. 1.4 ± 0.11, $P = 0.04$).

CONCLUSIONS — Our randomized trial demonstrates that excellent, but not normal, glycemic control can be achieved when either ultralente or glargine is used as a basal insulin. However, the use of glargine resulted in slightly lower HbA_{1c}, less nocturnal glycemic variation, and a decreased frequency of hypoglycemia, particularly during the day. In addition, use of glargine as a basal insulin resulted in patients worrying less about hypoglycemia.

Insulin secretion in nondiabetic individuals is a complex process requiring optimal coupling between glucose concentrations and insulin release. Insulin secretion is pulsatile, with release of bursts occurring every 4–6 min (10). Multiple daily insulin injections, at best, are a less than ideal substitute. Nevertheless, a long-acting insulin preparation that is uniformly released from a subcutaneous depot and achieves glucose concentrations close to normal throughout the night and between meals, without causing hypoglycemia, can result in a considerable improvement in glycemic control. Though ultralente insulin action lasts for nearly a day, NPH insulin once or twice daily has been more commonly used in practice. Therefore, clinical trials have so far compared NPH insulin with glargine. To our knowledge, our trial is the first to compare glargine with ultralente insulin in patients with type 1 diabetes using adequate randomized allocation to treatment, blinding of study personnel, and assessment of glycemic variability. Lack of evidence for a period effect argues against carryover effects and strengthens inferences about causal attributions to glargine and ultralente. However, the study was of short duration, excluded two participants lost during the first phase from the analysis (because they provided no second phase for comparison), and involved few participants, although we had adequate power to show important differences in our primary end points.

This was a partially blinded trial. Since the two insulin preparations look different, patients were not blinded to their treatment. However, the endocrinologists and study coordinators who ti-

Table 3—*Number of hypoglycemic events*

	On glargine	On ultralente	Glargine-ultralente	*P* (test of difference)
Total	27.5 (2.0–51)	31.5 (2–67)	−1.5 (−45–17.5)	0.0455
Day	23 (1–39)	27 (1–64)	−3 (−44–4)	0.0015
Night	3 (0–22)	2 (0–10)	1 (−5–17)	0.0725

Data are median (range). All patients experienced at least one episode of daytime hypoglycemia; 17 (77%) and 19 (86%) patients had nocturnal hypoglycemia on glargine and ultralente, respectively.

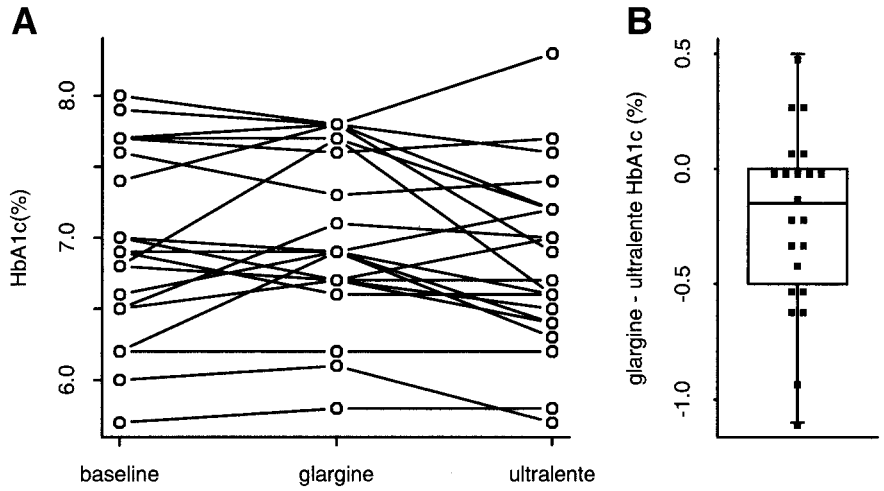

Figure 2—*HbA$_{1c}$ during the trial. Difference indicates the difference of HbA$_{1c}$ at the end of the glargine phase and at the end of the ultralente phase.*

trated the insulin dose were blinded to the basal insulin preparation being used. Patients on ultralente required more contact, longer titration periods, and more changes to their insulin program.

We could not blind patients to their treatments, so we can only derive inferences from self-assessments, such as the Fear of Hypoglycemia outcomes, or exclude cointerventions, such as stricter self-monitoring among patients who expected glargine to be superior to ultralente. We did not have statistical power to determine whether outcomes were better or worse for patients who were already using glargine before the trial. We have shown that HbA$_{1c}$ was better with glargine than with ultralente.

Our trial was designed as an equivalence trial of HbA$_{1c}$, comparing two basal insulin preparations. The Diabetes Control and Complications Trial (11) showed that a lower HbA$_{1c}$ is associated with a decreased risk of incidence and progression of microvascular complications and neuropathy. The relationship between HbA$_{1c}$ and complications is continuous without a threshold. The goal of treatment in type 1 diabetes is a normal or near-normal A1c. We showed that glargine is able to achieve a lower A1c compared with ultralente, though the difference is small.

A decrease in HbA$_{1c}$ is commonly associated with an increased frequency of total hypoglycemic episodes. Mild hypoglycemia is common in type 1 diabetes and may occur once a week or more frequently. Therefore, it is important to note in the present study that HbA$_{1c}$ was not only significantly lower during glargine than ultralente but also led to fewer episodes of mild hypoglycemia, particularly during the day. However, the risk of severe hypoglycemia did not differ between groups. On the other hand, since the risk of severe hypoglycemia was relatively low in both groups, a larger trial of longer duration would be required to rigorously examine this question.

Variation in glucose concentrations is frustrating to patients with type 1 diabetes and their health care providers (8). An attempt to improve HbA$_{1c}$ in type 1 diabetes needs to incorporate assessment of glycemic variation. We used multiple end points to assess glycemic stability. Measures we used included mean glycemia, fasting glucose, pre-evening meal glucose, 7-point glucose profile, and the CGMS. Fasting plasma glucose was lower with glargine. We were not able to detect a difference in any of these measures, except for the SD of glucose measurements, which showed a tendency to be better with glargine as assessed by CGMS. Obviously, hypoglycemia is worrisome to patients with type 1 diabetes. The Fear of Hypoglycemia Questionnaire measures the significance of hypoglycemia to the patient. The Worry scale is favorable in patients treated with glargine compared with ultralente insulin. This finding confirms the data we collected as consistent with patient perceptions of hypoglycemia.

In summary, both ultralente and glargine lower HbA$_{1c}$ to near-normal levels. However, glargine achieved a significantly lower HbA$_{1c}$ compared with ultralente insulin in patients with type 1 diabetes. The number of total and diurnal hypoglycemic events, as well as glycemic variability measured by CGMS, were also lower on glargine than ultralente. Taken together, these data indicate that glargine is a safer and more effective basal insulin than ultralente.

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Y.C.K. and G.D.J. take responsibility for integrity of data and analyses. We thank Dr. Daniel Cox for permission to use the Fear of Hypoglycemia Questionnaire, Dr. Victor Montori for helpful suggestions, Michelle Papaconstandinou for secretarial assistance, the Diabetes Endocrine and Nutrition Study Unit, and our patients for their cooperation.

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