Insulin Glargine Versus Intermediate-Acting Insulin as the Basal Component of Multiple Daily Injection Regimens for Adolescents with Type 1 Diabetes Mellitus

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Objectives To compare long-acting insulin glargine (Lantus) with intermediate-acting insulin (neutral protamine Hagedorn [NPH]/Lente) when used as the basal component of a multiple daily injection (MDI) regimen with prandial insulin lispro (Humalog) in adolescents with type 1 diabetes mellitus (T1DM).

Study design This was an active-controlled, randomized, open-label, sex-stratified, 2-arm, parallel-group comparison of once-daily insulin glargine with twice-daily NPH/Lente in an MDI regimen. Changes in glycated hemoglobin A1C (A1C), occurrence of hypoglycemia, and adverse events were assessed in 175 patients (age 9 to 17 years) with T1DM.

Results The overall mean change in A1C from baseline to week 24 was similar in the 2 groups: insulin glargine (n = 76), −0.25% ± 0.14%; NPH/Lente (n = 81), 0.05% ± 0.13% ($P = .1725$). However, an analysis of covariance, adjusting for baseline A1C, revealed a strong study arm effect on the slopes of the regression lines, indicating that the reduction in A1C was significantly greater with insulin glargine in those patients with higher baseline A1C values. The rate of confirmed glucose values <70 mg/dL was higher in the patients receiving insulin glargine ($P = .0298$). No differences in the rate of severe hypoglycemia ($P = .1814$) or the occurrence of glucose levels <50 mg/dL ($P = .82$) or <36 mg/dL ($P = .32$) were found between the 2 groups.

Conclusions Insulin glargine is well tolerated in MDI regimens for pediatric patients with T1DM and may be more efficacious than NPH/Lente in those with elevated A1C. *(J Pediatr 2008;153:547-53)*

In the United States, the prevalence of type 1 diabetes mellitus (T1DM) is estimated to be 1 in every 400 to 600 persons, affecting approximately 176 500 children and adolescents under age 20.[1] The long-term morbidity associated with diabetes-related microvascular and macrovascular complications is of particular concern in this age group, due to the greater number of years that they will be exposed to hyperglycemia if not properly controlled. However, the risk of these complications can be reduced markedly by using intensive insulin therapy to lower glycated hemoglobin A1C (A1C) values.[2,3]

In clinical practice, intensive insulin therapy in patients with T1DM often is administered using multiple daily injection (MDI) regimens that provide basal and premeal bolus insulin coverage.[4] Insulin glargine (Lantus; sanofi-aventis U.S., Bridgewater, NJ) is a soluble, long-acting insulin analog with a flat time-action profile and limited variation in insulin absorption.[5] The use of insulin glargine as the basal component of an MDI regimen has produced good glucose control with less hypoglycemia than neutral protamine Hagedorn (NPH) plus regular human insulin.[6] Reduced hypoglycemia is especially important in pediatric patients, in whom concerns about hypoglycemia may be a barrier to achieving lower A1C values.[7]

This active-controlled, randomized, parallel-group study was conducted to compare the efficacy and safety of once-daily long-acting insulin glargine with twice-daily inter-

A1C	Glycated hemoglobin A1C	DKA	Diabetic ketoacidosis
ANCOVA	Analysis of covariance	ITT	Intention to treat
BG	Blood glucose	MDI	Multiple daily injection
BMI	Body mass index	NPH	Neutral protamine Hagedorn
CGMS	Continuous Glucose Monitoring System	SMBG	Self-monitored blood glucose
CI	Confidence interval	T1DM	Type 1 diabetes mellitus

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mediate-acting (NPH/Lente) insulin when used as the basal insulin component in an MDI basal/bolus regimen with prandial insulin lispro (Humalog; Eli Lilly, Indianapolis, IN) in school-aged children and adolescents. The primary efficacy measure was the difference in A1C levels between the treatment groups. The major safety objective was to compare the occurrence of hypoglycemia and, in a subset of patients, the variability in blood glucose (BG) levels associated with the 2 insulin regimens.

METHODS

Study Design

This study was an active-controlled, randomized (1:1), open-label, sex-stratified, 2-arm, parallel-group comparison of long-acting insulin glargine with intermediate-acting insulin (NPH or Lente insulin) as part of an MDI regimen using the rapid-acting analog insulin lispro as the prandial component in both treatment groups. Patients received the study medication over a 24-week treatment period, which was preceded by a 2-week screening period and a 4-week educational run-in period (during which patients continued on their preexisting insulin regimen). The treatment period was followed by a 1-week follow-up (Figure 1; available at www.jpeds.com).

All patients were on intermediate-acting insulin at screening and maintained that therapy throughout the educational run-in period. During the educational run-in period, patients received instruction from a certified diabetes educator on carbohydrate counting and basal/bolus insulin regimens. Glucose meters (One-Touch Ultra; LifeScan, Milpitas, California) were provided to all patients to assess self-monitored blood glucose (SMBG) values. The patients were instructed on the proper use of the meter, and their capabilities were evaluated. Those patients who were able to use the glucose meters were then instructed on how to use the MiniMed continuous glucose monitoring system (CGMS; Medtronic, Northridge, California) to measure BG variability. Each patient was required to demonstrate his or her competence in these areas before randomization.

After the educational run-in period, the patients were randomized to either stay on their existing basal insulin (intermediate-acting NPH or Lente insulin) or to receive the once-daily morning insulin glargine as basal therapy. Throughout the study, blood was drawn for laboratory analysis (i.e., blood chemistries, hematology, fasting lipids, A1C), and urine samples were collected for analysis of urinary spot microalbumin:creatinine ratio.

The study design was approved by institutional review boards at the participating institutions and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from each patient's parent or legal guardian and, when required and age-appropriate, written informed assent was obtained from the patient before performance of any study-related procedures.

Patients

The study included pediatric patients (age, ≥9 to ≤17 years; Tanner stage, ≥2; A1C, ≥7.0% to ≤9.5%) who had a diagnosis of T1DM for at least 1 year and were receiving any daily insulin regimen consisting of 2 or more injections or a continuous subcutaneous insulin infusion. Patients also were required to have a fasting C-peptide concentration of ≤0.5 nmol/L and the ability and willingness to count carbohydrates and perform SMBG testing at least 4 times per day. Patients were excluded if they had clinically relevant cardiovascular, hepatic, renal, neurologic, endocrine, or other major systemic diseases; psychiatric problems; laboratory test abnormalities; a history of 2 or more episodes of severe hypoglycemia within the past 12 months or diabetic ketoacidosis (DKA) in the past 3 months; or hypersensitivity to the investigational product or treatment. Other exclusion criteria were lipohypertrophy, a history of drug or alcohol abuse, current use of systemic corticosteroids or large doses of inhaled corticosteroids, and pregnancy.

Treatment

Both treatment groups received insulin lispro for prandial insulin coverage and correction boluses. Patients were randomized to 1 of 2 basal insulin groups: insulin glargine, administered as a single subcutaneous injection before breakfast, or NPH or Lente insulin administered twice daily, before breakfast and in the evening. The evening NPH/Lente dose could be administered before supper or at bedtime (as determined by the investigator); however, the dosing time was to remain constant unless a change was indicated due to recurring nighttime hypoglycemia.

The starting dose of basal insulin was determined by the investigator and represented 40% to 50% of the total daily insulin dose (ie, basal plus prandial insulin doses). The total daily dose of insulin glargine and the evening dose of NPH/Lente were titrated weekly by the investigator to achieve a target fasting plasma glucose value between 70 and 100 mg/dL. The prebreakfast dose of NPH was titrated based on the investigator's clinical judgment. The weekly increase in the insulin dose could be divided across 2 or more incremental doses over the course of the week at the investigator's discretion.

Every day throughout the treatment period, each patient recorded his or her fasting, preprandial, and bedtime SMBG values and insulin dose in a diary. Study outcomes, such as A1C and hypoglycemia frequency, were documented during clinic visits. During the 1-week follow-up, the patient was contacted to review and document hypoglycemic episodes, adverse events, and concomitant medication use.

Efficacy Endpoints

The primary efficacy endpoint was the change in A1C from baseline (week 0) to endpoint (week 24 or the last available assessment postrandomization). Blood was drawn during visits at baseline and at weeks 6, 12, 18, and 24.