No Higher Dose Requirements with Insulin Detemir than Glargine in Type 2 Diabetes: A Crossover, Double-Blind, and Randomized Study Using Continuous Glucose Monitoring

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Abstract

Background:

In a previous publication we reported no difference in the 24-hour glucose response between two basal analog insulins, detemir and glargine, when taken once a day in type 2 diabetes mellitus (T2DM). We now report the dose comparison observed within this randomized, double-blind, crossover study.

Method:

Of 36 patients on basal insulin and other noninsulin treatments, 29 completed the study. Both insulins were given once a day at 8 pm and no food was taken between 6 pm and the following morning. The dose was titrated daily by continuous glucose monitoring (CGM) until the basal glucose (between 12 and 6 am) was <120 mg/dl but not >5% of CGM readings <70 mg/dl. Subjects were then crossed over to the other insulin and titrated similarly.

Results:

Glucose goals were achieved in all subjects. The mean dosage was 0.26 U/kg with very few subjects requiring >0.4 U/kg. Only 2 required an absolute dose less than 10 U/day and all others required more, some considerably higher. Of the 29 subjects, 7 required a greater, 6 a smaller, and 16 the same dose of detemir compared to glargine.

Conclusions:

When given once daily in T2DM and titrated using CGM to the same fasting glucose, there was no difference in the glucose response between basal insulins during the basal titration period (4–10 hours after injection) nor during the entire 24-hour period following the injection. Further, the mean dosage to achieve this glucose goal was the same with both insulins.

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Introduction

In a previous publication[1] we reported no difference in the 24-hour glucose profile between single injections of two basal analog insulins, insulin detemir and glargine, when injected once daily in type 2 diabetes subjects. This trial was a double-blind, randomized, crossover parallel trial using continuous glucose monitoring (CGM) first to guide dosage and then to compare control in an outpatient setting. This article presents post hoc analyses of the individual subject dosing requirements to achieve target glucose control.

Methods

The methods were reported previously.[1] From a single diabetes treatment center, 36 type 2 diabetes mellitus (T2DM) subjects treated with basal insulin and other agents but not bolus insulin were recruited. All subjects signed an informed consent in this institutional review board-approved study. Seven subjects did not complete the study due to progressive anasarca associated with dosage escalation (1 each with each basal insulin of detemir and glargine), protocol violation (1 subject changed an oral hypoglycemic medication dosage during the study), and titrating off of insulin (4 subjects) when eliminating eating after 6 pm.

Subjects were excluded if they were pregnant or nursing or if they had a significant change in hemoglobin A1c (HbA1c) prior to testing or a significant change in insulin sensitivity due to illness or stress, a change in renal status, medication, and so on.

Each subject was monitored by CGM (CGMS® Gold, Medtronics, Northridge, CA) starting the Friday before the beginning of the titration week. On Monday and on each day thereafter, the dosage of the basal insulin was titrated to achieve a basal glucose during the period of 12 to 6 am of less than 120 mg/dl but less than 5% of the readings <70 mg/dl. The type of basal insulin was blinded to the investigator adjusting the dosage. Either basal analog insulin was started on the Monday of the beginning of the titration week. All injections were given at 8 pm. After achieving the basal glucose goal for the second day, the 8 am to 8 am glucose profile was identified for comparison study. The mean ± standard deviation of the duration of treatment for those on insulin detemir was 3.8 ± 1.3 days and those on insulin glargine was 3.5 ± 1.8 days ($p = 0.360$).

To evaluate the exogenous insulin secretion of these subjects, we retrospectively identified all subjects that had a random C-peptide test recorded from the clinic charts.

Results

The mean and standard deviation of the 29 subjects that completed the study were as follow: age, 58.9 ± 11.6 years; duration of diabetes, 8.4 ± 4.6 years; HbA1c, 7.1 ± 0.9%; and body mass index (BMI), 34.9 ± 8.2 kg/m². Prior to the study, all subjects were taking basal but no bolus insulin. In addition, 21/29 were taking sulfonylureas, 16/29 were taking metformin, 9/29 were taking a thiazolidinedione, 2/29 were taking sitagliptin, and 9/29 were taking exenatide.

There was no statistical difference in the 24-hour glucose control between the two basal insulins. Although the mean dosage was not significantly different between groups ($p = 0.837$), some individual subjects required more, less, or the same amount of each insulin to achieve the target glucose. Approximately the same number of subjects and the same dosage difference were observed between basal insulin analogs. Most (16) subjects did not require a dosage change during the crossover (see **Figure 1**).
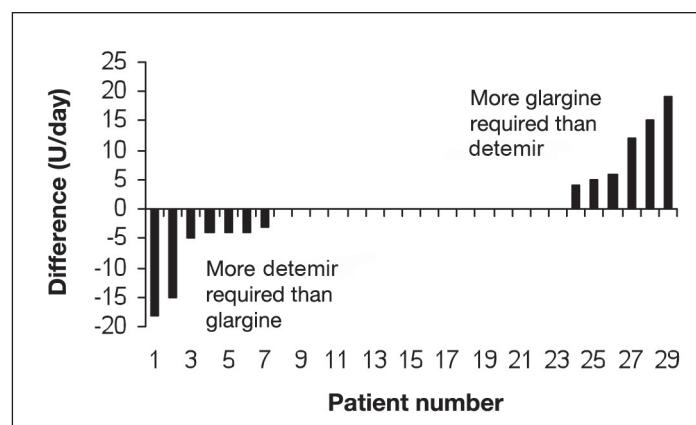
Figure 1. Comparison of once-daily evening dose of either insulin detemir or glargine to achieve the target basal glucose (<120 mg/dl between the hours of 12 midnight and 6 am) in 29 subjects with type 2 diabetes in a crossover, double blind, randomized prospective trial using continuous glucose monitoring for titration and for evaluation of the response. Note that 16 of 29 required no alteration in dosage when switched from glargine or detemir to the other.

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In most (26 of 29) subjects the dosage of insulin was ≤0.4 U/kg. A few (3 of 29) subjects required <10 units, but most required more.

Of 29 subjects studied, 21 had a random C-peptide test. The mean and standard deviation of the C-peptide test was 3.28 ± 2.20 ng/ml performed 3.57 ± 2.71 years before this study was conducted. Because different laboratories with different upper limits of normal performed these tests, we also determined the mean value as a ratio of a subject's value to the upper limit of normal for the specific laboratory. The result was 0.79 ± 0.51.

Discussion

In the two published clinical trials comparing the basal insulin analogs[2,3] in T2DM, a higher dose per kilogram was needed with detemir than glargine to achieve the glucose goal. Glargine was administered only once each evening and in an amount to achieve a target fasting morning glucose of ≤108 mg/dl. Detemir, however, was not only given at night to achieve the same morning glucose target; a second injection of detemir was also given in the morning aiming for a predinner glucose level of ≤108 mg/dl. Our study could be considered as having a stronger design for comparing the 24-hour glucose response of once daily injection of basal insulins, as our titration was more intense (CGM versus intermittent self-monitored glucose); we only injected either insulin only once daily, and we used a crossover design. It is important to note that in the detemir-treated group, the mean predinner (at 5 pm) glucose level was 145 mg/dl *and* that of the glargine-treated group was 142 mg/dl ($p = 0.746$). If detemir but not glargine was titrated to cover this predinner (and postlunch) glucose level, one would also observe a higher dose of detemir needed to control glucose. At this same time the basal glucose level, between 12 midnight and 6 am, was not significantly different and was at goal (105 ± 23 and 98 ± 19 mg/dl for detemir and glargine, respectively, $p = 0.204$).

Owens and Bolli[4] suggested that our failure to detect a difference in duration of action between the basal insulins was due to a higher endogenous insulin secretion of our subjects, as suggested by a higher BMI, mean of 34.9 kg/m², and low insulin dose, 0.26 U/kg. However, the mean age of our patients, 58.9 years, was similar to those of the other two clinical trials of 58–59[2] and 58.4[3] years. The duration of diabetes, 8.4 years in our study, was similar to the one by Rosenstock and colleagues,[3] 9.1 years. All of our patients were taking basal insulin prior to enrolling in our study but no patients were previously on insulin in the study by Rosenstock and colleagues[3] and 18.5% were insulin naïve in the study by Hollander and colleagues.[2] Noninsulin antidiabetic prior treatment was used in 100% of our subjects and in the study by Rosenstock and colleagues,[3] but in only 63.6% of Hollander's subjects.[2] In addition, the mean C-peptide level in our subjects from whom we could obtain information was not elevated. This further suggests a failure to demonstrate a difference in control based on an increase in endogenous insulin secretion.

Our mean basal insulin dose of 0.26/kg is low compared to other reported basal insulin trials.[5] This could be a result of more sensitive glucose monitoring provided by CGM versus a single daily fasting glucose, our limiting the evening meal to 6 pm, our not attempting to treat postmeal glucose with basal insulin, and the shorter duration of this trial. In the two previous clinical comparisons[2,3] of the two basal insulins in type 2 diabetes, a higher dose of detemir than glargine was observed due to the possible titration of detemir but not glargine to an additional dose of morning insulin to lower before-supper (and after lunch) glucose. We believe our titrating four subjects off of basal insulin when eating was restricted to before 6 pm is evidence that the fasting morning glucose level may be influenced by the prior evening's meal. In these cases, a more appropriate treatment would be premeal rapid-acting insulin prior to the evening meal.

Strange[5] has proposed that excess basal insulin therapy may be common in clinical trials. Hypoglycemia resulting when meals are missed may be evidence of such dosing excess. Shanik and associates[6] suggested that increased insulin resistance is created by the exogenous hyper-insulinemia by receptor or postreceptor adaptation and that perhaps hypoglycemia is not detectable. We may not have experienced this increased resistance and higher doses because of our more intense glucose monitoring using CGM, shorter duration of study, and targeting only basal glucose between 12 am and 6 pm.

Only 3 of 29 patients required more than 0.4 U/kg. We would recommend that if more insulin is required, the provider should consider noncompliance with therapy, inappropriate injection technique including not altering the injection sites, or marked insulin ineffectiveness from reduced blood flow, e.g., marked inactivity, congestive heart failure, β blockers, or from poor absorptive tissue, e.g., edema, lipohypertrophy, or from systemic insulin resistance states, e.g., glucocorticoid treatment, systemic infections.

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From an uncontrolled, unblinded, nonrandomized, and not crossed over three-subject study,[7] it was suggested that higher doses of detemir were required to achieve the same glucose control. The authors suggested that the resulting greater financial cost of higher dosage would offset any advantage to insulin detemir. Our crossover design removes the variable of the potential markedly different insulin sensitivity between individuals. In our double-blind, crossover, and randomized study there was no difference in mean dosage when subjects were switched from one to the other insulin. Some subjects required more detemir and a nearly equal number required more glargine insulin.

In conclusion, if both basal insulins are given once daily in T2DM and titrated using CGM to the same fasting glucose, then there is no difference in glucose response during both the active titration period (4–10 hours after injection) and the entire 24-hour period following injection. Further, the mean dosage to achieve this glucose goal is the same with both insulins, with some patients requiring more and some less.

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