Glulisine Versus Human Regular Insulin in Combination With Glargine in Noncritically Ill Hospitalized Patients With Type 2 Diabetes

A randomized double-blind study

OBJECTIVE — To compare the efficacy and safety of the rapid-acting insulin analog glulisine and regular insulin in hyperglycemic hospitalized patients.

RESEARCH DESIGN AND METHODS — A total of 180 hospitalized patients with type 2 diabetes received either glulisine (n = 88) or regular insulin (n = 92) before each meal in combination with insulin glargine at bedtime in a randomized double-blind fashion. All previous diabetes medications were discontinued if applicable. Doses of insulin were adjusted to obtain target blood glucose concentrations of <130 mg/dl before meals and at bedtime while avoiding hypoglycemia.

RESULTS — Overall mean blood glucose concentrations were ~8 mg/dl lower in the glulisine group than in the regular insulin group (152.6 ± 66.6 vs. 160.4 ± 70.8 mg/dl; P < 0.0002). This improvement was wholly due to ~22 mg/dl lower levels after 4 days of therapy (140 ± 55 vs. 162 ± 71 mg/dl, P < 0.0007); after day 4, this difference progressively increased such that mean blood glucose concentrations from day 7 onward were ~31 mg/dl lower in the glulisine group. The mean daily incidence of hypoglycemia was slightly but not significantly lower in the glulisine group (0.10 ± 0.02 vs. 0.14 ± 0.03 episode/day; P > 0.35).

CONCLUSIONS — In hospitalized type 2 diabetic patients, glulisine may provide better glycemic control than regular insulin, especially in those who have a prolonged length of stay.

Diabetes Care 33:2496–2501, 2010

From the Department of Endocrinology, Carl T. Hayden VA Medical Center, Phoenix, Arizona.

Corresponding author: Christian Meyer, christian.meyer@va.gov.

The study sponsors were not involved in the design of the study; the collection, analysis, or interpretation of the data; or the preparation of the manuscript. The contents of this article do not represent the views of the Department of Veterans Affairs or the U.S. government.

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Table 1—Supplemental insulin sliding scale

| Blood glucose | BMI <25 kg/m² | BMI 25–30 kg/m² | BMI >30 kg/m² |
|---------------|--------------|----------------|-------------|
| 131–170 mg/dl | 1            | 2              | 3           |
| 171–210 mg/dl | 2            | 4              | 5           |
| 211–250 mg/dl | 3            | 6              | 8           |
| 251–290 mg/dl | 5            | 8              | 10          |
| 291–330 mg/dl | 7            | 10             | 13          |
| 331–370 mg/dl | 9            | 12             | 15          |
| >371 mg/dl    | 12           | 14             | 18          |

Data are units of insulin.

Insulin was 0.4 IU/(kg · day)⁻¹ if BMI was <25 kg/m², 0.5 IU/(kg · day)⁻¹ if BMI was 25–30 kg/m², and 0.6 IU/(kg · day)⁻¹ if BMI was >30 kg/m². One-half of the total daily insulin dose was given as glargine once daily at bedtime, and the other half was given as glulisine or regular insulin in equally divided doses before breakfast, lunch, and dinner. All insulin doses were administered by nurses, who were not blinded to the study medications. Glulisine was administered immediately before meals, regular insulin was administered ~30 min before meals. Glulisine and regular insulin were not given if a subject was unable to eat to avoid hypoglycemia. Fingertip stick blood glucose (FSBG) was tested daily before each meal, at bedtime, and whenever subjects reported symptoms of hypoglycemia; 2-h postprandial and 2:00 A.M. FSBG were tested every 3rd day starting on day 2 of study participation. All FSBG measurements were obtained using the Roche Accu-Chek Inform glucose meter (Roche Diagnostics, Indianapolis, IN) and down-loaded to the VA Computerized Patient Record System. Insulin doses were adjusted daily by the investigators (who were blinded to the short-acting insulin) to target blood glucose concentrations of <130 mg/dl before meals and at bedtime while avoiding hypoglycemia using the following guidance: for fasting blood glucose concentrations of 130–160, 161–200, and >200 mg/dl, increase glargine by 10, 20, and 30%, respectively; for pre-lunch, predinner, and bedtime blood glucose concentrations of 130–160, 161–200, and >200 mg/dl, increase regular insulin or glulisine at the prior meal by 10, 20, and 30%, respectively. Supplemental glulisine or regular insulin was given in addition to the scheduled insulin dose before each meal for blood glucose concentrations >130 mg/dl according to a sliding scale protocol (Table 1). Serum creatinine, white blood cell count, and A1C were measured on the 1st day of hospitalization. Fasting plasma C-peptide with the concurrent plasma glucose concentration was measured on day 1 of study participation. All measurements were performed by the Carl T. Hayden VA Medical Center central laboratory using standard assays.

Hypoglycemia was defined as a blood glucose concentration <60 mg/dl. Severe hypoglycemia was defined as an event that required assistance from another person for recovery. Nocturnal hypoglycemia was defined as an event that occurred between the injection of glargine at bedtime and before the subject awoke in the morning. As an index of β-cell function, homeostasis model assessment of percent β-cell function (HOMA-%B) was calculated as [fasting plasma insulin [picomoles per liter] × 3.33/(fasting plasma glucose [millimoles per liter] – 3.5)] (11).

The primary end points were glycemic control, measured by the mean daily blood glucose concentration, and the incidence of hypoglycemia. Length of stay was the secondary end point. Sample sizes were calculated for 80% power at an α of 0.05 for both primary end points. We assumed an average length of stay of 7 days, a within-group SD of 45 mg/dl in mean daily blood glucose concentrations, and a 30% incidence of subjects experiencing at least one episode of hypoglycemia as found in a previous similar study (12). Under these assumptions, power calculations indicated the need for 80 subjects to detect a 10 mg/dl difference in mean daily blood glucose concentrations and the need for 565 subjects to detect a 25% difference in the incidence of hypoglycemia. However, before reaching the latter sample size, at 194 subjects, the decision was made to terminate the study because of slower than expected enrollment. Baseline characteristics of subjects and outcome variables were compared using the Student t test or the χ² test as appropriate. Multiple comparisons of blood glucose concentrations over the course of the subjects’ study participation were performed using repeated-measures ANOVA. Statistical analyses were performed using the SPSS 16.0 (SPSS, Chicago, IL). P < 0.05 was considered statistically significant. Data are presented as means ± SD unless otherwise indicated.

RESULTS

Patient characteristics

Of the 194 enrolled subjects, 96 were randomly assigned to glulisine and 98 were randomly assigned to regular insulin. Fourteen subjects dropped out for personal nonmedical reasons before receiving any insulin as part of this study: 8 subjects assigned to glulisine and 6 subjects assigned to regular insulin. Therefore, data from 88 subjects in the glulisine group and 92 subjects in the regular insulin group were used for statistical analyses. As shown in Table 2, both groups were well matched for age, sex, BMI, previously unrecognized type 2 diabetes, and prior history of type 2 diabetes, diabetes duration, prior diabetes treatment, blood glucose concentration on admission, A1C, β-cell function, renal function, and white blood cell count. The most common admitting diagnoses were cardiovascular disease, infection, and pulmonary disease (Table 2). The length of time of hospitalization was not significantly different between the glulisine and the regular insulin group (7.3 ± 0.5 vs. 8.4 ± 0.6 days; P > 0.13).

Insulin doses

In the glulisine and the regular insulin group, the mean total daily dose of insulin was similar (69 ± 33 vs. 71 ± 45 units; NS) and was accounted for by a comparable amount of short-acting insulin (36 ± 18 vs. 38 ± 24 units; NS).

Glycemic control

During the entire period of the subjects’ study participation, mean blood glucose concentrations were ~8 mg/dl lower in the glulisine group than in the regular insulin group (152.6 ± 66.6 vs. 160.4 ± 70.8 mg/dl; P < 0.0002). This reduction was wholly due to the on average ~22 mg/dl lower blood glucose concentrations after 4 days of therapy (140 ± 55 vs. 162 ± 71 mg/dl; P < 0.0007), because...
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Table 2—Baseline clinical and biochemical characteristics of the study groups

|                          | Regular insulin | Glulisine  |
|--------------------------|-----------------|------------|
| n                        | 92              | 88         |
| Age (years)              | 65.1 ± 9.1      | 65.6 ± 10.1|
| Sex (male/female)        | 91/1            | 87/1       |
| BMI (kg/m²)              | 32.1 ± 7.0      | 32.6 ± 7.6 |
| Race/ethnicity           | 72/10/10        | 64/12/12   |
| History of type 2 diabetes| 86 (96)         | 86 (98)    |
| Diabetes duration        | 11.9 ± 8.0      | 11.6 ± 8.8 |
| Diabetes treatment       |                |            |
| before hospitalization   |                |            |
| No pharmacological agents| 5 (5.4)         | 3 (3.4)    |
| Oral agent monotherapy   | 12 (13)         | 22 (25)*   |
| Multiple oral agents     | 13 (14)         | 18 (20)    |
| Insulin plus oral agents | 34 (37)         | 27 (31)    |
| Insulin only             | 28 (30)         | 18 (20)    |
| A1C (%)                  | 7.7 ± 1.7       | 7.7 ± 1.8  |
| HOMA-%B                  | 1.03 ± 0.95     | 0.96 ± 1.06|
| Admission blood glucose  | 189 ± 86        | 187 ± 95   |
| White blood cell count   | 10.4 ± 4.6      | 10.1 ± 4.4 |
| Serum creatinine (mg/dl) | 1.6 ± 1.3       | 1.6 ± 1.3  |
| Admission diagnosis (%)  |                |            |
| Cardiovascular disease   | 30 (32)         | 30 (34)    |
| Infection                | 23 (25)         | 18 (20)    |
| Pulmonary disease        | 11 (12)         | 9 (10)     |
| Uncontrolled diabetes    | 1 (1)           | 1 (1)      |
| Renal disease            | 1 (1)           | 3 (3)      |
| Amputation/diabetic foot ulcer | 7 (8) | 5 (6) |
| Other                    | 19 (21)         | 22 (25)    |

Data are means ± SD or n (%). To convert the values for glucose from milligrams per deciliter to millimoles per liter, multiply by 0.05531. *P < 0.05.

levels were virtually identical in both groups during the first 4 days (159 ± 71 vs. 159 ± 71 mg/dl, P > 0.9). After day 4, the target blood glucose level of <130 mg/dl before meals was achieved in 48% of subjects in the glulisine group and in 38% of subjects in the regular insulin group (P < 0.0003); 66% of all blood glucose readings in the glulisine group were 90–180 mg/dl compared with 54% in the regular insulin group (P < 0.0001). The difference in glycemic control between both groups progressively increased such that blood glucose concentrations from 7 day onward were ~31 mg/dl lower in the glulisine group (133 ± 51 vs. 164 ± 72 mg/dl, P < 0.0001). The time course of mean daily blood glucose concentrations (premeal and bedtime blood glucose concentrations) in both groups of subjects is shown in Fig. 1A.

To examine whether the reduction in glycemia by glulisine could have been due to its direct actions, we separately analyzed blood glucose concentrations that were expected to be predominantly determined by the actions of glargine (e.g., fasting and 2:00 A.M. blood glucose concentrations) and blood glucose concentrations that were expected to be predominantly determined by the actions of glargine (e.g., concentrations (138 ± 51 vs. 162 ± 72 mg/dl; P < 0.000002) and 2-h postprandial blood glucose concentrations (164 ± 70 vs. 191 ± 71 mg/dl; P < 0.0026) were significantly lower in the glulisine group than in the regular insulin group whereas fasting (125 ± 49 vs. 141 ± 54 mg/dl; P = 0.06) and 2:00 A.M. blood glucose concentrations (150 ± 52 vs. 160 ± 67 mg/dl; P > 0.8) were not significantly different.

Subgroup analysis

To examine whether the improved glycemia with glulisine past day 4 could potentially be explained by different characteristics of subjects who stayed hospitalized for a longer period of time, we compared subjects participating >4 days (n = 39 in the glulisine group; n = 54 in the regular insulin group) with subjects participating ≤4 days in separate analyses. Age, sex, BMI, A1C, HOMA-%B, diabetes duration, and admission diagnosis were comparable between these subgroups in both the glulisine group and the regular insulin group (all P > 0.3). Moreover, in subjects who participated >4 days, glycemic control was similar in the glulisine and the regular insulin group during the first 4 days of study participation (P > 0.9) as found when we analyzed data for all subjects.

Hypoglycemia

Throughout the study, there were 123 hypoglycemic events: 56 in the glulisine group and 67 in the regular insulin group. However, neither the number of subjects with one or more hypoglycemic episodes (30 vs. 35%; P > 0.5) nor the average daily incidence of hypoglycemia was significantly different (0.3 ± 0.02 vs. 0.14 ± 0.03 episode/day; P > 0.35). Furthermore, the incidence of hypoglycemia was not significantly different between both groups during the first 4 days of therapy (0.11 ± 0.03 vs. 0.14 ± 0.03 episode/day; P > 0.4), during which glycemica was comparable, and after day 4 (0.07 ± 0.02 vs. 0.06 ± 0.02 episode/day; P > 0.6), during which glycaemia was significantly reduced in the glulisine group. The severity and the time of day of hypoglycemic events were also similar in both groups (Table 3). Only one hypoglycemic event, which occurred in the regular insulin group, was severe.

CONCLUSIONS—In hospitalized patients, hyperglycemia is a frequent, serious, and costly problem, and tight
Glycemic control is recommended by the American Diabetes Association (7). The present trial is the first to compare the efficacy and safety of the rapid-acting insulin analog glulisine and regular insulin in hospitalized patients with type 2 diabetes. Using a randomized double-blind study design, we found that treatment with glulisine resulted in lower blood glucose concentrations than treatment with regular insulin without increasing the risk of hypoglycemia. When all blood glucose readings during the study are considered, the reduction in glycemia by glulisine was 110 mg/dl. This reduction was highly significant but arguably modest. However, if only data past day 4 of therapy are considered, glulisine resulted in 22 mg/dl reduced blood glucose concentrations, because both groups had similar levels during the first 4 days. Thereafter, the differences in glycemic control between the two groups disappeared.

Table 3—Frequency and severity of hypoglycemia

| Hypoglycemic episodes | Regular insulin | Glulisine |
|-----------------------|----------------|----------|
| Blood glucose < 50 mg/dl | 67 | 56 |
| Blood glucose 50–59 mg/dl | 40 | 34 |
| Blood glucose 40–49 mg/dl | 19 | 17 |
| Blood glucose < 40 mg/dl | 8 | 5 |
| Subjects with ≥1 hypoglycemic episode | 32 | 26 |
| Incidence of hypoglycemia (episodes/day) | 0.136 ± 0.027 | 0.103 ± 0.020 |

Data are n or means ± SD.
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Glucose control was very much consistent with those of Dailey et al. (8) in that twice-daily glulisine in combination with NPH insulin improves glycemic control without increasing the frequency of hypoglycemia (11). This observation demonstrates the efficacy of glulisine in hospitalized patients in hands of less well-trained providers and with less careful blood glucose monitoring may need to be tested. Third, it is possible that some of our study patients were not completely blinded regarding the type of mealtime insulin because of their knowledge of the different administration times of regular and glulisine relative to meals. And fourth, we unfortunately did not achieve our estimated sample size needed for detecting differences in the incidence of hypoglycemia because of slower than expected patient recruitment.

In critically ill patients, hypoglycemia has been found to be associated with poor clinical outcome (13). Although the causality of hypoglycemia leading to poor clinical outcome has been questioned (14), hypoglycemia or the fear of it in health care providers and patients is undoubtedly the major barrier for the control of glycemia. In the present study, 30–35% of patients experienced at least one episode of hypoglycemia with an incidence of 0.1–0.14 episode/day, comparable to the rates of hypoglycemia in the previous similar study by Umpierrez et al. (12). This observation demonstrates the difficulty of achieving tight glycemic control and underscores the importance of improving our treatment modalities in hospitalized patients with type 2 diabetes.

In summary, the present study provides evidence suggesting that treatment with glulisine can provide superior glycemic control compared with regular insulin in hospitalized patients with type 2 diabetes, especially in those who have a prolonged length of stay. Further studies are needed to examine whether these results can be generalized to other populations and hospital settings, and whether the benefits of glulisine persevere with the usual standard of care for glycemic control.

Acknowledgments—This investigator-initiated study was supported by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs and by an unrestricted grant from sanofi-aventis (to C.M.).

No other potential conflicts of interest relevant to this article were reported.

C.M. researched data, contributed to discussion, and wrote the manuscript. A.B., E.P., M.V., and R.V. researched data and contributed to discussion.

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