A Randomized Trial of Two Weight-Based Doses of Insulin Glargine and Glulisine in Hospitalized Subjects With Type 2 Diabetes and Renal Insufficiency

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OBJECTIVE—Renal insufficiency may increase the risk of hypoglycemia in hospitalized patients with diabetes who are treated with insulin. We randomized inpatients with type 2 diabetes and chronic renal failure to treatment with two different dose levels of insulin glargine and glulisine and studied control of hyperglycemia and the frequency of hypoglycemia.

RESEARCH DESIGN AND METHODS—We conducted a multicenter, prospective, randomized trial to compare the efficacy of once-daily glargine and three-times daily glulisine at 0.5 vs. 0.25 units/kg/day. A total of 107 subjects had type 2 diabetes for >1 year, had a glomerular filtration rate <45 mL/min but did not require dialysis, and had an initial blood glucose (BG) >180 mg/dL. Doses were adjusted based on four-times daily BG measurements for 6 days.

RESULTS—Mean BG on the first day was 196 ± 71 mg/dL in the group receiving 0.5 units/kg (0.5 group) and 197 ± 55 mg/dL in the group receiving 0.25 units/kg (0.25 group; $P = 0.94$). On days 2 to 6, mean BG was 174 ± 52 mg/dL in the 0.5 group and 174 ± 46 mg/dL in the 0.25 group ($P = 0.96$). There were no significant differences between groups in the percentage of BG values within the target range of 100 to 180 mg/dL on any of the 6 study days. In the 0.5 group, 30% experienced hypoglycemia (BG <70 mg/dL) compared with 15.8% of the 0.25 group ($P = 0.08$).

CONCLUSIONS—Reduction of initial glargine/glulisine insulin weight-based dosing in hospitalized patients with diabetes and renal insufficiency reduced the frequency of hypoglycemia by 50% without compromising the control of hyperglycemia.

Diabetes Care 35:1970–1974, 2012

Diabetes is encountered very commonly in hospitalized patients. More than 20% of hospital inpatient days can be attributed to patients with diabetes (1). Multiple studies have highlighted associations between hyperglycemia and adverse outcomes in hospitalized patients with diabetes and have focused attention on approaches to improve inpatient glycemic control (2–9). Current guidelines recommend avoiding oral antidiabetic agents in this setting and using scheduled subcutaneous insulin for basal, nutritional, and correctional components in noncritically ill patients (10–12). Current glycemic targets for patients on general medical and surgical units are premeal blood glucose (BG) levels <140 mg/dL and random BG levels <180 mg/dL. The challenge in this patient setting is to achieve these goals while avoiding hypoglycemia as much as possible.

Hypoglycemia is a common problem in hospitalized patients being treated for diabetes and is correlated with increased morbidity and mortality (13–18). Excessive insulin dosing is a common risk factor for hypoglycemia in the inpatient setting where nutritional intake may be erratic. Renal insufficiency is commonly encountered in hospitalized patients with diabetes. Hypoglycemia is more common in patients with renal insufficiency than in those without for many reasons, including decreased insulin clearance, insulin resistance, reduced gluconeogenesis, and decreased food intake due to attendant anorexia (19,20). In addition, hypoglycemic unawareness and gastroparesis may accompany diabetes and renal failure and may increase the risk for hypoglycemia if standard insulin protocols based on body weight and insulin sensitivity are applied. Decreased insulin requirements have been demonstrated for insulin-treated type 1 and type 2 diabetic patients with renal insufficiency (21–24). Thus, an insulin-dosing algorithm that accounts for decreased glomerular filtration rate (GFR) could be an important tool to reduce the risk of hypoglycemia in this patient setting.

No prior literature has addressed this question. Many patients with type 2 diabetes and renal insufficiency are treated with oral antidiabetic agents before hospital admission, and current guidelines recommend switching to insulin for their hospital stay. In addition, inpatient measurement of HBA_{1c} will reveal many with poor control who may benefit in the long run if they are converted to insulin therapy before discharge. The aim of this study was to compare two weight-based insulin doses for inpatients with type 2 diabetes and renal insufficiency. Insulin glargine and glulisine were used in a basal-bolus approach to try to maintain good glycemic control while determining the relative frequency of hypoglycemia with each of the two dosing regimens.

RESEARCH DESIGN AND METHODS

This prospective randomized trial was carried out at Loyola University Medical Center, Rush University

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Received 26 March 2012 and accepted 17 April 2012.
DOI: 10.2337/dc12-0578. Clinical trial reg. no. NCT00911625, clinicaltrials.gov.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0578/-/DC1.

Medical Center, and Northwestern University Medical Center between June 2009 and June 2011. Study staff screened electronic medical records for patients admitted to general medical or surgical units for possible eligibility.

Patients with type 2 diabetes of >1 year duration and age >18 years with a GFR ≤45 mL/min/1.73m^2 were eligible to participate. The three hospital laboratories automatically calculated an estimated GFR with the Modification of Diet in Renal Disease formula, which uses age, sex, African American versus non-African American, and serum creatinine. Every effort was made to exclude any patients whose serum creatinine level might have been acutely elevated. GFR on the day of enrollment was always used. Patients were required to have at least one hospital blood glucose (BG) >180 mg/dL and, if on insulin, the outpatient insulin dose needed to be ≥0.5 units/kg/day. Exclusion criteria included type 1 diabetes, pregnancy, chronic dialysis, solid-organ transplant within the past 12 months, steroid therapy >7.5 mg/day of prednisone or equivalent, known hypopituitarism or adrenal insufficiency, known hypoglycemia unawareness, length of stay <48 h, and severe liver disease.

Eligible patients gave informed consent and were randomized 1:1 into two protocol groups by a research pharmacist. The standard-dose group received a total daily insulin dose of 0.5 units/kg and the reduced-dose group received a total daily insulin dose of 0.25 units/kg. Half of the total insulin dose was given as glargine once daily, either in the AM or in the PM, depending on when the patient was enrolled. The other half of the total daily insulin dose was given as glulisine; doses were divided equally between breakfast, lunch, and dinner. An additional correctional dose of glulisine was given for any BG >180 mg/dL. If subjects were not eating, they received glargine once daily and could also receive correctional doses of glulisine. Correctional glulisine could be given four times daily with meals or at bedtime.

Correctional dosing of glulisine was based on total daily insulin requirements. Subjects receiving <40 units of insulin daily could receive 2 additional units of glulisine for BG 181–220, 3 units for BG 221–270, 4 units for BG 271–320, and 5 units for BG >320 mg/dL. Subjects receiving 40–80 units of insulin daily could receive 3 additional units of glulisine for BG 181–220, 5 units for BG 221–270, 7 units for BG 271–320, and 9 units for BG > 320 mg/dL. Subjects receiving > 80 units of insulin daily could receive 5 additional units of glulisine for BG 181–220, 7 units for BG 221–270, 9 units for BG 271–320, and 11 units for BG >320. If the BG was >180 mg/dL at bedtime, a correctional dose of glulisine was given that was 50% of the above doses. For study protocol details, see Supplementary Data online.

After enrollment, data were collected for up to 6 hospital days. Subjects who were discharged from the hospital <48 h after enrollment were not included in the analysis. All oral antidiabetic agents were stopped on hospital admission. BG was measured using point-of-care meters before meals, at bedtime, and whenever necessary for signs or symptoms of hypoglycemia. Insulin doses were adjusted daily to maintain BG in the range of 100 to 180 mg/dL. If fasting BG was <100 mg/dL, the glargine dose was decreased by 20%, if fasting BG was 100 to 140 mg/dL, the glargine dose was not changed, if fasting BG was 140 to 180 mg/dL, the glargine dose was increased by 10%, and if fasting BG was >180 mg/dL, the glargine dose was increased by 20%. If the daily dose of glargine changed, the mealtime dose of glulisine would move proportionately in the same direction.

The primary end points were the percentage of BG levels within the range of 100 to 180 mg/dL, and the percentage of subjects experiencing a hypoglycemic event defined as a BG <70 mg/dL. Hypoglycemic events were further separated into moderate hypoglycemia (50–69 mg/dL) and severe hypoglycemia (<50 mg/dL).

Statistical analysis was performed using SPSS 11.5 software (SPSS, Chicago, IL). Descriptive statistics were performed on all data. Comparisons between groups were tested using *t* tests, χ^2 tests, and Fisher exact tests, as appropriate. Results were considered statistically significant when $P < 0.05$.

RESULTS

Baseline characteristics

The demographics and clinical characteristics of the subjects are summarized in Table 1. Of 123 patients who met eligibility criteria and were approached for consent, 9 patients declined; thus, 114 patients were randomized, of whom 107 (54% women) were treated for at least 48 h and were included for analysis. The other 7 subjects were discharged in <48 h. Seventy-five subjects (70%) were admitted to general medical units, and 32 (30%) were admitted to general surgical units, usually after an operative procedure. General medical subjects were enrolled after a mean hospital stay of 1 day (range 0–4), whereas general surgical subjects were enrolled after a mean hospital stay of 2 days (range 0–7).

Fifty subjects received the standard dosage (0.5 units/kg/day) and 57 received the reduced dosage (0.25 units/kg/day). Patients were a mean age of 64 ± 11 years, and their mean GFR was 29.9 ± 9.0 mL/min/1.73m^2. The average duration of diabetes was 17.6 ± 10.0 years, and mean HBA_{1c} was 8 ± 2%. Seventy-six percent of subjects were treated with insulin before admission, with a mean

Table 1—*Patient demographics and baseline characteristics*

Characteristic	0.5 units/kg *n* = 50	0.25 units/kg *n* = 57	*P*
Age (years)	65.3 ± 10.6	63.7 ± 13.0	0.5
Weight (kg)	89.4 ± 22.3	93.9 ± 29.4	0.4
Female	30.0 (60.0)	28.0 (49.1)	0.3
Race			
African American	17.0 (34.0)	22.0 (38.6)	0.9
Asian	0.0 (0.0)	1.0 (1.8)	
Caucasian	21.0 (42.0)	22.0 (38.6)	
Hispanic	11.0 (22.0)	10.0 (17.5)	
Other	1.0 (2.0)	2.0 (3.5)	
GFR (mL/min/1.73 m^2)	30.4 ± 8.3	29.6 ± 10	0.7
Duration of diabetes (years)	18.6 ± 8.8	16.6 ± 9.9	0.4
HBA_{1c} in the last 3 months	8.2 ± 2.1	7.9 ± 1.9	0.6
Previous insulin therapy	39.0 (78.0)	42.0 (73.7)	0.6
Total home daily insulin dose	54.3 ± 40.7	51.6 ± 46.3	0.8

Data are means ± SD or *n* (%).

daily dose of 52 ± 43 units. Outpatient insulins included long-acting analogs (40%), short-acting analogs (31%), and NPH (34%). In addition, 25% of subjects were treated with a sulfonylurea, 15% with metformin, and 12% with other antidiabetic agents. Baseline characteristics did not differ significantly between the two study groups.

Insulin dose

Subjects in the standard-dosage group received significantly more insulin on all study days, except for the last day, compared with the reduced-dosage group (Fig. 1). Total daily insulin administered to the standard and reduced groups was 33.4 ± 15.1 vs. 21.1 ± 12.7 units on day 1, 38.6 ± 18.4 vs. 27.3 ± 15.2 units on day 2, 40.3 ± 22.7 vs. 30.6 ± 17.0 units on day 3, 39.5 ± 17.2 vs. 26.7 ± 16.4 units on day 4, 39.9 ± 14.5 vs. 23.9 ± 15.7 units on day 5, and 36.1 ± 16.0 vs. 33.7 ± 3.1 units on day 6. The amount of insulin glargine administered to each of the study groups was significantly different on all study days except for day 6. Subjects received a mean of 21.4 ± 6.1 vs. 13.1 ± 5.4 units on day 1 ($P < 0.0001$) and 23.6 ± 9.3 vs. 17.3 ± 2.3 units on day 6 ($P = 0.30$) in the standard- and reduced-dosage groups, respectively.

Glycemic control

The mean BG for study day 1 was 196.1 ± 71 vs. 196.9 ± 55 mg/dL ($P = 0.94$) and the mean BG for all of the subsequent study days was 174 ± 52.3 vs. 174.5 ± 46 mg/dL ($P = 0.96$) in the standard- and reduced-dosage groups, respectively (Fig. 2). There was no significant difference in glycemic control between treatment groups at any specific time point during the day or any specific study day (Fig. 3). The mean fasting BG was 151.9 ± 62.7 vs. 155.1 ± 53.4 mg/dL ($P = 0.78$), the mean prelunch BG was 193.0 ± 68.4 vs. 189.2 ± 60.3 mg/dL ($P = 0.76$), the mean predinner BG was 169.9 ± 54.9 vs. 184.7 ± 62.1 mg/dL ($P = 0.22$), and the mean bedtime BG was 181.5 ± 65.4 vs. 178.4 ± 44.5 mg/dL ($P = 0.82$) in the standard- and reduced-dosage groups, respectively.

There were no significant differences between treatment groups in the percentage of BG values that fell within the target range of 100 to 180 mg/dL during any of the 6 study days. On the first study day, this target was achieved in 30% of BG measurements in the standard-dosage group and in 33% of BG measurements in the reduced-dosage group ($P = 0.57$). On the last study day, this target was achieved in 46% of all measurements in the standard-dosage group and in 56% of measurements in the reduced-dosage group ($P = 0.61$). In addition, there were no significant differences in daily mean BG on any of the 6 study days when the general medical subjects were compared with the general surgical subjects (data not shown).

Hypoglycemia

Subjects in the standard-dosage group experienced almost twice as many episodes of hypoglycemia as the reduced dosage group: 30% in the standard-dosage group experienced at least one BG <70 mg/dL in contrast to 15.8% in the reduced-dosage group. The difference nearly reached significance ($P = 0.08$). At least one severe hypoglycemic episode (BG <50 mg/dL) occurred in 6% of the standard-dosage group in contrast to 1.8% of the reduced

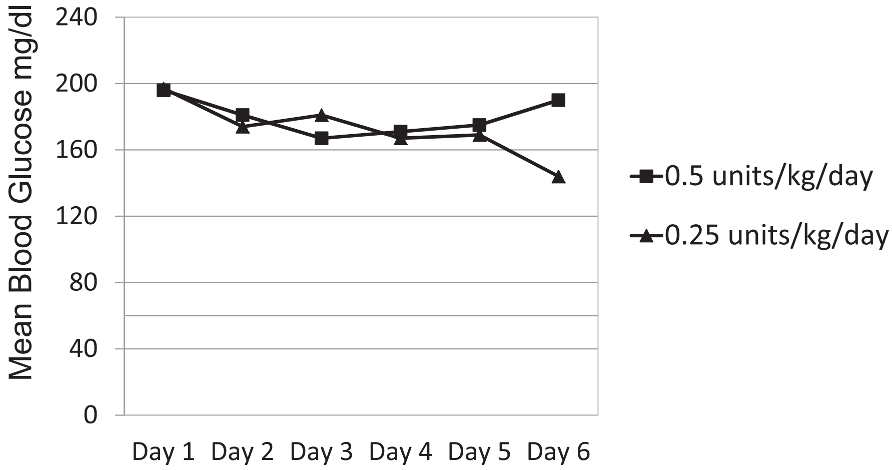

Figure 2—*Mean daily blood glucose: 0.5 vs. 0.25 units/kg/day*.

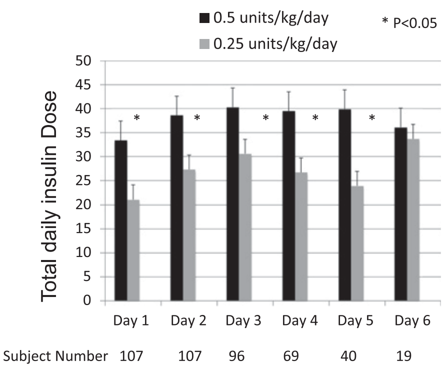

Figure 1—*Total daily insulin dose: 0.5 vs. 0.25 units/kg/day. Data are presented with the SD* (error bars).

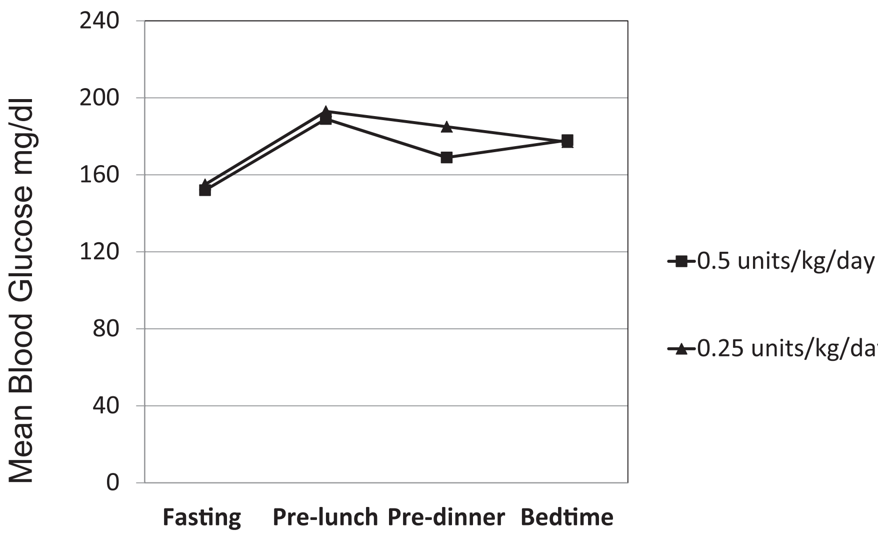

Figure 3—*Mean premeal and bedtime blood glucose: 0.5 vs. 0.25 units/kg/day*.

dosage group ($P = 0.34$). The general medical subjects were somewhat more likely to experience a BG <70 mg/dL than their general surgical counterparts. Of the subjects who experienced at least one BG level of <70 mg/dL, 88% were general medical, whereas only 70% of the total study population were general medical.

CONCLUSIONS—Achieving reasonable BG control in hospitalized patients with acute illness is always challenging. Patients with diabetes and renal insufficiency present a greater challenge because of their increased risk for hypoglycemia, especially when the GFR is <60 mL/min (21). Insulin-treated patients with renal failure are more susceptible to hypoglycemia because of diminished insulin clearance. After the liver, the kidney is the most important site for insulin elimination. In the normal kidney, insulin is freely filtered at the glomerulus and subsequently reabsorbed in the proximal tubule. However, insulin clearance decreases as renal failure progresses, resulting in a prolonged pharmacokinetic profile. Rave et al. (22) found a 30–40% reduction in the clearance of regular and lispro insulin in patients with a mean GFR of 54 mL/min. The phenomenon is more striking when GFR falls <40 mL/min (23). Biesenbach et al. (24) found that the insulin requirements were reduced by 51% in type 2 diabetes as GFR deteriorated from 80 to 10 mL/min.

Current guidelines for insulin dosing in hospitalized patients do not suggest specific modifications depending on the level of GFR. Our study is the first to provide direct evidence for the benefit of a dose reduction for such patients. We find that patients with type 2 diabetes and renal insufficiency can achieve equivalent control of hyperglycemia by starting with 0.25 or 0.5 units/kg/day of glargine and glulisine insulin. However, twice as many subjects who received 0.5 units/kg/day experienced hypoglycemia compared with those who received 0.25 units/kg/day. The equivalent control of hyperglycemia between the two groups was unexpected. We speculate that it may reflect increased insulin resistance during the acute illness of hospitalization. On the last study day of each subject, only 46–56% of BG readings were in the target range of 100 to 180 mg/dL. This result is likely due to our protocol that only allows 10–20% titrations in insulin dose per day and also reflects the difficulty in achieving control of hyperglycemia while striving to avoid hypoglycemia in the short time span of the usual hospital stay. To achieve these results, it is important to avoid giving mealtime short-acting insulin when the patient does not receive the meal and to adjust doses of both basal and mealtime insulin every day based on individual BG trends. The general medical subjects were somewhat more likely to experience hypoglycemia than the general surgical subjects; however, the absolute number of subjects and hypoglycemic episodes was too small to allow any firm conclusions. The daily mean BG levels and the frequency of hypoglycemia in the current study are similar to previous inpatient diabetes trials (6–8).

This study has several limitations. First, although it was a multicenter study, a relatively small number of subjects were enrolled. Second, although the reduction in the frequency of hypoglycemia seen with 0.25 units/kg/day seems highly clinically relevant, it did not reach statistical significance in our study, perhaps because of the small size of the study groups. Third, although house-staff teams cared for all subjects in our study, clinicians experienced in the art of inpatient insulin management supervised all insulin dose titrations. Thus, our results may be difficult to replicate in hospital settings that do not have a dedicated glucose management team.

In summary, control of hyperglycemia in noncritical hospitalized patients with type 2 diabetes and renal insufficiency was equivalent with 0.5 compared with 0.25 units/kg/day using a glargine and glulisine insulin regimen. However, the patients who received the reduced doses of insulin experienced only half as much hypoglycemia. We conclude that this optimized approach for this patient population is a significant improvement over current inpatient protocols that suggest initial insulin doses based solely on weight.

Acknowledgments—This study was sponsored by an investigator-initiated grant from sanofi-aventis. D.B. acknowledges research support from sanofi-aventis and Novo Nordisk. M.A.E. serves on the speaker's bureau for Lilly and Merck and acknowledges research support from sanofi-aventis. M.M. acknowledges research support from sanofi-aventis, Novo Nordisk, Eli Lilly, Corcept, Ipsen, and Endo and consulting for Abbott, Corcept, and Novartis. No other potential conflicts of interest relevant to this article were reported.

D.B. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. J.Z. researched data, contributed to discussion, and wrote the manuscript. C.M., P.R., S.D.-H., H.L., V.G., and K.S. researched data. M.A.E. and M.M. researched data, contributed to discussion, and reviewed and edited the manuscript. D.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Preliminary results from this study were presented at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

The authors gratefully acknowledge the assistance of Kathleen Schmidt, APN; Diana Johnson Oakes, APN; and Grazia Aleppo, MD, all at Northwestern University.

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