Insulin Analogs Versus Human Insulin in the Treatment of Patients With Diabetic Ketoacidosis

A randomized controlled trial

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OBJECTIVE — To compare the safety and efficacy of insulin analogs and human insulins both during acute intravenous treatment and during the transition to subcutaneous insulin in patients with diabetic ketoacidosis (DKA).

RESEARCH DESIGN AND METHODS — In a controlled multicenter and open-label trial, we randomly assigned patients with DKA to receive intravenous treatment with regular or glulisine insulin until resolution of DKA. After resolution of ketoacidosis, patients treated with intravenous regular insulin were transitioned to subcutaneous NPH and regular insulin twice daily ($n = 34$). Patients treated with intravenous glulisine insulin were transitioned to subcutaneous glargine once daily and glulisine before meals ($n = 34$).

RESULTS — There were no differences in the mean duration of treatment or in the amount of insulin infusion until resolution of DKA between intravenous treatment with regular and glulisine insulin. After transition to subcutaneous insulin, there were no differences in mean daily blood glucose levels, but patients treated with NPH and regular insulin had a higher rate of hypoglycemia (blood glucose <70 mg/dl). Fourteen patients (41%) treated with NPH and regular insulin had 26 episodes of hypoglycemia and 5 patients (15%) in the glargine and glulisine group had 8 episodes of hypoglycemia ($P = 0.03$).

CONCLUSIONS — Regular and glulisine insulin are equally effective during the acute treatment of DKA. A transition to subcutaneous glargine and glulisine after resolution of DKA resulted in similar glycemic control but in a lower rate of hypoglycemia than with NPH and regular insulin. Thus, a basal bolus regimen with glargine and glulisine is safer and should be preferred over NPH and regular insulin after the resolution of DKA.

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D iabetic ketoacidosis (DKA) is the most serious hyperglycemic emergency in patients with type 1 and type 2 diabetes. DKA is the most common cause of death in children and adolescents with type 1 diabetes and accounts for half of all deaths in diabetic patients aged <24 years (1). Recent series in adult patients with DKA have reported a mortality rate of <5% (2,3). DKA is responsible for >100,000 hospital admissions in the U.S. and substantial spending related to direct and indirect costs (2). It has been estimated that treatment of DKA episodes represent more than one of every four health care dollars spent on direct medical care for adult patients with type 1 diabetes (4).

The mainstay in the treatment of DKA involves the administration of regular insulin via continuous intravenous infusion or by frequent subcutaneous or intramuscular injections of regular insulin or rapid-acting insulin analogs (5–7). Although several controlled studies have shown that low-dose insulin therapy is effective regardless of the route of administration, most patients are treated with intravenous regular insulin until resolution of DKA (8). When this occurs, subcutaneous insulin therapy can be started. The American Diabetes Association recommends the transition to NPH and regular insulin twice daily or to a multidose regimen of short- or rapid-acting and intermediate- or long-acting insulins (2,8). Several studies have reported hospital rates of hypoglycemic events up to 37% with the use of NPH and regular insulin after discontinuation of intravenous insulin (3,9). The inadequate duration of action of NPH insulin and an undesirable peak activity at 4–6 h after injection (10) as well as the high day-to-day variability in absorption (11) partially explains the high rate of hypoglycemic events. In recent years, the use of long-acting basal and rapid-acting insulin analogs has been recommended as a more physiological approach than NPH and regular insulin for glucose control in the hospital (12,13); however, no previous studies have evaluated the safety and efficacy of insulin analogs in the management of patients with hyperglycemic crises. Accordingly, the aim of this multicenter, randomized, open-label study was 1) to determine differences in treatment response between regular insulin and rapid-acting insulin analogs during the acute intravenous treatment of DKA and 2) to determine differences between treatment with glargine plus glulisine and a split-

mixed regimen of NPH plus regular insulin after the transition to subcutaneous insulin following resolution of DKA.

RESEARCH DESIGN AND METHODS

A total of 74 patients with DKA were randomly assigned in this study. Of them, six patients were excluded because four withdrew consent before or shortly after initiation of insulin therapy, one patient received glargine insulin before resolution of DKA, and one patient was treated with intravenous aspart insulin instead of regular insulin. The remaining 68 patients served as the study population. The diagnosis of DKA was established by standard criteria (8). We excluded patients with systolic blood pressure <90 mmHg after the administration of 1 l of normal saline, patients in a comatose state, and patients with acute myocardial ischemia, congestive heart failure, end-stage renal or hepatic failure, dementia, and pregnancy. This study was conducted at Grady Memorial Hospital, Atlanta, Georgia, and at Hennepin County Medical Center, Minneapolis, Minnesota, and was approved by dual institutional review boards.

Patients with DKA were randomly assigned in the emergency department to receive treatment with regular ($n = 34$) or glulisine ($n = 34$) insulin intravenously until resolution of DKA. After resolution of DKA, patients treated with intravenous regular insulin were transitioned to receive subcutaneous NPH and regular insulin twice daily. Patients treated with intravenous glulisine insulin were transitioned to glargine once daily and glulisine before meals.

Treatment protocols

Patients were managed by members of the internal medicine residency programs of the respective institutions, who received copies of the assigned treatment protocol (supplementary Table A in an online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc09-0169/DC1). Orders for intravenous fluids, potassium, and bicarbonate administration were similar in both groups and followed current American Diabetes Association guidelines (2,8). Initial orders for intravenous regular and glulisine insulin included an initial bolus of 0.1 unit/kg, followed by a continuous intravenous infusion calculated to deliver 0.1 unit $\cdot$ kg^{-1} $\cdot$ h^{-1} until blood glucose levels decreased to <250 mg/dl (<13.8 mmol/l). At that time, intravenous fluids

were changed to dextrose-containing solutions, and the insulin infusion rate was decreased to 0.05 unit $\cdot$ kg^{-1} $\cdot$ h^{-1} to maintain blood glucose of ~200 mg/dl (~11.1 mmol/l) until resolution of DKA. DKA was considered resolved when blood glucose was <250 mg/dl, the serum bicarbonate level was ≥18 mmol/l, and venous pH was >7.30 (2).

After resolution of DKA, insulin infusion was discontinued 2 h after the administration of subcutaneous insulin. Patients with newly diagnosed diabetes received an initial total daily dose (TDD) of insulin of 0.6 unit $\cdot$ kg^{-1} $\cdot$ day^{-1}. Subjects receiving insulin therapy before admission received the same outpatient insulin amount, with the TDD switched to glargine and glulisine or to NPH and regular insulin on a unit-for-unit basis.

Patients treated with subcutaneous glargine and glulisine received 50% of the TDD as glargine and 50% as glulisine insulin. Glargine was given once daily at the same time of day and glulisine was given in three equally divided doses before each meal. Glargine was given at the full dose independently of food intake, but to prevent hypoglycemia, the dose of glulisine was held if a subject was not able to eat a given meal. Patients treated with NPH and regular insulin received two-thirds of the TDD before breakfast and one-third of the TDD before dinner. The insulin dose was given as two-thirds NPH and one-third regular insulin in the morning with breakfast and two-thirds NPH and one-third regular insulin in the evening with dinner. To prevent hypoglycemia, regular insulin was held if a subject was not able to eat a given meal; in addition, the dose of NPH was reduced by 50% if a patient was kept NPO all day. Insulin dosage was adjusted daily according to glucose values to maintain target blood glucose <140 mg/dl before meals. The insulin dose was adjusted, and supplemental insulin was given based on blood glucose levels (supplementary Table B, available in an online appendix).

The primary outcome of the study was the determination of differences in the rate of hypoglycemic events (blood glucose <70 mg/dl) during the transition period between treatment groups. Secondary outcomes included differences in the time to resolution of DKA and hyperglycemia, average blood glucose during intravenous insulin infusion, mean daily blood glucose after resolution of DKA, length of hospital stay, and hospital complications between treatment groups.

Statistical analysis

Based on previous reports, the rate of hypoglycemic events (primary end point) in patients treated with subcutaneous NPH and regular insulin was estimated to be 37% (3,9). The rate of hypoglycemic events with basal bolus insulin was estimated to be <10% (14). Using two-sided χ^2 tests and a type I error of 0.05, we calculated that 32 patients per group were needed to have 80% power to detect the difference in hypoglycemia rate of 30%. Allowing for 15% loss to follow-up, we recruited a total of 74 patients with DKA, of which 34 patients per group completed the study.

All data in the text, tables, and figures are means ± SD. Two-sample Wilcoxon tests or Pearson's χ^2 tests were used to compare patient demographic and clinical characteristics as well as outcomes measures between treatment groups. Cross-sectional analyses based on two-sample Wilcoxon tests were used to assess the group differences in blood glucose and acid-based parameters during DKA treatment and mean daily blood glucose after DKA resolution. In addition, we used repeated-measures linear models to examine the group differences while adjusting for subject's age, sex, race, and BMI. $P < 0.05$ was considered significant. Statistical analysis was performed using SAS.

RESULTS

The clinical characteristics of study patients on admission are shown in Table 1. The mean age, duration of diabetes, and precipitating cause for DKA were similar between treatment groups. Poor adherence with insulin therapy was the most common precipitating cause of DKA and was recorded in 59% of patients treated with glulisine and in 79% of patients in the regular insulin group. The length of hospital stay was similar between patients treated with glargine and glulisine (2.9 ± 2.2 days) and NPH and regular insulin (3.3 ± 2.2 days) (NS).

Biochemical parameters on admission and during treatment were similar in patients treated with intravenous glulisine and regular insulin (NS). Changes in blood glucose and acid-base parameters during treatment are shown in Fig. 1. As suggested by the repeated-measures analyses, the rate of decline of blood glucose concentration and changes in acid base parameters during treatment were not significantly different between treatment groups with adjustment for age, sex, race, and BMI (NS). The mean duration of

Table 1—*Patient characteristics on admission*

	Insulin analogs (glulisine/glargine)	Human insulin (NPH/regular)
n	34	34
Age (years)	39 ± 12	38 ± 12
Sex (male/female)	22/12	23/11
Race		
African American	29	27
Caucasian	4	6
Other	1	
BMI (kg/m^2)	29 ± 9	27 ± 7
Precipitating cause of DKA		
Poor compliance	20 (59)	27 (79)
New-onset diabetes	6 (18)	
Other medical illness	8 (23)	7 (21)
Glucose (mg/dl)	529 ± 173	564 ± 164
Bicarbonate (mEq/l)	12.8 ± 4.5	12.5 ± 5.0
Venous pH	7.2 ± 0.1	7.1 ± 0.2
Anion gap (mEq/l)	22 ± 6	22 ± 6
β-Hydroxybutyrate (mmol/l)	8.0 ± 3.4	7.4 ± 3.3
A1C (%)	11.7 ± 2.2	11.7 ± 2.9

Data are means ± SD or *n* (%).

treatment until resolution of ketoacidosis was not statistically different between those treated with glulisine (8.9 ± 4.7 h) and regular insulin (10.5 ± 6.3 h) (NS).

At resolution of DKA, the mean blood glucose concentration and acid-base parameters in patients treated with glulisine insulin (glucose 153 ± 61 mg/dl, bicar-

bonate 20 ± 3 mmol/l, pH 7.33 ± 0.04, and anion gap 8.3 ± 2.1 mEq/l) were similar to those in patients treated with intravenous regular insulin (glucose 185 ± 58 mg/dl, bicarbonate 19.5 ± 3.7 mEq/l, pH 7.32 ± 0.04, and anion gap 9 ± 3 mEq/l). During the insulin infusion, six patients treated with glulisine and four patients treated with regular insulin developed one or two episodes of blood glucose <70 mg/dl, but none of them were <40 mg/dl. The amount of insulin administered until resolution of DKA (70 ± 33 and 76 ± 46 units) and the mean total duration of insulin infusion (15.7 ± 4.5 and 20.5 ± 12 h) were not different between glulisine and regular insulin, respectively (NS). There was no mortality, and none of the patients had a recurrence of DKA during their hospital stay.

After transition to subcutaneous insulin therapy, cross-sectional analyses based on two-sample Wilcoxon tests showed that there were no significant differences in the mean daily glucose concentration between treatment groups. However, fitting of a repeated-measures linear model with or without adjustment for age, sex, race, and BMI indicated a
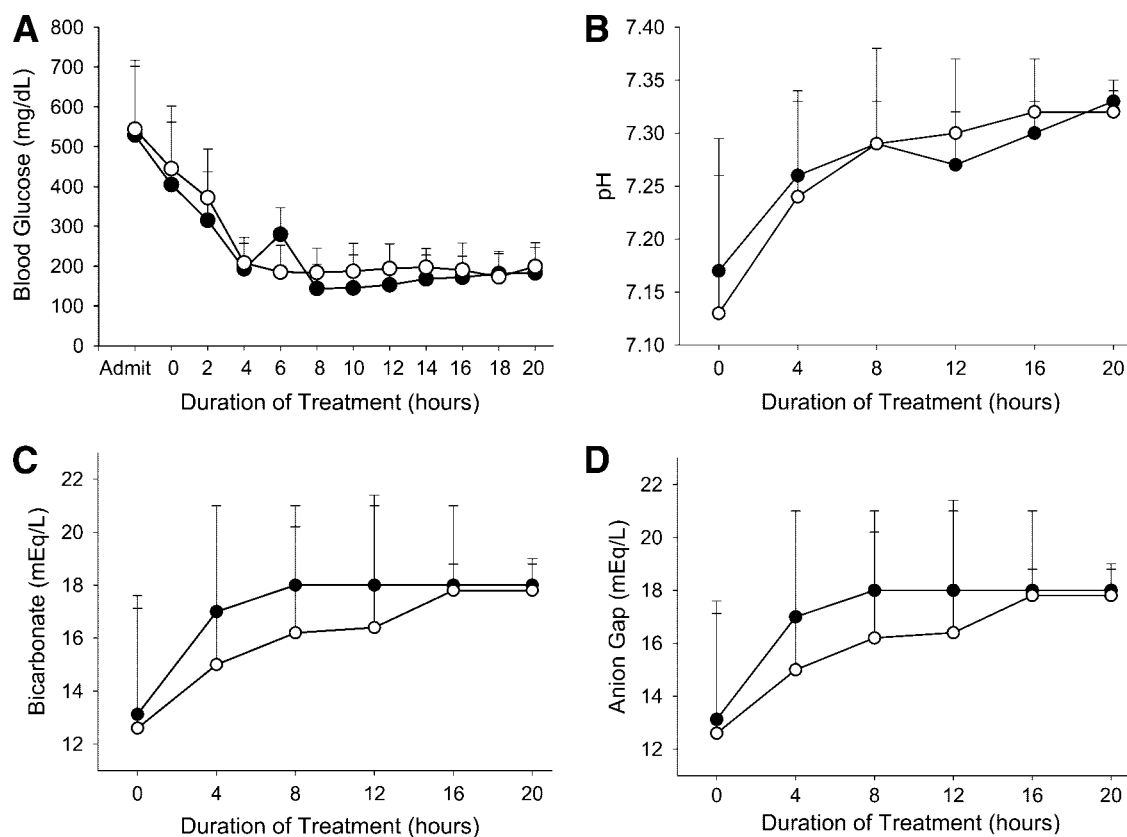

Figure 1—*Changes in metabolic profile in patients with DKA treated with intravenous glulisine (○) and regular insulin (●). To convert the values for glucose from milligrams per deciliter to millimoles per liter, multiply by 0.05551. A: glucose; B: pH; C: bicarbonate; D: anion gap.*

Table 2—Hypoglycemic events during intravenous and subcutaneous insulin treatment

Intravenous insulin therapy	Glulisine	Regular
Patients with BG <70 mg/dl (%)	4 (12)	6 (18)
Episodes of BG <70 mg/dl	6	7
Patients with BG <40 mg/dl, n (%)	0 (0)	0 (0)
Episodes of BG <40 mg/dl	0	0

Subcutaneous insulin therapy	Glargine/glulisine	NPH/regular
Patients with BG <70 mg/dl (%)	5 (15)	14 (41)*
Episodes of BG <70 mg/dl	8	26†
Patients with BG <40 mg/dl, n (%)	1 (3)	2 (6)
Episodes of BG <40 mg/dl	1	2

Data are n or n (%). *$P = 0.03$; †$P = 0.019$. BG, blood glucose.

greater decline rate of blood glucose in the glargine and glulisine group than that in the NPH and regular insulin group ($P < 0.01$).

Patients treated with NPH and regular insulin had a higher rate of hypoglycemic events than those treated with a basal bolus regimen (Table 2). Fourteen patients (41%) treated with NPH and regular insulin had 26 episodes of hypoglycemia and five patients (15%) in the glargine and glulisine group had 8 episodes of hypoglycemia ($P < 0.01$). Three of these episodes in the NPH and regular insulin group and one in the glargine/glulisine group were <40 mg/dl. None of the episodes of hypoglycemia in either group were associated with loss of consciousness or seizure.

The TDD of subcutaneous insulin was similar between groups (Table 3). The mean total daily insulin dose including supplemental insulin was 60 ± 30 units in the glargine and glulisine group and 58 ± 24 units in the NPH and regular insulin group (NS). In addition, there were no differences in the amount of supplements of insulin glulisine (13 ± 10 units) and regular insulin (12 ± 6 units) (NS).

CONCLUSIONS — This is the first prospective randomized trial to compare the use of insulin analogs and human insulins both during acute intravenous treatment and during the transition to subcutaneous insulin in patients with DKA. During the initial treatment phase, we observed no differences in the mean duration of treatment or in the amount of intravenous insulin administration until resolution of DKA between regular and glulisine insulin. After resolution of ketoacidosis, the transition to subcutaneous glargine and glulisine insulin resulted in glycemic control similar to that for NPH and regular insulin; however, treatment with glargine and glulisine insulin is safer and is associated with a significantly lower rate of hypoglycemia. A total of 14 patients (41%) treated with NPH and regular insulin and 5 patients (15%) in the glargine and glulisine group had one or more episodes of hypoglycemia ($P < 0.03$).

The comparable response to intravenous glulisine and regular insulin during the acute resolution of DKA in this study is in line with previous reports of generally equal efficacy and in vivo potency of intravenous rapid-acting insulin analogs (glulisine, aspart, and lispro) and regular insulin in animal and human studies (15,16). Pharmacokinetics and pharmacodynamic studies comparing the intravenous administration of glulisine and regular insulin have shown a similar onset of action within 20 min, a similar distribution and elimination profile, and equivalent glucose utilization and disposal on a molar, unit-per-unit basis (16,17). The present study confirms these observations and provides evidence of the equal efficacy and in vivo potency of intravenous rapid-acting insulin analogs and regular insulin in patients with severe hyperglycemia and ketoacidosis. Their comparable in vivo potency is attributable to their similar receptor binding affinity and receptor-mediated clearance (18). Our study and these previous reports indicate that treatments with intravenous glulisine and regular insulin are equally safe and efficacious in the acute management of patients with DKA. However, intravenous regular insulin is more cost-effective and should be preferred over rapid-acting insulin analogs during the acute intravenous treatment phase of DKA.

Previous randomized studies in patients with DKA have focused on the amount and route of insulin administration during the acute resolution phase of ketoacidosis (2,3). Few studies, however, have focused on the transition period to subcutaneous insulin after the resolution of DKA. Accordingly, in this study we aimed to compare differences between treatment with basal bolus insulin analogs and NPH and regular insulin after resolution of DKA. We found no differences in the daily glucose concentration between treatment groups; however, patients treated with NPH and regular insulin had higher rates of hypoglycemia (41%) than subjects treated with basal bolus (15%) insulin ($P < 0.03$). The rate of hypoglycemic events in this study is similar to the rate reported previously with the use of NPH and regular insulin after discontinuation of intravenous therapy (3,9).

The higher rate of hypoglycemia with human insulins is explained by the pharmacological features and peak duration of

Table 3—Mean blood glucose concentration and daily insulin doses during subcutaneous insulin treatment after resolution of DKA

	Mean daily blood glucose (mg/dl)			Mean daily insulin dose (units/day)		
	NPH/regular	Glargine/glulisine	P	NPH/regular	Glargine/glulisine	P
Day 1*	188 ± 61	213 ± 76	0.234	50 ± 28	58 ± 33	0.304
Day 2	206 ± 71	220 ± 61	0.370	70 ± 37	73 ± 47	0.877
Day 3	207 ± 86	180 ± 80	0.417	77 ± 45	62 ± 49	0.364
Day 4	211 ± 63	158 ± 44	0.068	70 ± 47	67 ± 50	0.999
Day 5	190 ± 45	124 ± 41	0.068	50 ± 30	47 ± 41	0.302

Data are means ± SD. *Day 1 = depending on the time of resolution of ketoacidosis and transition to subcutaneous insulin, a patient could have received one or two doses of NPH/regular insulin or one dose of glargine and one to three doses of glulisine insulin per day.

action of NPH and regular insulin (10) as well as the high day-to-day variability in absorption (11). NPH has an onset of action ranging between 2 and 4 h, a peak concentration of ~6–8 h, and a duration of action up to 20 h (19). Regular human insulin has an onset of action in 30 min, peaks at 2–3 h when given subcutaneously, and has a duration of action of 6–8 h (19). The combination of basal and rapid-acting insulin analogs represents a more physiological approach to glucose control in the hospital. Glargine is a peakless, long-acting basal insulin with an onset of action of ~2 h, a plateau of biological action at 4–6 h, and duration of action up to 24 h (20). Glulisine has a faster onset of action and a shorter duration of action after subcutaneous injection compared with regular insulin (21,22). In agreement with these results, we recently reported that a basal bolus algorithm with glargine and glulisine is an effective intervention for glucose control with a low rate of hypoglycemic events (3%) in hospitalized patients with type 2 diabetes (14). More recently, we reported that 38% of hospitalized patients treated with a combination of NPH and regular insulin experienced one or more episodes of blood glucose <70 mg/dl during the hospital stay (23). Minimizing the rate of hypoglycemia events is of major importance in hospitalized patients because it may represent an independent risk factor of poor clinical outcome (24).

We acknowledge several limitations in our study, including a relatively small number of patients and the fact that the large majority of patients were African Americans with poor adherence to therapy as the primary precipitating cause of DKA. We also excluded patients with hypovolemic shock, patients in a comatose state, and patients who had acute myocardial ischemia, congestive heart failure, end-stage renal or hepatic failure, or pregnancy. A large prospective, randomized clinical trial of strict glycemic control is certainly needed to address these important issues.

In summary, our study indicates that intravenous treatments with regular insulin and glulisine insulin are equally effective with no differences in the mean duration of treatment or in the amount of insulin infusion until resolution of DKA. After resolution of DKA, transition to subcutaneous glargine once daily and glulisine before meals resulted in similar glycemic control but in a lower rate of

hypoglycemic events than treatment with NPH and regular insulin twice daily. These findings indicate that a basal bolus insulin regimen with glargine and glulisine is safer and should be preferred over NPH and regular insulin after the resolution of DKA.

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