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Original Research

Pharmacokinetics and pharmacodynamics of insulin glargine–insulin glulisine basal-bolus and twice-daily premixed analog insulin in type 1 diabetes mellitus patients during three standardized meals

Elizabeth Mary Lamos [a], Lisa M. Younk [b], Donna B. Tate [c], Stephen N. Davis [d,*]

[a] Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, 827 Linden Ave, 2nd Floor, Baltimore, MD 21201
[b] Department of Medicine, University of Maryland School of Medicine, 3-013 Bressler Research Building, 655 W. Baltimore St., Baltimore, MD 21201
[c] Department of Medicine, University of Maryland School of Medicine, 3-019 Bressler Research Building, 655 W. Baltimore St., Baltimore, MD 21201
[d] University of Maryland Medical Center, 22 South Greene St. N3W42, Baltimore, MD 21201

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ABSTRACT

Aims: To evaluate the pharmacokinetics and pharmacodynamics of basal insulin glargine with mealtime insulin glulisine or twice daily 75/25 premixed neutral protamine insulin lispro and insulin lispro in individuals with type 1 diabetes during three standardized meals over a 24 hour duration and compare to physiologic insulin and glucose responses in healthy non-diabetic individuals.
Methods: Twelve healthy (4 male/8 female) and thirteen individuals with type 1 diabetes (8 male/5 female) were studied during three sequential standardized meals. Individuals with type 1 diabetes received either glargine and glulisine injected 5 minutes subcutaneously before each meal or premixed insulin lispro injected 5 minutes before breakfast and dinner in a randomized fashion separated by eight weeks.
Results: The incremental systemic insulin AUC, maximal insulin concentration, and rate of rise of systemic insulin (0–30 minutes) during all three meal intervals were similar between glargine/glulisine and healthy controls. Incremental glucose AUC with glargine/glulisine was similar to controls at lunch and dinner. With premix 75/25 insulin, insulin AUC was lower and incremental glucose AUC was greater at lunch compared to the healthy and glargine/glulisine. Hypoglycemic events before lunch were greater with premix insulin group than with glargine/glulisine ($p < 0.0001$).
Conclusions: Glargine/glulisine pharmacokinetics in type 1 diabetes can closely approximate physiologic insulin responses in healthy individuals during a day in which three standardized meals are consumed. Additionally, when glulisine is dosed only five minutes pre-meal, systemic insulin concentration rises as rapidly as prandial endogenous insulin levels. This present study compared glargine and glulisine administered in an approximate 50/50 proportion. Future studies of alternate meal times, meal content and differing premixed insulin preparations are indicated.

Introduction

In healthy individuals, low levels of circulating insulin are maintained during interprandial periods, while during a meal, insulin levels rise rapidly and then taper to fasting concentrations as glucose levels return to baseline [1]. In order to improve glycemic control and reduce microvascular complications in patients with diabetes, substantial effort has been directed toward the development of insulin analog formulations, delivery methods and dosing schedules that more closely match physiologic insulin profiles [2].

One common insulin replacement regimen involves multiple daily injections (basal-bolus therapy), consisting of a longer-acting insulin (insulin glargine, degludec, detemir, or NPH insulin injected once or twice daily) and rapid-acting insulin (glulisine, aspart or lispro) injected prior to a meal to provide prandial insulin coverage. Another option for insulin replacement is premixed analog insulin, typically injected twice daily, which contains either neutral protamine lispro and insulin lispro (as a 75:25 ratio) or protamine crystalline aspart and insulin aspart (as a 70:30 ratio). The protamine portion of premix insulin is similar to NPH insulin and functions as intermediate-acting insulin to cover basal insulin requirements. The rapid-acting component is aimed to cover breakfast and dinner prandial insulin requirements [3].

* Corresponding author. Tel.: +1 410 328 2488; fax: +1 410 328 8688.
E-mail address: sdavis@medicine.umaryland.edu (S.N. Davis).

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While pharmacokinetic (PK) and pharamacodynamic (PD) studies of long-acting and rapid-acting insulin analogs have been published [4,5], previous studies often involved injection of these insulins under fasting conditions or involved injection prior to only one standardized meal challenge. Comparison groups usually consisted of patients receiving regular human insulin and/or NPH insulin as part of their basal-bolus therapy. To further examine the PK and PD of insulin analogs used in contemporary basal-bolus regimens in the treatment of type 1 diabetes mellitus, the aim of this study was to determine an entire day-long profile of insulin and glucose levels over the course of three standardized meal challenges. Insulin glargine (glargine) was injected prior to breakfast, and insulin glulisine (glulisine) was used as the pre-meal bolus insulin. A comparison group of non-diabetic healthy individuals served as a control group to demonstrate normal physiologic insulin and glucose responses during the three meals. A second comparison group consisted of patients with type 1 diabetes who consumed all three standardized meals and received pre-mixed injections of neutral protamine lispro and insulin lispro prior to breakfast and dinner.

Subjects

All healthy subjects had normal liver, kidney, electrolyte and blood count values and had a normal response to an oral glucose tolerance test. Individuals with type 1 diabetes also had normal liver, kidney, electrolyte and blood count values. Apart from one subject with mild background retinopathy, all type 1 diabetes patients were free from tissue complications of diabetes. Twelve healthy subjects [4 males and 8 females, age 27 ± 6 years, BMI 24 ± 2 kg/m^2, hemoglobin A1c (HbA1c) 5.2 ± 0.3%] and thirteen subjects with type 1 diabetes (8 male and 5 female, age 30 ± 11 years, BMI 24 ± 3 kg/m^2, and HbA1c 7.3 ± 1.1%, diabetes duration 9.9 ± 10.2 years) were studied in a single blind randomized fashion (Table 1). Background insulin treatment in the individuals with type 1 diabetes consisted of basal-bolus (glargine/aspart or glargine/lispro) or insulin pump (aspart or lispro) therapy. With the exception of one subject who completed only the lispro premix portion of the study, all participants with type 1 diabetes completed both treatment arms. Studies were approved by the Vanderbilt University Human Subjects Institutional Review Board, and all subjects gave written and verbal informed consent.

Materials and methods

Individuals with type 1 diabetes were randomly assigned in a 1:1 ratio to one of two treatment sequences (A or B), with a minimum 8-week washout period between treatment visits. In sequence A, subjects received a basal-bolus insulin regimen of insulin glargine and insulin glulisine (glargine/glulisine) during the first treatment period and received premixed neutral protamine lispro and insulin lispro 75/25 (lispro premix) during the second treatment period. Those randomized to sequence B received lispro premix and then glargine/glulisine. Healthy subjects did not receive exogenous insulin and participated in only one study visit.

Table 1
Baseline demographics and clinical characteristics

Characteristic	Healthy (N = 12)	Type 1 diabetes (N = 13)
Age (years)[a]	26.7 (6.0)	30.3 (10.6)
Sex (n)		
Male	4	8
Female	8	5
Height (cm)	167 (10.8)	176 (10.3)
Weight (kg)	67.9 (13.0)	74.5 (12.0)
BMI (kg/m^2)	24.3 (2.4)	24.1 (2.9)
HbA1c (%)	5.2 (0.3)	7.3 (1.1)

[a] Values are expressed as mean (standard deviation); HbA1c = glycated hemoglobin a1c; BMI = body mass index.

All participants were admitted to the Vanderbilt General Clinical Research Center the evening prior to the study period. Upon admission of patients with type 1 diabetes, a retrograde intravenous cannula (I.V.) was inserted under local anesthesia into the back of a hand for blood sample collection, and a second I.V. was inserted in an antegrade fashion in the forearm for infusions. Upon I.V. insertion, patients with type 1 diabetes suspended their usual insulin regimen (long-acting insulin was taken no later than the morning prior to admission), and intravenous regular human insulin was infused to maintain euglycemia (target blood glucose ~5–6.7 mmol/L). Non-diabetic controls received placement of a retrograde I.V., as above, in the morning preceding the study. Each subject received a standardized dinner meal and then fasted overnight for ≥8 hours.

Meal challenge

On the study day, all subjects received three meal challenges (08:00, 13:00 and 18:00), standardized for total caloric content and tailored to provide a daily total of 30 kcal/kg actual body weight, which is considered standard calorie content based on estimated energy expenditure of moderately active healthy individuals [6]. Meals were consumed within 20 minutes. The total calories per day were divided among meals: 1/6th at breakfast (17%), 2/6th at lunch (33%) and 3/6th at dinner (50%) by convention. Meal calories were approximately 50% carbohydrate, 30% lipid and 20% protein, in accordance with healthy macronutrient meal composition standards [6].

Insulin regimens

In the diabetes groups, overnight intravenous insulin infusion was continued until 07:45 on the morning of the study day. In the glargine/glulisine group, glargine was dosed at 0.35 units/kg administered subcutaneously at 07:00 (1 hour prior to breakfast). Glulisine was dosed at 1 unit/10 g carbohydrate per meal, administered subcutaneously 5 minutes prior to each meal (07:55, 12:55 and 17:55). In the lispro premix group, total lispro premix dose was determined by referencing the total daily dose as calculated for the glargine/glulisine treatment period, with two-thirds administered at 07:55 (5 minutes prior to breakfast) and one-third administered at 17:55 (5 minutes prior to dinner). Thus, an equivalent insulin dosage was administered to each type 1 diabetes patient during both protocols.

Sample collection

The hand with the retrograde I.V. was placed in a heated box (55–60 °C) during the study so that arterialized blood could be obtained for measurement of glucose and insulin [7]. Samples were collected hourly from 06:00 to 24:00 and every 15 minutes for 2 hours directly following each meal.

Bioanalytical methods

Blood glucose concentrations were measured using a point-of-care glucometer (Ascensia Elite XL, Bayer, Leverkusen, Germany) and were subsequently confirmed by measuring plasma glucose levels using the glucose oxidase method with a glucose analyzer (Beckman, Fullerton, CA). Total serum insulin concentrations were measured using radioimmunoassay, based on guinea pig polyvalent anti-rat insulin antibody and radioactive iodine-labeled human insulin, validated for appropriate cross-reactivity to human insulin and each