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ORIGINAL ARTICLE

Reduction of Postprandial Glycemic Excursions in Patients with Type 1 Diabetes: A Novel Human Insulin Formulation versus a Rapid-Acting Insulin Analog and Regular Human Insulin

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Abstract

Background:

Evaluation of postprandial glycemic excursions in patients with type 1 diabetes with three prandial insulins: VIAject™ (Linjeta™), an ultra-fast insulin (UFI); insulin lispro (LIS); and regular human insulin (RHI).

Methods:

After stabilization of preprandial glycemia, 18 patients received a subcutaneous injection with an individualized insulin dose prior to a meal.

Results:

Injection of UFI resulted in a more rapid insulin absorption than with either LIS or RHI (time to half-maximal insulin levels: 13.1 ± 5.2 vs 25.4 ± 7.6 and 38.4 ± 19.5 min; $p = .001$ vs LIS and $p < .001$ vs RHI, LIS vs. RHI $p < .001$). Maximal postprandial glycemia was lower with UFI (0–180 min; 157 ± 30 mg/dl; $p = .002$ vs RHI) and LIS (170 ± 42 mg/dl; $p = .668$ vs RHI) than after RHI (191 ± 46 mg/dl; RHI vs LIS $p = .008$). The difference between maximum and minimum glycemia was smaller with UFI (70 ± 17 mg/dl) than with either RHI (91 ± 33 mg/dl; $p = .007$ vs UFI) or LIS (89 ± 18 mg/dl; $p = .011$ vs UFI). Also, the area under the blood glucose profile was lower with UFI than with RHI (0–180 min; 21.8 ± 5.8 vs 28.4 ± 7.6 g·min/dl; $p < .001$).

Conclusions:

The rapid absorption of UFI results in a reduction of postprandial glycemic excursions.

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Abbreviations: (AUC) area under the curve, (BG) blood glucose, (Cmax) maximum insulin concentration, (GIR) glucose infusion rate, (IV) intravenous, (LIS) insulin lispro, (NPH) neutral protamine Hagedorn, (RHI) regular human insulin, (SC) subcutaneous, (SD) standard deviation, (*t*) time, (UFI) ultra-fast insulin

Keywords: insulin therapy, meal-time insulin, prandial insulin, rapid-acting insulin analogs, ultra-fast insulin, ultra-rapid insulin

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Introduction

Optimal coverage of prandial glycemic excursions requires high circulating insulin levels while glucose is being absorbed from the gut after a meal and a simultaneous suppression of hepatic glucose production. If this could be achieved by subcutaneous (SC) insulin administration, postprandial glycemic excursions would be comparable to that of healthy subjects.[1] However, due to its slow absorption, this cannot be achieved with regular human insulin (RHI). Rapid-acting insulin analogs were developed to meet prandial insulin requirements more effectively; the more rapid absorption reduces the need for an injection-meal interval while also achieving greater suppression of hepatic glucose production.[2] However, available rapid-acting insulin analogs have not been effective in controlling postprandial glucose when administered immediately prior to a meal.[3,4] This is particularly true in the setting of high carbohydrate meals.

Because there is an emerging understanding of the need for a more rapidly acting prandial insulin, several methods, such as intradermal injection of insulin, warming of the injection site, and adding an enzyme to dissolve connective tissue have all been studied to assess if they could further increase insulin absorption.[5–7] An ultra-fast insulin formulation has been developed [UFI; VIAject™ (Linjeta™), Biodel Inc., Danbury, CT]. Clinical experimental studies with healthy subjects have shown more rapid onset of absorption/action with UFI in comparison to insulin lispro (LIS) and RHI.[8,9] The aim of this study was to assess postprandial glycemic excursions in patients with type 1 diabetes with SC administration of three different prandial insulins.

Methods

The data from 18 patients (age 39 ± 10 years, 8 females; 15 Caucasian; body mass index 24.4 ± 2.2 kg/m²; duration of diabetes >5 years; hemoglobin A1c 8.1 ± 1.5%) participating in all experiments were analyzed. Data of an additional study day with a 50% reduced dose of UFI are not shown. This good clinical practice study was performed in accordance with the principles of the Declaration of Helsinki (revised version from 2000) and with approval from the local ethics committee. All patients signed an informed consent prior to study start.

On the evenings before the treatment days, the normal long-acting insulin formulation of patients who were not using neutral protamine Hagedorn (NPH) were replaced by NPH. The patients came to the study site on the morning of the study day after a 10-hour overnight fasting period without administration of the morning insulin treatment. Upon arrival at the study site, the preprandial glycemia of the patients was stabilized at a target level of 120 mg/dl (6.7 mmol/liter) in a 4-hour period during this open-label crossover study by a variable basal intravenous (IV) insulin infusion (varied manually) and an automated glucose clamp (Biostator, mtb Medizintechnik, Ulm, Germany; ended at $t = 0$ min). The patients were restricted from excessive physical activity and intake of alcohol for 24 hours before each treatment day. They were also questioned to ensure that there were no significant changes to their medical condition since their medical examination at the screening visit. In addition, a breath alcohol test was given and vital parameters, i.e., blood pressure, temperature, and pulse, were measured.

Prior to ingestion of a standardized mixed meal consisting of 984 kcal, 27.8 g protein, 140.3 g carbohydrate, 34.5 g fat (17 fl. oz. apple juice, two pieces whole wheat toasted bread, 2.7 tbsp. peanut butter, 8 fl. oz. whole milk, 0.5 cup granola cereal with 100% natural raisins and low fat; to be consumed in this order within 20 minutes), patients received a SC injection of UFI (U-25; Biodel Inc., Danbury, CT), insulin lispro (LIS; Humalog® U-100; Eli Lilly and Company, Indianapolis, IN) or RHI (Humulin® R U-100; Eli Lilly and Company) in a fixed order by means of a syringe in the abdomen. The insulin dose [11.4 ± 3.2 IU; mean ± standard deviation (SD)] was determined for each patient on an individual basis and kept constant for that patient throughout the study. Basal insulin requirements were covered by a fixed IV insulin infusion during the postprandial period (0.2 mU·min/kg). Hypoglycemia [<60 mg/dl (3.3 mmol/liter)] was prevented by an IV glucose infusion controlled by the Biostator.

Plasma insulin levels (after administration of RHI and UFI) were measured by means of a chemoluminescence assay (MLT Research, Cardiff, UK). Insulin lispro was measured by means of a lispro-specific commercial radio-immunoassay kit (LINCO Research, Inc., St. Charles, MO). Because LIS and UFI/RHI levels were measured by different assays, no statistical analysis of concentration-dependent variables was made. Pharmacokinetic and pharmacodynamic variables were analyzed (SAS version 9.1,

SAS Institute Inc., Cary, NC) using a mixed model with the subject as a random effect. Insulin area under the curve (AUC) values were log-transformed prior to analysis and analyses of maximum glucose levels included predose baseline glucose levels as a covariate. This study was designed to explore postprandial glucose profiles and was not powered for a specific endpoint.

Results

Starting from comparable basal human insulin levels (**Table 1**), early half-maximal and maximal plasma insulin levels were reached sooner after injection of UFI than after either LIS or RHI (**Figure 1A**). Decline of insulin concentrations (late half-maximal plasma insulin levels) also occurred earlier with UFI than with RHI; it was also earlier compared to LIS, yet not statistically significant. Maximal plasma insulin levels were not different between UFI and RHI, but AUC of the insulin profile in the first 180 min was higher after injection with UFI than with RHI, and lower in the time from 180 to 300 min. Total insulin exposure (AUC 0–300 min) was not different.

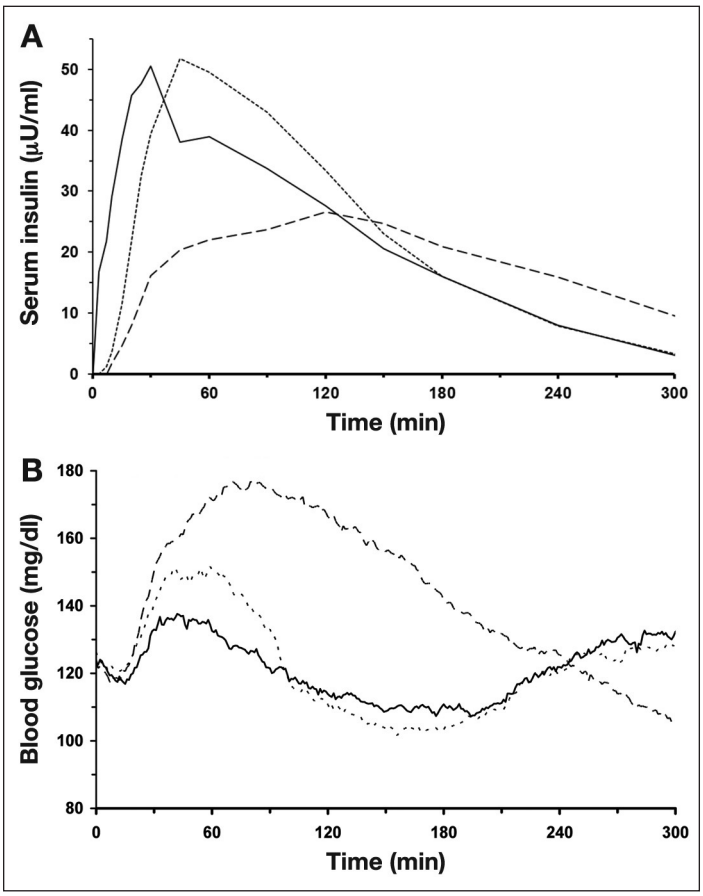

Figure 1. Mean plasma insulin profiles **(A)** with baseline correction (mean of the last three samples prior to injection) and mean blood glucose profiles **(B)** measured by the Biostator, obtained after SC injection of regular human insulin (dashed line), insulin lispro (dotted line), and an ultra-fast insulin (continuous line) in 18 patients with type 1 diabetes.

The maximum postprandial glycemia in the first 180 min after injection with either UFI or LIS was lower than with RHI (**Table 1** and **Figure 1B**). Also, the difference between maximum and minimum glucose concentrations observed during this time was smaller with UFI than with either RHI or LIS; it was also greater with LIS than with UFI. The AUC of the blood glucose profile in the first 180 min after start of the meal was lower with UFI than with either RHI or LIS (no significant difference); it also tended to be directionally lower with UFI than with RHI in the first 300 min (p = .057). The AUC was also lower with LIS than with RHI.

Subsequent to peak glucose concentration, glucose levels declined steadily thereafter (**Figure 1B**). The amount of glucose infused intravenously to prevent hypoglycemia over the entire duration of the experiment as well as the duration of IV glucose infusion (p = .076) and time spent in the euglycemia target range (blood glucose between 80 and 140 mg/dl) (p = .284) tended to be lower with UFI than with RHI (p = .057).

Discussion

This study confirmed the rapid absorption of UFI in patients with type 1 diabetes. It also demonstrated that this leads to reduced postprandial glycemic excursions.

A published study showed convincingly that the improved pharmacokinetic properties of LIS in comparison to RHI translate to reduced postprandial glycemic excursions.[10] The novel formulation of human insulin studied here, which has an even faster absorption rate than LIS, provided better glycemic control without using a modified insulin molecule. This proves that the time point when high circulating insulin levels are achieved after a meal is of more relevance to controlling postprandial glycemic excursions than the absolute levels established; the maximal levels were comparable between UFI and RHI, but the time until these were achieved was clearly not.

The concentration of UFI (U-25) used in this study was lower than that of LIS and RHI (U-100). While we have shown that a lower RHI insulin concentration was associated with more rapid absorption, another study showed that a U-100 formulation of this UFI was bioequivalent to the U-25 formulation used in this study.[11,12] Therefore, it would be expected that the observed

Table 1.
Pharmacokinetic and Pharmacodynamic Summary Measures after SC Injection of Regular Human Insulin (RHI), Insulin Lispro (LIS), and Ultra-Fast Insulin (UFI) in 18 Patients with Type 1 Diabetes Immediately Prior to a Standardized Mixed Meal (Mean ± SD)[a]

Variables	RHI	LIS	UFI	*p* values[b]
Pharmacokinetic				
Baseline insulinemia (mU/liter) (only human insulin measured)	19.0 ± 14.2	21.4 ± 16.3	19.4 ± 19.2	RHI vs UFI .385 LIS vs UFI .080 RHI vs LIS .348
Early tC_{max} (min)	38.4 ± 19.5	25.4 ± 7.6	13.1 ± 5.2	**<.001** **.001** **<.001**
tC_{max} (min)	131.7 ± 49.5	65.6 ± 34.5	28.4 ± 17.4	**<.001** **.001** **<.001**
Late tC_{max} (min)	268.3 ± 54.3	147.5 ± 51.7	135.2 ± 45.7	**<.001** .391 **<.001**
C_{max} (μU/ml)	32.8 ± 20.3	57.5 ± 20.9	55.5 ± 24.8	.135 NA NA
AUC 0–180 (mU·min/liter)	3854 ± 2551	5850 ± 2106	5627 ± 2322	**<.001** NA NA
AUC 0–300 (mU·min/liter)	5905 ± 3274	6876 ± 2619	6749 ± 2740	.068 NA NA
AUC 180–300 (mU·min/liter)	2051 ± 1169	1026 ± 960	1123 ± 727	**.003** NA NA
Pharmacodynamic				
Baseline BG (mg/dl)	124 ± 5	127 ± 6	123 ± 5	RHI vs UFI .444 LIS vs UFI **.046** RHI vs LIS .211
Baseline GIR (mg·min/kg)	1.1 ± 1.3	0.7 ± 1.1	1.0 ± 1.1	.784 .507 .350
tBG_{max} (min)	83 ± 43	125 ± 146	181 ± 171	**.014** .153 .274
$Glucose_{max}$ (mg/dl)	191 ± 46	178 ± 46	174 ± 44	.262 .555 .090
$Glucose_{max\ 0–180}$ (mg/dl)	191 ± 46	170 ± 42	157 ± 30	**.002** .668 **.008**
$Glucose_{max–min\ 0–180}$ (mg/dl)	91 ± 33	89 ± 18	70 ± 17	**.007** **.011** .858
$AUC_{Glucose\ 0–180}$ (g·min/dl)	28.4 ± 7.6	22.4 ± 7.3	21.8 ± 5.8	**<.001** .681 **<.001**
$AUC_{Glucose\ 0–300}$ (g·min/dl)	43.3 ± 13.0	36.8 ± 13.0	36.3 ± 10.3	.057 .591 **.016**

Continued →

Table 1. Continued

Variables	RHI	LIS	UFI	*p* values
Pharmacodynamic				
$AUC_{Glucose\ 181–300}$ (g·min/dl)	14.7 ± 5.7	14.2 ± 6.0	14.4 ± 5.1	.989 .524 .524
Amount glucose $infused_{0–300}$ (g)	28 ± 100	40 ± 58	24 ± 89	.863 .470 .582
Duration $BG_{80–140}$ no GIR 0–180 (min)	74 ± 60	81 ± 45	100 ± 58	.131 .250 .711
Duration $BG_{80–140}$ no GIR 0–300 (min)	137 ± 85	136 ± 91	167 ± 92	.284 .266 .965
Duration of glucose infusion to prevent hypoglycemia (hour)	1.0 ± 1.2	0.8 ± 1.4	0.5 ± 0.8	.076 .330 **.411**

[a]BG, blood glucose; GIR, glucose infusion rate;
[b]NA, not applicable; bold font, significant differences.

differences in postprandial glucose excursions would be preserved with the newer neutral 100 U/ml formulation of UFI.

In this study, the prandial insulins were injected immediately prior to a high carbohydrate meal, the injection-meal interval that patients tend to use in reality.[13] A paper by Cobry and colleagues[3] suggested that even with insulin glulisine, an injection-meal interval of 20 minutes is optimal for achieving good postprandial glucose control. Ultra-fast insulin injected without an injection-meal interval, at least in this study, considerably reduced postprandial glycemic excursions.

The reduced risk of late postprandial hypoglycemia is of clinical relevance. The reduced need for snacks between meals—and the lower insulin levels between meals—suggests that patients treated with UFI may show a more stable weight or a reduced increase in body weight. The results of two phase III trials with UFI in comparison to RHI in >400 patients with type 1 and 2 diabetes in each trial confirms these assumptions,[14,15] The extent to which the observed differences between UFI and LIS are of clinical relevance awaits further evaluation in head-to-head multiple dose trials.

The reduced variability in glycemia in principle allows the application of higher insulin doses with a meal without increased risk of hypoglycemia. This could widen the therapeutic index for insulin. The more rapid increase in insulinemia seen with UFI can be assumed to also induce a rapid and complete suppression of hepatic glucose production, which still remains to be studied.

In conclusion, a formulation of human insulin with very rapid absorption properties helps to reduce postprandial glycemic excursions without an increased risk of late postprandial hypoglycemia.

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Disclosures:

Solomon Steiner is the inventor of VIAject™ (Linjeta™) and Chief Scientific Officer of Biodel Inc. Marcus Hompesch is Chief Executive Officer of Profil Institute for Clinical Research, San Diego, California. Rody Pohl, Patrick Simms, and Frank Flacke are employees of Biodel and own shares/options. Andrea Pfützner is a consultant for Biodel Inc. and owns shares/options. Lutz Heinemann is a consultant for Biodel Inc. and is a partner of Profil Neuss, Germany and Profil, San Diego, California. He is also Director of Scientific Services of Profil, San Diego, California.

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