

ABSTRACT

Technosphere® Insulin (TI) is an ultra rapid-acting insulin with insulin peak 10-15 min after dosing. To assess this kinetic property of TI on metabolism, various endpoints were compared following TI and lispro (LI; Humalog®, Eli Lilly) administration. Single doses of 60 U (n=6) and 90 U (n=6) TI were compared with 10 U (n=12) subcutaneous LI in an open-label, 2-way crossover study incorporating a meal challenge (BoostPlus® 12 fl oz enriched with U-¹³C glucose) in insulin-treated subjects with type 2 diabetes and normal pulmonary function. 6,6-²H₂ glucose from a continuous infusion was used to assess endogenous glucose production (EGP). Prior to the meal, subjects' blood glucose (BG) was kept at 110±10 mg/dL using a continuous low-dose iv insulin infusion fixed 90 min before dosing. If needed, glucose was infused post-dose to maintain BG at ≥75 mg/dL.

Maximal EGP suppression occurred markedly earlier with TI (45 and 60 min for 60 and 90 U, respectively) than with LI (105 min) based on mean profiles, and the greatest decrease from baseline EGP was observed following 90 U TI (10.3 μmol/kg/min) compared with 60 U TI and LI (6.9 and 7.1 μmol/kg/min, respectively). Total EGP areas over curve (AOC) were comparable across groups. A significantly greater proportion of EGP AOC was observed with TI up to 140 min post-dose (p <0.03) compared with LI. TI effect on free fatty acids (FFA) and glucagon was dose dependent, with an earlier (TI 90 and 60 U) and greater (TI 90 U) decrease from baseline. The highest FFA AOC was observed following TI 90 U; LI and 60 U TI were comparable. Peak glucagon concentrations and AUC were substantially lower following 90 U TI dose than either LI or 60 U TI.

The suppression of EGP is a critical part of postprandial metabolism and, together with other metabolic measures, occurred more rapidly following TI dosing as compared to LI.

INTRODUCTION

The development of hyperglycemia results from an imbalance between systemic glucose delivery and glucose utilization. In type 2 diabetes (T2DM), hyperglycemia related to an increase in endogenous glucose production develops in the presence of normal or increased plasma insulin concentrations and is present in T2DM patients even with modest hyperglycemia.¹ The objective of this trial was to compare the effect of Technosphere® Insulin Inhalation Powder (AFREZZA™) and lispro on post-meal EGP.

MATERIALS AND METHODS

Study Population

This was a randomized, open label, 2-way cross-over study in 12 nonsmoking insulin-treated subjects with a clinical diagnosis of T2DM currently on a stable antidiabetic regimen that included insulin ≥3 months and an HbA1c ≤8.5%. The study was approved by the local ethics committee, and all subjects gave their written informed consent prior to starting the study.

Study Procedures

In this study, stable isotopes were used to distinguish between endogenous glucose production and exogenous glucose. At study start, 12 hours before dosing, subjects received an initial priming dose of 6 mg/kg of 6,6-²H₂ glucose, followed by a constant infusion of 6,6-²H₂ glucose for a 7-hour equilibration period to attain a steady-state tracer enrichment level. At 7 hours, the subjects received an individualized iv infusion of insulin lispro (fixed 90 min prior to dosing and continued until 480 min post-dose), and a 20% glucose solution, enriched with 8 mg of 6,6-²H₂ glucose per gram of glucose, to maintain a target blood glucose (BG) level of 110 mg/dL for at least 5 hours before dosing. Following an overnight fast, at each of the three treatment visits, each subject received a single dose during the test treatment immediately prior to consuming a nutritional energy drink (Boost Plus®) [12 fl oz] enriched with U-¹³C glucose. If needed, glucose was infused post-dose to maintain BG ≥75 mg/dL. The treatment periods were separated by a washout period of 7 to 21 days. (Figure 1)

Pharmacokinetic Analysis

The sum of lispro and regular human insulin concentrations were used for the insulin PK analysis. The following PK parameters were derived using noncompartmental analysis (NCA) using WinNonlin® v 5.2 (Pharsight Corporation, Mountain View, CA): observed peak insulin concentration (C_{max}), time to peak insulin (t_{max}), and area under the insulin concentration-time curve AUC.

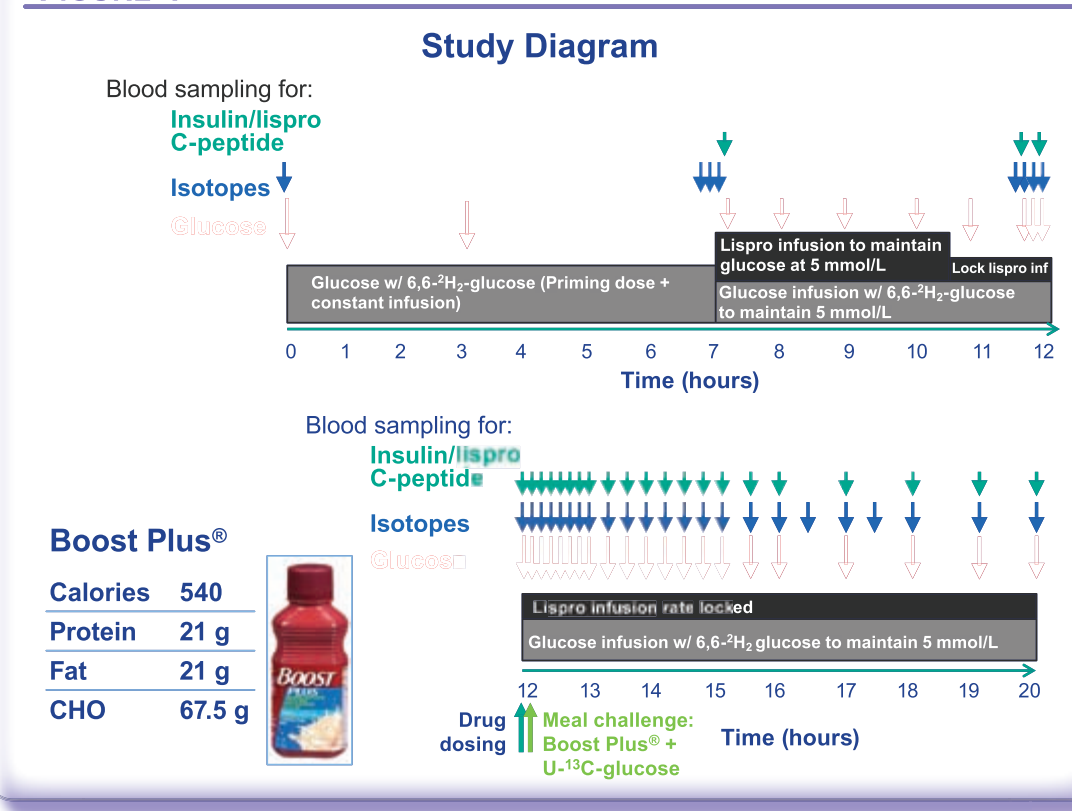
Pharmacodynamic Analysis

Glucose disposal (Rd) and EGP were estimated as described by Hovorka et al.² Change from baseline values were used to calculate all pharmacodynamic parameters, with the exception of blood glucose, where total glucose values were used to determine AUC.

Statistical Analysis

EGP AOCs within the timeframe of meal absorption were compared. A statistical analysis was performed on the percent of the EGP AOC calculated at 10-minute increments for the first hour and 20-minute increments after that, by subject and treatment. The incremental % AOCs were compared using a mixed effects analysis of variance model, with fixed effects of treatment, period and sequence and random effect of subject, with Dunnett's adjustment for multiple comparisons with TI as the control. The Wilcoxon rank sum test was used to compare the time of maximal effect and time to half-maximal effect on EGP and Rd between the two treatments.

FIGURE 1



RESULTS

Patient Population

Twelve subjects were enrolled in the study. (Table 1)

Reconstruction of glucose fluxes amplifies the measurement error. In consequence non-physiological oscillatory fluxes may be obtained. A population-tuned maximum likelihood method was used to minimize such occurrences. However, on visual inspection three EGP and Rd profiles were deemed non-physiological and excluded from analysis of the maximum effect and the time of maximum effect, as these parameters are sensitive to extreme values.

Insulin Pharmacokinetics

FIGURE 2

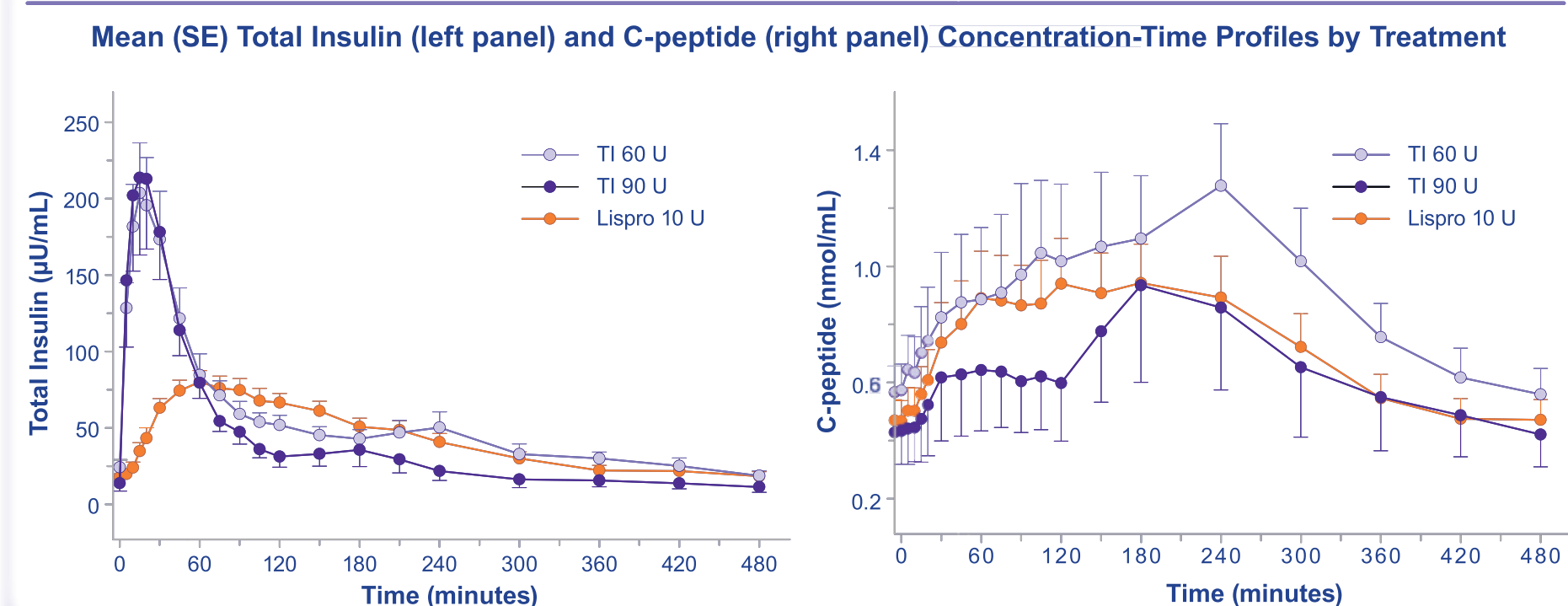


Table 1

Demographics and Other Baseline Characteristics		
	Category/Statistics	Value
Age (y)	Mean ± SD	55.3 ± 7.6
Gender (n)	Female	3
	Male	9
Race (n)	Caucasian	12
BMI (kg/m ²)	Mean ± SD	29.3 ± 2.5
HbA1c (%)	Mean ± SD	6.93 ± 0.87

RESULTS (CONTINUED)

Average total insulin exposure was highest following 60 U TI and comparable following 10 U lispro and 90 U TI (Table 2). However, when corrected for the contribution of the endogenous component, the highest insulin exposure was observed following the 90 U TI dose. This observation can be attributed to endogenous insulin response, which contributed to the total insulin profile for each treatment, and was highest following 60 U TI. This finding was not unexpected in light of the considerable beta cell function remaining in subjects with type 2 diabetes and in whom endogenous insulin secretion works in concert with exogenous insulin treatment to satisfy the body's prandial insulin needs. As can be seen in the mean total insulin and C-peptide profiles, endogenous insulin contribution increases within 30 minutes of dosing with 60 U TI, but only at 120 minutes following 90 U TI (Figure 2), completing the total insulin response and resulting in very similar total exposure following both TI groups.

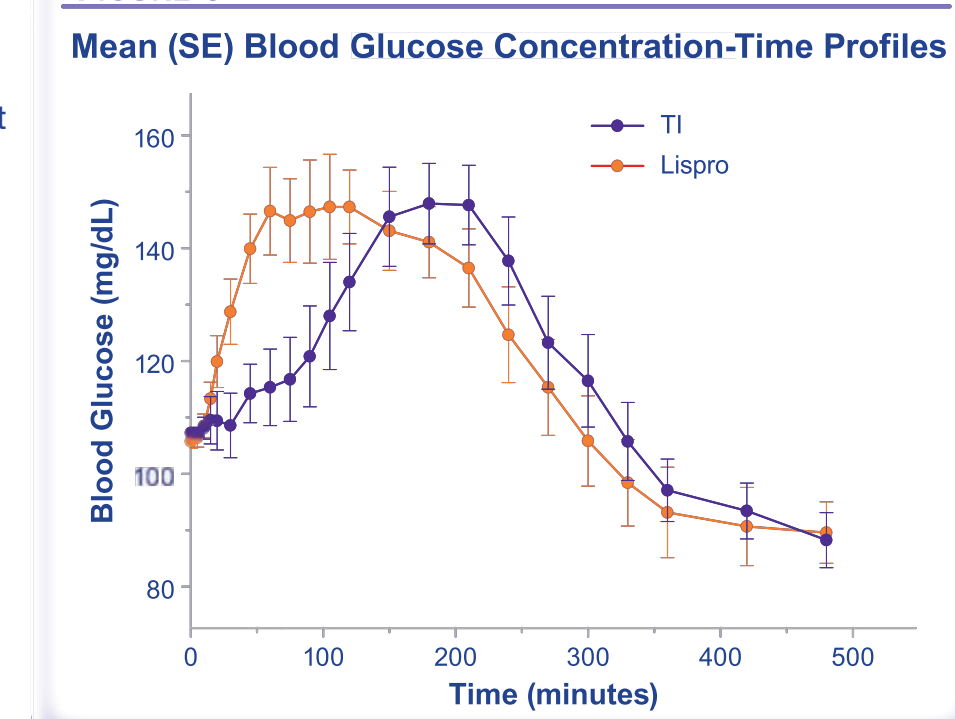
The insulin effect is attributable to the total systemic insulin concentration. Because there is overlap in the total insulin profiles between the two TI groups, both groups were combined for the assessment of TI effect.

Insulin Pharmacodynamics

Blood Glucose Concentrations

Due to the rapid rise in insulin concentrations following TI dosing, blood glucose levels remained lower subsequent to TI administration (Figure 3). In the TI 90 U group, 2 out of 6 subjects required glucose infusion within the first hour post-dose to maintain blood glucose ≥75 mg/dL, versus 3 subjects in the lispro group who received the glucose infusion in the latter part of the profile. No subjects treated with 60 U TI needed additional glucose.

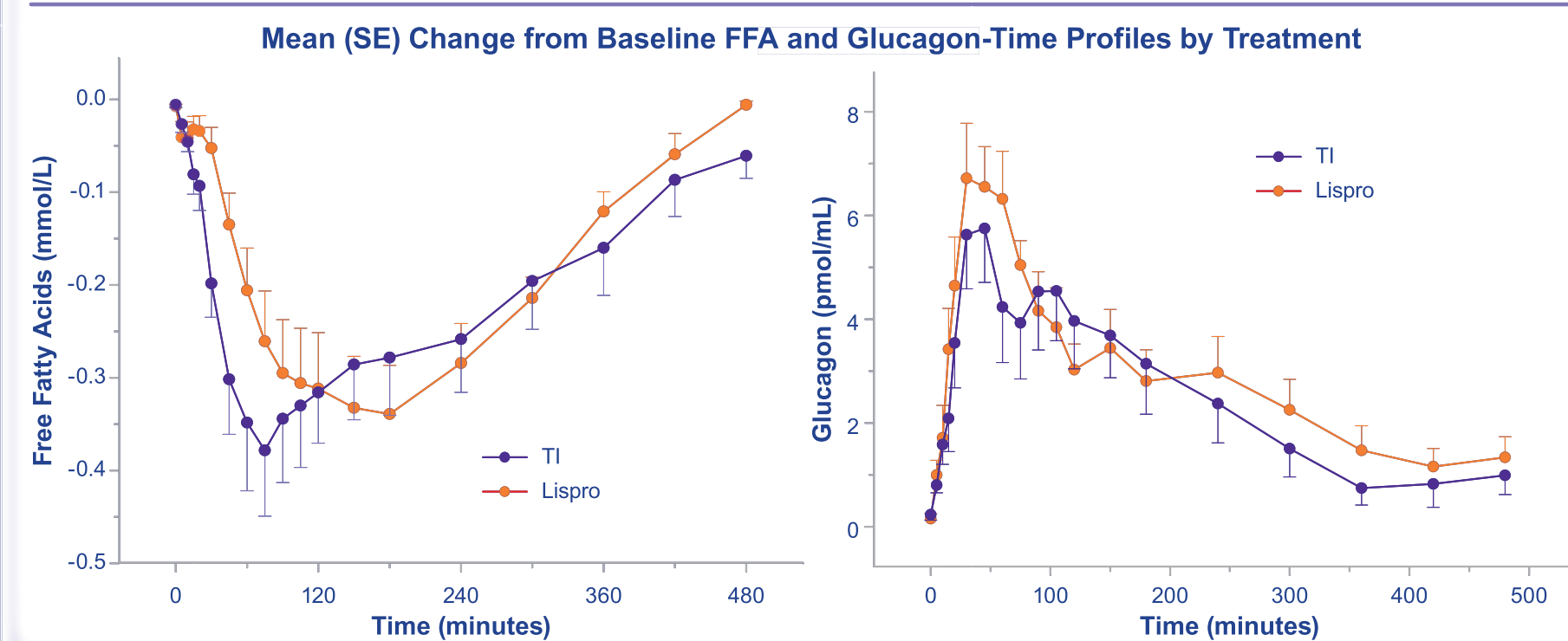
FIGURE 3



Free Fatty Acids and Glucagon

The effect of TI on FFA was observed earlier compared to lispro (median t_{max} of 75 min vs 127.5 min, respectively), although no discernible difference was seen with the timing of maximal effect on glucagon between the treatments (Figure 4). Both FFA and glucagon were suppressed to a greater extent over 480 minutes following TI compared to lispro when mean FFA AOC and glucagon AUC values were compared. (Table 2)

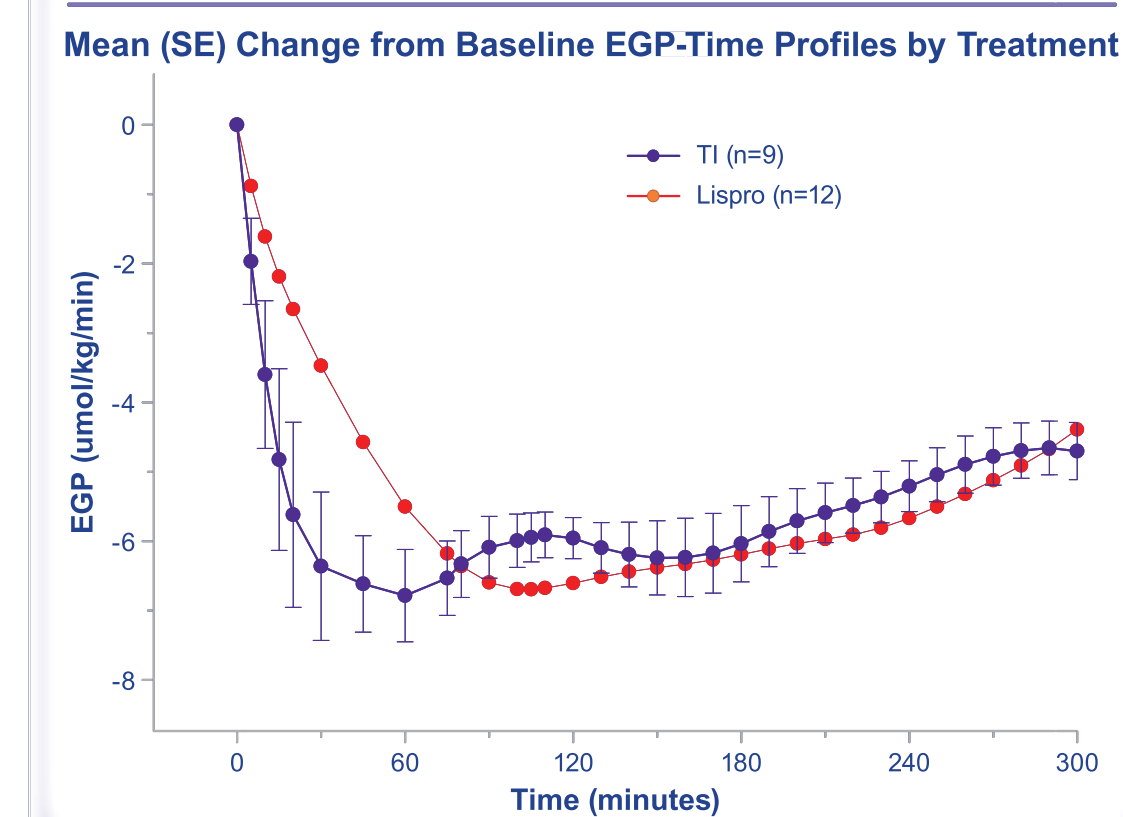
FIGURE 4



Endogenous Glucose Production

Following Boost Plus ingestion, subjects in all three treatment groups had similar absorption rate profiles, returning to baseline values at approximately 300 minutes post-meal. All three treatments did suppress EGP. EGP AOCs within the time frame of meal absorption (0-300 minutes post-dose) were similar (Table 3); however, a significantly greater proportion of EGP AOC was observed with TI up to 140 minutes post-dose (p <0.0261), with a significantly shorter time to the half maximal EGP suppression with TI (15 min) compared to lispro (37.5 min) (p <0.0056) (Figure 5)

FIGURE 5



RESULTS (CONTINUED)

Glucose Disposal Rate

Peak rate of glucose disposal was similar following both treatments (Figure 6, Table 3), but the peak effect was observed significantly earlier following TI (p <0.0413).

FIGURE 6

Mean (SE) Change from Baseline Rd-Time Profiles by Treatment

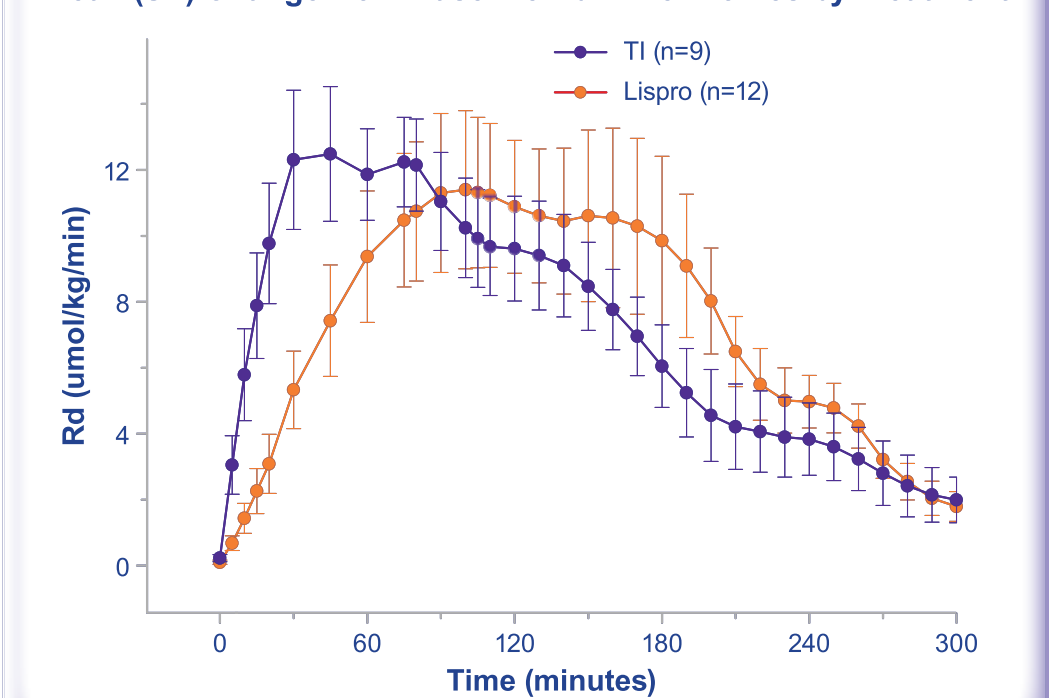


Table 3

	Mean (%CV) Parameters	
	TI Combined	10 U Lispro
EGP*		
AOC ₀₋₄₈₀ (μmol/kg·min)	2,191 (18)	2,191 (31)
EGP _{max} (μmol/kg)	-8.04 (38)	-7.105 (28)
t _{max} (min)	75 (20-310)	125.0 (80-210)
Early t _{EGP50%} (min)	15 (5-30)	37.5 (10-45)
Rd*		
AUC ₀₋₄₈₀ (μmol/kg·min)	2,454 (22)	2,287 (52)
Rd _{max} (μmol/kg)	15.73 (24)	13.99 (69)
t _{max} (min)	45 (30-200)	160 (30-220)
Early t _{Rd50%} (min)	15 (5-80)	45 (15-75)

*n=12 for lispro; n=12 for TI AUC and AOC; n=9 otherwise

CONCLUSIONS

- Following administration of 60 and 90 U TI and 10 U lispro, total insulin exposure was similar between treatments, with greater endogenous insulin contributions following lispro and TI 60 U treatments compared to TI 90 U. Blood glucose profiles peaked earlier following lispro treatment compared to TI, and postprandial glucose excursions were lower for the first two hours following TI treatment compared to lispro.
- The extent of EGP suppression was comparable for both treatments in the post-meal period; however, a significantly greater proportion of EGP AOC was observed with TI up to 140 minutes post-dose (p <0.0261) compared with insulin lispro with a significantly shorter time to the half maximal EGP suppression with TI (p <0.0056). Similarly, TI exerted its effect earlier on the rate of glucose disposal. The effect of TI on FFA occurred earlier and both FFA and glucagon were suppressed to a greater extent following TI compared to lispro. This early effect on metabolic parameters associated with TI treatment is most likely attributable to the rapid and sharp increase evident in insulin concentrations following TI.

REFERENCES

- Perriello, G., et al., Evidence of increased systemic glucose production and gluconeogenesis in an early stage of NIDDM. *Diabetes*. 1997;46(6):1010-6.
- Hovorka, R., et al., Calculating glucose fluxes during meal tolerance test: a new computational approach. *Am J Physiol Endocrinol Metab*. 2007;293(2):E610-9.

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