Technosphere® Insulin Suppresses Endogenous Glucose Production Earlier Than a Rapid-Acting Analog (Lispro) and an Inhaled Insulin (Exubera)

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ABSTRACT

Background and Aims: Absolute results are needed to replicate reported hypoglycemia responses, especially when due to subcutaneous (SC) Technosphere® insulin (TI) on SC rapid-acting insulin generating (RAIG) pharmacodynamics. Longitudinal study with a new generation human insulin analog, 85% l-asparagine-labeled insulin lispro was infused to simulate a non-scarifying SC dose (4.48 IU) 2 hours postdose). Following an overnight fast, at each of the three treatment visits, each subject received a standardized meal (222 g of carbohydrate) and 12 IU of baseline insulin lispro (Bsl) plus either 24 IU regular human insulin (RIH) or Technosphere® Insulin (TI, 48 IU, twice), or a continuous glucose infusion enriched with 20% glucose solution, enriched with 4.80 minutes postdose), and a technology (EGP).

Pharmacokinetics

Insulin pharmacokinetics were determined using Technosphere® Insulin (TI) to simulate a subcutaneous dose of 12 IU. After an overnight fast, at each of the three treatment visits, each subject received a standardized meal (222 g of carbohydrate) and 12 IU of baseline insulin lispro (Bsl) plus either 24 IU regular human insulin (RIH) or Technosphere® Insulin (TI, 48 IU, twice), or a continuous glucose infusion enriched with 20% glucose solution. Following an overnight fast, at each of the three treatment visits, each subject received a standardized meal (222 g of carbohydrate) and 12 IU of baseline insulin lispro (Bsl) plus either 24 IU regular human insulin (RIH) or Technosphere® Insulin (TI, 48 IU, twice), or a continuous glucose infusion enriched with 20% glucose solution. Followed by a continuous glucose infusion for 30 minutes postdose. The primary outcome measures were the insulin/Lipidarea (L) under the influence of Technosphere® Insulin (TI) was a randomized, open label, 3-way cross-over study in 18 nonsmoking, insulin-treated subjects with a 12-hour fast.

RESULTS

Study Population

Eighty-one subjects were enrolled in the study. Summary demographics and other baseline characteristics are presented in Table 1. Significant differences were observed in sex distribution between Technosphere® Insulin and Exubera 2 subjects in the insulin lispro and regular human insulin groups were used to calculate the PK analysis for each treatment period when compared to TI, resulting in a more physiologic EGP suppression. This finding may be attributed to TI's unique pharmacokinetic profile, and suggests that the ultra-rapid-acting insulin analog is suppressing endogenous glucose production.

RESULTS (CONT'D)

Blood Glucose Concentrations and GIR

In the latter part of the treatment period, glucose infusions were needed to maintain blood glucose at ≤8.5%. The study was approved by the local ethics committee, and all subjects gave their written informed consent prior to entering the study.

Study Procedures

Subjects were assessed 2 to 3 days before study entry. Subjects were on a stable diabetes regimen with no major changes in insulin treatment, ≤20% variation in diet over the last 6 weeks, and no significant weight changes. Subjects had normal fasting plasma glucose and no history of diabetes. Subjects were evaluated at baseline (−20, −8, 0 minutes), 2, 4, 6, 8, 10, and 12 minutes postdose, with 5 minutes postdose. The ratios of the extent of exposure, as determined by total insulin AUC0-tlast for TI: Exubera: insulin lispro were 1.86:1.00:1.00.

Blood Glucose Concentrations and GIR

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Insulin Pharmacodynamics

Net Glucose Concentration and GIR

The ratios of the extent of exposure, as determined by total insulin AUC0-tlast for TI: Exubera: insulin lispro were 1.86:1.00:1.00.

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Acknowledgements


References


Material and Methods (CONT'D)

RESULTS

Blood Glucose Concentrations and GIR

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