Coverage of Postprandial Blood Glucose Excursions With Inhaled Technosphere® Insulin in Comparison to Subcutaneously Injected Regular Human Insulin in Subjects With Type 2 Diabetes

Klaus Rave, MD*, Tim Heise, MD*, Andreas Pfützner, MD, PhD†, and Anders H. Boss, MD, MFPM‡

*Profil Institute for Metabolic Research, Neuss, Germany
†IKFE Institute for Clinical Research and Development, Mainz, Germany
‡MannKind Corporation, Danbury, CT, USA

Running title: Postprandial glucose with Technosphere® Insulin

Correspondence to:
Klaus Rave, MD
Profil Institute for Metabolic Research
Hellersbergstr. 9, 41460 Neuss, Germany
email: klaus.rave@profil-research.de

Received for publication 9 March 2007 and accepted in revised form 13 June 2007.
Introduction
Technosphere® Insulin (TI) is a formulation of regular human insulin (RHI) that provides efficient pulmonary administration (1) and demonstrates unique pharmacokinetic and pharmacodynamic properties compared with subcutaneous RHI, rapid-acting insulin analogs, and other inhaled insulins (2). Administration of TI results in a time to maximum insulin concentration of about 15 min with almost complete absorption within 3 h (3,4). With an onset of action comparable to intravenous insulin, TI represents the first formulation that approaches the physiological early insulin release. In this study, we evaluated the efficacy and safety of TI compared with subcutaneous RHI in covering prandial insulin needs. We measured blood glucose excursions after a meal challenge after individual titration of either insulin formulation during a 7-day treatment period in subjects with type 2 diabetes.

Research Design and Methods
This prospective, open-label, randomized, two-period cross-over study was conducted at one center (Profil Institute for Metabolic Research, Neuss, Germany). The study included a screening visit, 24-hour in-house exposure to TI to establish initial dosing, two 7-day ambulant periods of daily mealtime TI or subcutaneous RHI separated by a 2- to 7-day washout, and a final visit. In-house meal challenges, using a standardized mixed meal with 496 kilocalories, were conducted at the end of each ambulant period. During treatment periods, each subject inhaled TI via a MedTone® Model C Inhaler (MannKind Corporation, Valencia, CA) or subcutaneously injected RHI (Actrapid HM®, Novo Nordisk, Bagsvaerd, Denmark) at mealtime. Subjects continued their prior activities, diet, and basal insulin throughout the study.

Primary efficacy variables, all baseline adjusted, were area under curve of postprandial blood glucose excursion (BG-AUC0-240min), maximum blood glucose concentration (BG-Cmax), and time to BG-Cmax (BG-Tmax). Baseline-adjusted secondary efficacy variables were total serum insulin exposure (INS-AUC0-240min), maximum insulin concentration (INS-Cmax), time to INS-Cmax (INS-Tmax), and time to 50% concentration before/after INS-Tmax (INS-Tmax early/late 50%). Treatment comparisons were made using the Sign test for BG-Tmax and INS-Tmax and the Wilcoxon Signed-Rank test for INS-Tmax late 50%. Analysis of variance was performed for treatment comparisons of all other efficacy variables using the Mixed Effect Models procedures in SAS (version 8.02; SAS Institute, Cary, NC). A P < 0.05 was regarded as statistically significant. Results are expressed as mean±SE throughout the text unless otherwise stated.

Results
Sixteen non-smoking subjects with type 2 diabetes (age 59±8 y; BMI 29.6±3.3 kg·m⁻²; HbA₁c 7.5±0.8%) were enrolled and completed the study. Subjects’ insulin dose for the meal challenge was 48±9 U (nominal dose) for TI and 14±5 IU for subcutaneous RHI, respectively.

Pharmacokinetics
Following inhalation of TI, serum insulin concentration increased rapidly within the initial 5 min, peaked at 15 min, and declined thereafter. In contrast, after subcutaneous RHI administration, serum insulin concentration increased more slowly, peaking at 120 min and decreasing thereafter. However, INS-AUC0-240min was nearly identical for both treatments (56.9±7.1 vs. 57.7±7.3 nmol·L⁻¹, P = 0.927; Figure 1A). INS-Cmax was 45% greater with TI (691.0±77.6 vs. 377.1±42.3 pmol·L⁻¹, P = 0.001). Median INS-Tmax and INS-Tmax early 50% were 8 times shorter with TI (15/8 vs. 120/60 min, P < 0.001). Median INS-Tmax late 50% was twice as short with TI (61 vs. 130 min, P = 0.011).

Pharmacodynamics
Fasting blood glucose levels were similar for both treatments. Thirty to 120 min after the start of the meal, postprandial blood glucose excursion was lower with TI than with subcutaneous RHI. BG-AUC0-240min following inhalation of TI was about 52% of that with subcutaneous RHI (282.8±39.3 vs. 546.7±76.1 mmol·min·L⁻¹, P = 0.007; Figure 1B). Likewise, BG-Cmax for TI was significantly lower than for subcutaneous RHI by about 40% (2.7±0.3 vs. 4.5±0.6 mmol·L⁻¹, P = 0.002). Median BG-Tmax was about 25% longer for TI than for subcutaneous RHI (120 vs. 90 min, P = 0.021).

Safety
Overall, similar numbers of subjects experienced one or more treatment-emergent adverse events (AEs) during each treatment (TI 5/16, 31%; subcutaneous RHI 4/16, 25%). These AEs were considered treatment-related in 3/16 (19%) subjects during TI treatment and 1/16 (6%) during subcutaneous RHI treatment.
Hypoglycemia was reported in 4/16 (25%) subjects during TI treatment and 2/16 (13%) during subcutaneous RHI treatment. Hyperglycemia was observed in 5/16 (31%) subjects during TI treatment and 3/16 (19%) during subcutaneous RHI treatment.

A total of 3/16 (19%) subjects reported treatment-emergent cough, all during the ambulant period with TI. Flow-volume spirometry values (FEV₁ and FVC) did not change between baseline and follow-up.

Conclusions
In this study, inhalation of TI led to markedly improved postprandial glycemic control compared with subcutaneous RHI – whereas total serum insulin exposure was almost identical with each treatment. TI had a more rapid absorption and achieved higher peak insulin levels than subcutaneous RHI. These unique pharmacokinetic properties of TI may provide a better postprandial glucose control compared to RHI - achieved with a similar insulin exposure.

Occurrences of hypoglycemia and hyperglycemia were similar with TI and subcutaneous RHI treatment, with no severe occurrences. The incidence of treatment-emergent mild to moderate AEs was comparable between treatments. Three subjects reported a single event of cough during TI treatment.

The results of our clinical-experimental study support the utility of TI as an alternative to subcutaneous RHI to cover postprandial insulin requirements. TI markedly improved postprandial blood glucose control in subjects with type 2 diabetes. Use of prandial TI as part of an intensified insulin therapy might provide better glycemic control than subcutaneous RHI. Long-term studies are under way to confirm the promising efficacy, safety, and tolerability profile of TI seen in our study.
References
Figure Legend

**Figure 1.** Changes in serum insulin concentration (A) and blood glucose (B) registered in 16 subjects with type 2 diabetes who received either 48 U (nominal dose) Technosphere®/Insulin (open circles) or 14 IU subcutaneous Regular Human Insulin (black circles) prior to a standardized meal of 496 kilocalories; mean±SE. Data presented in graph is non-baseline corrected.