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

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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 ~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-h 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 kcal, 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; 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 the curve (AUC) of postprandial blood glucose excursion (BG-$AUC_{0-240\ min}$), maximum blood glucose concentration (BG-C_{max}), and time to BG-C_{max} (BG-T_{max}). Baseline-adjusted secondary efficacy variables were total serum insulin exposure (INS-$AUC_{0-240\ min}$), maximum insulin concentration (INS-C_{max}), time to INS-C_{max} (INS-T_{max}), and time to 50% concentration before/after INS-T_{max} (INS-$T_{max\ early/late\ 50\%}$). Treatment comparisons were made using the Sign test for BG-T_{max} and INS-T_{max} and the Wilcoxon signed-rank test for INS-$T_{max\ early/late\ 50\%}$. ANOVA 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). $P < 0.05$ was regarded as statistically significant. Results are expressed as means ± SE throughout the text, unless otherwise stated.

RESULTS

— A total of 16 nonsmoking subjects with type 2 diabetes (aged 59 ± 8 years; BMI 29.6 ± 3.3 kg/m^2, A1C 7.5 ± 0.8%) were enrolled and completed the study. Subjects' insulin dose for the meal challenge was 48 ± 9 units (nominal dose) for TI and 14 ± 5 units for subcutaneous RHI.

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-$AUC_{0-240\ min}$ was nearly identical for both treatments (56.9 ± 7.1 vs. 57.7 ± 7.3 nmol·l^{-1}, $P = 0.927$) (Fig. 1*A*). INS-C_{max} was 45% greater with TI (691.0 ± 77.6 vs. 377.1 ± 42.3 pmol·l^{-1}, $P = 0.001$). Median INS-T_{max} and INS-$T_{max\ early/late\ 50\%}$ were eight times shorter with TI (15/8 vs. 120/60 min, $P < 0.001$). Median INS-$T_{max\ early/late\ 50\%}$ 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-$AUC_{0-240\ min}$ following inhalation of TI was ~52% of that with subcutaneous RHI (282.8 ± 39.3 vs. 546.7 ± 76.1 mmol·min·l^{-1}, $P = 0.007$) (Fig. 1*B*). Likewise, BG-C_{max} for TI was significantly lower than subcutaneous RHI by ~40% (2.7 ± 0.3 vs. 4.5 ± 0.6 mmol·l^{-1}, $P = 0.002$). The median BG-T_{max} value was ~25% longer for TI than subcutaneous RHI (120 vs. 90 min, $P = 0.021$).

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Abbreviations: AUC, area under the curve; RHI, regular human insulin; TI, Technosphere Insulin.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

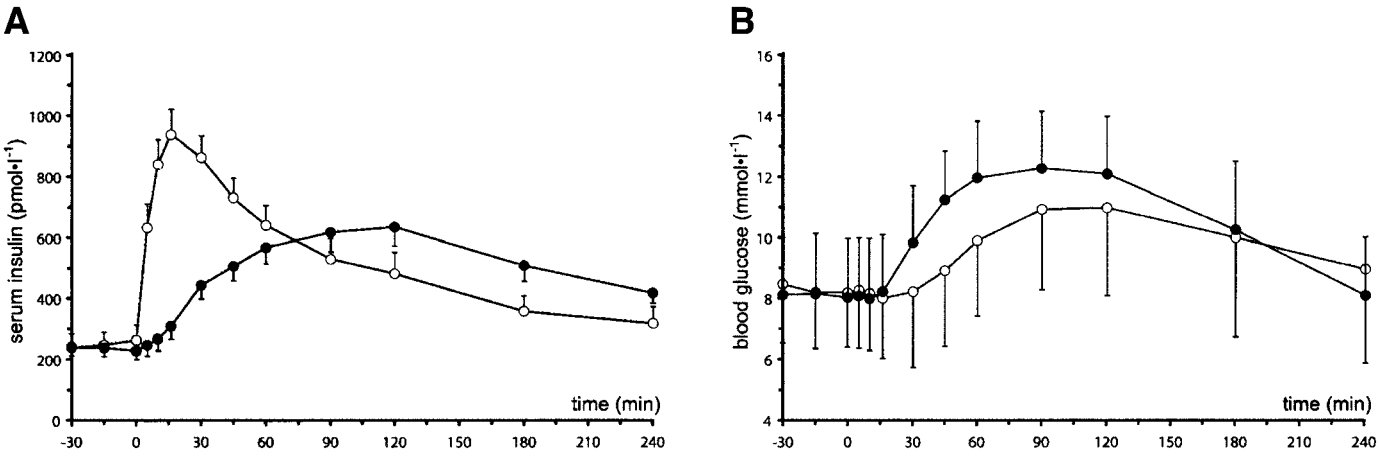

Figure 1— *Changes in serum insulin concentration (A) and blood glucose (B) registered in 16 subjects with type 2 diabetes who received either 48 units (nominal dose) TI (○) or 14 units subcutaneous RHI (●) before a standardized meal of 496 kcal. Data are means ± SE, and the data presented are nonbaseline corrected.*

Safety

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

A total of 3 of 16 (19%) subjects reported treatment-emergent cough, all during the ambulant period with TI. Flow-volume spirometry values (FEV_1 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 better postprandial glucose control compared with 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 adverse events 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.

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