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BRIEF REPORT

Time–Action Profile of Technosphere Insulin in Children with Type 1 Diabetes

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ABSTRACT

Introduction: Technosphere insulin (TI) is an inhaled dry powder ultra-rapid-acting insulin. This report describes the results of the first study of TI in children with type 1 diabetes (T1D).

Methods: Pharmacokinetics (PK) of TI and the effect of TI on circulating glucose concentrations were evaluated in a single-arm study that enrolled children ages 8–17 years with T1D for more than 1 year, on a stable multiple daily insulin injection (MDI) regimen, and meeting pre-defined pulmonary function testing criteria (at least 70% predicted). To assess PK, subjects received an individualized single preprandial dose of TI (4–12 U, in 4-U increments) via oral inhalation, based on their usual meal-time subcutaneously injected rapid-acting insulin dose and meal content. Serum insulin and blood glucose were measured at − 30 to 250 min relative to dosing.

Results: Twenty-seven children with T1D participated in this single-dose PK study. Mean subject age was 13.3 years (59% female; 81.5% White). Mean serum insulin C_{max} (maximum concentration) was 77.3, 119.15, and 207.7 μU/mL for doses of 4, 8, and 12 U, respectively. T_{max} occurred at 10.5, 13.9, and 14.6 min post-dose for 4, 8, and 12 U. Glucose lowering 30–60 min post-dose was consistent with the PK profile.

Conclusion: Serum insulin rapidly increased post-dose and returned to baseline by 120 min. The data suggests the PK of TI in youth with T1D ages 8–17 years was similar to that seen in previous adult studies.

Trial Registration: ClinicalTrials.gov identifier, NCT02527265.

Keywords: Type 1 diabetes; Pediatric; Inhaled insulin; Pharmacokinetics; Postprandial glucose

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Key Summary Points

Why carry out this study?

Management of type 1 diabetes (T1D) with intensive insulin therapy provides the most physiologic approach to achieving optimal glycemic control.

However, current subcutaneously administered rapid-acting analogue insulins (RAA) are less than ideal given the prolonged duration of activity, which can increase the risk for postprandial hypoglycemia.

Although use of mealtime TI has been studied in adult patients with T1D, the PK and safety of TI therapy have not previously been evaluated in children with T1D.

What was learned from the study?

Serum insulin rapidly increased post-dose and returned to baseline by 120 min. Mean serum insulin C_{max} (maximum concentration) was 77.3, 119.15, and 207.7 μU/mL for doses of 4, 8, and 12 U, respectively. T_{max} occurred at 10.5, 13.9, and 14.6 min post-dose for 4, 8, and 12 U.

Our findings demonstrate that the TI administered to youth with T1D ages 8–17 exhibits a PK similar to that seen in previous adult studies.

The use of TI for mealtime coverage may reduce burden on patients, as an alternative to subcutaneously administered RAA, while promoting improved postprandial control. Rapid TI clearance, on the other hand, may require additional TI dose depending on the meal composition, as previously shown.

INTRODUCTION

Management of type 1 diabetes (T1D) with intensive insulin therapy provides the most physiologic approach to achieving optimal glycemic control. However, current subcutaneously administered rapid-acting analogue insulins (RAA) are less than ideal given the prolonged duration of action [1, 2]. In addition, while some RAA are labelled for administration at the start of a meal [2, 3] or immediately thereafter [4], RAA administration 15–20 min pre-meal is required to achieve optimal postprandial glucose control [5, 6] because of the delayed onset of action. Both limitations negatively impact the safety and efficacy of RAA by increasing risk for postprandial hypoglycemia [7]. In children with T1D, eating can be erratic or continuous throughout the day (e.g., "grazing") [8, 9], and preprandial injections are a common source of parental and patient anxiety as dosing calculations can easily overestimate the carbohydrates consumed [10, 11]. The extended duration of action of subcutaneously delivered RAA further increases hypoglycemia risk in active children as exercise accelerates subcutaneous (SQ) insulin absorption and increases glucose demand. Because of its more rapid kinetics, Technosphere® insulin (TI) inhalation powder (Afrezza, MannKind Corporation, Westlake Village, CA) may be a superior prandial insulin replacement than injectable RAA.

TI is an ultra-rapid-acting insulin that is administered by oral inhalation using a breath-powered inhaler at the time of the meal. TI particles have a median diameter of approximately 2–2.5 μm, a size appropriate for inhalation into the lung. Following inhalation, TI particles dissolve immediately at the physiologic pH of the lung, and insulin is absorbed systemically. After administration of TI in adults, the maximum serum insulin concentration occurs in approximately 12–15 min (versus

45–60 min for RAA via subcutaneous route) and returns to near baseline levels in approximately 3 h [12] compared with approximately 5 h for RAA [2, 3].

Although use of mealtime TI has been studied in adult patients with T1D [13–15], the pharmacokinetics (PK) and safety of TI therapy have not previously been evaluated in children with T1D. We report findings from a phase 2 clinical study that characterized the PK of mealtime T1 in youth with T1D.

METHODS

Study Design

This was an open-label, single-arm pharmacokinetic study of TI in youth with T1D conducted between September 2017 and September 2019. The study was registered with ClinicalTrials.gov (NCT02527265), approved by a central (Advarra) or local institutional review boards, and monitored by an independent data safety monitoring board. The study was conducted in accordance with the Declaration of Helsinki [16]. The aims, methods, and potential hazards of the study were explained to prospective subjects and their parents or legally authorized representatives at the clinical study sites. Subjects and their parents or legally authorized representatives were informed of the experimental nature of the study and the possibility that they might not derive any health benefit from participating. As part of the consent process, subjects and their parents or legally authorized representatives were assured that they could withdraw from the study at any time without compromising the quality of future treatment. Subjects were informed they will not be personally identified in any reports or publications that may result from the research study. All patients provided written or oral informed consent in addition to written informed consent from the parent(s) or legal guardian and a witness.

Main inclusion criteria were age at least 4 to at most 17 years, clinical diagnosis of T1D for at least 12 months, basal-bolus MDI insulin regimen for at least 6 weeks prior to enrollment, and pre-breakfast self-monitored blood glucose (BG) values between 80 and 250 mg/dL for five of seven documented daily readings obtained prior to dosing with TI. Main exclusion criteria were body mass index (BMI) below 25th or above 95th percentile for age and gender, unstable diabetes control, history of physician diagnosis of asthma or any other clinically important pulmonary disease (pulmonary function at least 70% predicted). A complete listing of inclusion/exclusion criteria is presented in Supplemental Material.

Study Procedures

The study involved a 7–21-day screening period (visit 1), followed by a 1-day in-clinic PK assessment (visit 2). At screening (visit 1), written or oral assent from the pediatric subject and written informed consent from the parent(s) or legal guardian and a witness were obtained before physical and laboratory assessments were performed.

For the PK assessment (visit 2), study staff reviewed subject e-diaries to confirm five of the seven fasting BG values obtained during the week prior were between 80 and 250 mg/dL. Staff also confirmed that each subject fasted overnight for at least 8 h and the last dose of basal insulin was administered the night before visit 2. Insulin PK and BG were assessed in this paper following a single preprandial dose of TI (4, 8, or 12 units) calculated on the basis of the subject's insulin-to-carbohydrate ratio and the content of the standardized test meal. Carbohydrates accounted for 50% of the meal content up to a maximum of 70 g of carbohydrate. Thirty minutes prior to the assessment, subjects' BG was measured to ensure the minimum $\geq$ 80 mg/dL level. Glucose was then measured every 30 min via the local or central laboratory.

Endpoints

Primary PK endpoints were onset, peak and duration of insulin activity, and magnitude of postprandial glucose following a standardized meal during the 4-h observation period for TI doses of 4, 8, and 12 units. Measurements of

insulin C_{max} (maximum observed concentration after correction for baseline) and insulin time to C_{max} (T_{max}) were quantified.

Statistical Analysis

All subjects who received a dose of TI were included in the safety population. All analyses were performed in a descriptive manner. The safety analysis was based on the review of the individual values and descriptive statistics.

RESULTS

PK data were obtained for 27 subjects (4 units, $n = 6$; 8 units, $n = 14$; 12 units, $n = 7$). Mean age, BMI, and duration of T1D were 13.3 ± 2.9 years, 20.8 ± 3.6 kg/m^2, and 4.5 ± 3.2 years, respectively. Sixteen subjects (59.3%) were female. Twenty-two (81.5%) were White, two were Black, and two were Other Race.

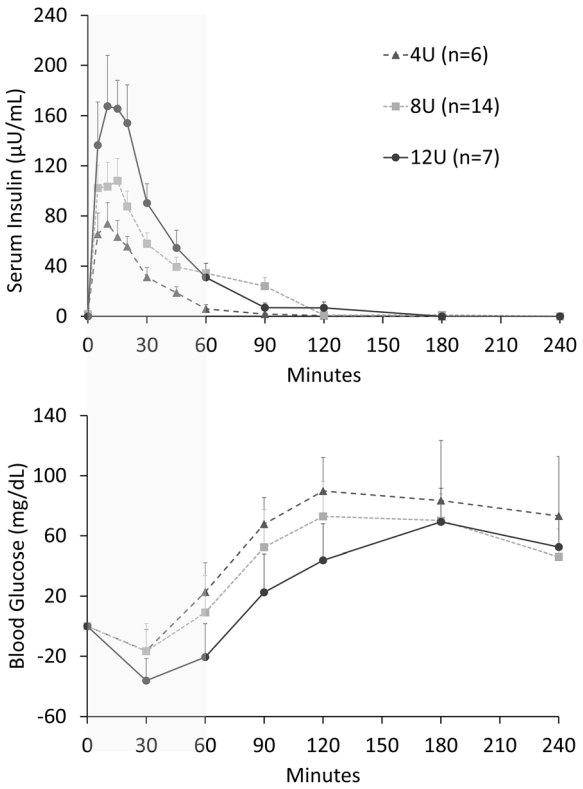

Fig. 1 Insulin concentration and postprandial glucose excursion (PPGE) over time. **a** Mean serum insulin concentration after 4-, 8-, and 12-unit doses of TI. **b** Postprandial glucose excursions (PPGE) after 4-, 8-, and 12-unit doses of TI

Insulin Exposure and Postprandial Glucose Excursions

Insulin concentrations rapidly increased in the first 10–15 min after inhaled administration for the 4-, 8-, and 12-unit doses of TI (Fig. 1a), and then rapidly declined. Mean serum insulin C_{max} (maximum concentration) was 77.3, 119.15, and 207.7 µU/mL for doses of 4, 8, and 12 U. T_{max} occurred at 10.5, 13.9, and 14.6 min post-dose for 4, 8, and 12 U, respectively.

A dose-related change in postprandial glucose excursions (PPGE) was observed during the first 60 min after inhaled administration of TI (Fig. 1b). Mean BG values at nadir did not drop below 70 mg/dL for any dose. Glucose lowering 30–60 min post-dose was consistent with the PK profile and similar to previously published data in adult subjects.

Safety

There was one measurement of level 1 (less than 70 mg/dL) hypoglycemia in three subjects, and one measurement of level 2 (less than 54 mg/dL) hypoglycemia in one subject during the first 60 min of TI dosing. No incidents of severe hypoglycemia were observed.

DISCUSSION

TI elicited a rapid PK response in children aged 8–17 years with T1D. The time–action profile of TI in children was similar to that seen in adults [17], with no new or unexpected safety signals during the PK assessment. Importantly, this study demonstrates that mealtime TI may enable pediatric patients to improve prandial control through its unique time–action profile, which demonstrated an ultra-rapid onset of insulin effect with shorter duration of action than subcutaneously delivered RAA [2, 3, 12].

Pediatric and adolescent patients are at higher risk for hypoglycemia and diabetic ketoacidosis than adults with T1D and often have difficulty achieving and maintaining their glycemic targets [7]. As reported by Foster et al., only 5% of the 4346 pediatric patients enrolled in the T1D Exchange registry had an HbA1c at or below the target of less than 7.0% [7, 18]. Moreover, the ability to match mealtime insulin with carbohydrate intake helps address the erratic eating patterns often observed in younger patients [8, 9]. Although use of the new automated insulin delivery (AID) systems has been shown to be effective in reducing hypoglycemia in this population [19, 20], these technologies still require users to manually enter their mealtime insulin doses as well as undergo the burden of wearing multiple devices [21]. Thus, use of TI for mealtime coverage may reduce burden on patients while promoting improved postprandial control. Rapid TI clearance, on the other hand, may require additional TI dose depending on the meal composition, as previously shown [22].

Some limitations of the study are notable. The study was originally designed to investigate the use of TI in pediatric patients as young as 4 years old; however, this posed significant recruitment challenges. Nevertheless, the objectives of the study were accomplished in the subjects aged 8–17. Another limitation is that it did not follow the postprandial glucose levels for more than 240 min post dose, as well as the long-term safety of TI in this population. But the similar PK and safety demonstrated during the PK assessment in this study allowed for moving forward with a phase 3 clinical trial of the safety and efficacy of TI in the pediatric population. This multicenter, randomized phase 3 trial with a 6-month primary efficacy endpoint and 6-month safety extension is currently enrolling patients (https://clinicaltrials.gov/ct2/show/NCT04974528). The purpose of the treatment extension is to assess safety and efficacy with continued use of TI in the pediatric population.

CONCLUSION

This phase 2, open-label, single-arm study of TI in youth with T1D assessed the PK of mealtime TI in children. Our findings demonstrated that the TI administered to youths with T1D ages 8–17 exhibits a PK similar to that seen in previous adult studies, which allowed for moving forward with an ongoing phase 3 clinical trial of the safety and efficacy of TI in the pediatric population. Thus, TI could provide an alternative to subcutaneously administered RAA in youth with T1D.

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Author Contributions. KBK and SB wrote the manuscript, SB and MCJ provided the statistical analysis, MJH conducted the study and edited the manuscript. All authors reviewed the final manuscript prior to submission. KBK takes full responsibility for the accuracy of its content.

Disclosures. KBK, MCJ and SB are current or former employees of MannKind Corporation. The University of Florida received research funding from MannKind to support MJH's work on this study. MJH has received consulting fees from MannKind.

Compliance with Ethics Guidelines. The study was registered with ClinicalTrials.gov (NCT02527265), approved by a central (Advarra) or local institutional review boards, and monitored by an independent data safety monitoring board. The study was conducted in accordance with the Declaration of Helsinki. The aims, methods, and potential hazards of the

study were explained to prospective subjects and their parents or legally authorized representatives at the clinical study sites. Subjects and their parents or legally authorized representatives were informed of the experimental nature of the study and the possibility that they might not derive any health benefit from participating. As part of the consent process, subjects and their parents or legally authorized representatives were assured that they could withdraw from the study at any time without compromising the quality of future treatment. Subjects were informed they will not be personally identified in any reports or publications that may result from the research study. All patients provided written or oral informed consent in addition to written informed consent from the parent(s) or legal guardian and a witness.

Prior Presentation. Findings from the study were presented at the 81st Annual Meeting of the American Diabetes Association (Virtual Meeting), June 25–29, 2021. Poster #923-P.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Thanking Patient Participants. The authors wish to thank all of the patients who participated in the study.

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