Impact of symptomatic upper respiratory tract infections on insulin absorption and action of Technosphere inhaled insulin

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ABSTRACT

Objective: Uncomplicated, acute upper respiratory tract infections (URTIs) occur in patients with diabetes at a similar frequency to the general population. This study (NCT00642681) investigated the effect of URTIs on the pharmacokinetic (PK) and pharmacodynamic (PD) properties of Technosphere inhaled insulin (TI) in patients with type 1 or type 2 diabetes.

Research design and methods: This was a phase 2 study conducted in patients who developed a URTI while being treated with TI in a phase 3 study (N=20, mean age 50 years, 60% men). Patients underwent two 4-hour meal challenges, during which blood samples were drawn to measure serum fumaryl diketopiperazine (FDKP; the excipient representing an essential part of TI), serum insulin, serum C-peptide, and plasma glucose. The primary outcome was the ratio of serum FDKP area under the concentration–time curve from 0 to 240 min ($AUC_{0-240\ min}$) during URTI and after clinical resolution of URTI symptoms ($\geq$15 to $\leq$45 days).

Results: No significant differences in PK parameters were seen during URTI versus post-URTI for FDKP. The ratio of serum FDKP $AUC_{0-240\ min}$ during URTI and post-URTI was 1.1 (SD 0.6), p=0.4462. Plasma glucose concentrations during each 4-hour meal challenge were similar, showing small non-significant differences. No adverse events, including hypoglycemia, occurred during meal challenge visits.

Conclusions: Development of an active, symptomatic URTI during treatment with TI had no significant impact on the PK/PD properties of TI, suggesting that no adjustment in prandial insulin dosing is needed. However, if patients are unable to conduct proper inhalation, they should administer their prandial insulin subcutaneously.

Trial registration number: NCT00642681; Results.

Key messages

- Uncomplicated, acute upper respiratory tract infections are expected to occur in patients with diabetes at a similar frequency to the general population. Given the route of administration of Technosphere inhaled insulin, it is clinically relevant for healthcare providers to know whether an upper respiratory tract infection may have an effect on the glucose-lowering properties of Technosphere inhaled insulin and thus an impact on glycemic control.
- The data from this study suggest that the development of an upper respiratory tract infection during treatment with Technosphere inhaled insulin had no significant impact on the pharmacokinetic or pharmacodynamic properties of Technosphere inhaled insulin, suggesting that no adjustment in prandial insulin dosing is needed.
- If patients are unable to conduct proper inhalation, their prandial insulin should be administered subcutaneously.

INTRODUCTION

Technosphere inhaled insulin (Afrezza (insulin human) inhalation powder, MannKind Corporation, Valencia, California, USA) is a dry powder formulation of recombinant human insulin for inhalation, via the Gen2 inhaler device, in patients with diabetes. Technosphere inhaled insulin consists of Technosphere powder (microparticles of fumaryl diketopiperazine (FDKP)) to which insulin is adsorbed. When the microparticles are exposed to physiological pH in the deep lung after inhalation of Technosphere inhaled insulin, they rapidly dissolve, allowing insulin and FDKP to be absorbed rapidly into the blood. FDKP is biologically inactive and is excreted unchanged in the urine; FDKP and insulin, delivered as Technosphere inhaled insulin, have a terminal clearance half-life from the lung of ~1 hour.[1 2]

After subcutaneous injection, regular human insulin has a time to maximum concentration of 80–120 min and a duration of action of 5–8 hours. Rapid-acting insulin analogs (eg, insulin aspart and insulin lispro) have a time to maximum concentration of around 50–120 min, and a duration of action of 3–5 hours.[3–6] Technosphere inhaled

insulin, however, has a shorter time to maximum concentration of 12–17 min as well as a shorter duration of action of ~2–3 hours.[7] The faster absorption and shorter duration of Technosphere inhaled insulin is closer to the physiological release of mealtime insulin boluses, and provides the potential for faster glucose-lowering onset, improved postprandial glucose control, reduced hypoglycemia, and less weight gain, resulting from reduced lag time and less likelihood of overinsulinization.[8] Furthermore, Technosphere inhaled insulin use avoids the inconvenience associated with subcutaneous injections and might be helpful for insulin requiring individuals with 'injection or needle phobia'.

In a 2-year, phase 3 clinical study comparing Technosphere inhaled insulin with subcutaneous injection of rapid-acting insulin analogs in patients with type 1 or type 2 diabetes, a gradual decrease in lung function was observed in the treatment groups. Differential changes in lung function associated with Technosphere inhaled insulin were small: ~1% reduction in forced expiratory volume in 1 s, ~1% reduction in forced vital capacity, and ~2% reduction in diffusing capacity of the lung for carbon monoxide. All of these changes occurred early after treatment initiation, were nonprogressive, resolved rapidly after discontinuation of Technosphere inhaled insulin, and are considered not to be clinically meaningful.[6] On the other hand, acute bronchospasm has been observed in patients with asthma and chronic obstructive pulmonary disease. Technosphere inhaled insulin has a black box warning contraindication in patients with chronic lung disease.[9]

Uncomplicated, acute upper respiratory tract infections (URTIs; eg, common colds) are the most common infectious illness in the general population, represent the most frequent acute diagnosis in the primary care setting, and occur in adults 2–4 times per year with symptoms persisting up to 7–10 days.[10] URTIs are expected to occur in patients with diabetes at a similar frequency to the general population.[11] Given the inhaled method of administration of Technosphere inhaled insulin, it is clinically relevant for healthcare providers to know whether a URTI may have an effect on the glucose-lowering properties of Technosphere inhaled insulin and thus impact on glycemic control; that is, is there an increased risk of hypoglycemic or hyperglycemic events when using this product? In fact, inquiries relating to the effect of URTIs on insulin therapy with inhalation of Technosphere inhaled insulin are among the most frequent questions healthcare providers ask the manufacturer.

Here, we report results of a phase 2 study conducted in patients already enrolled in a phase 3 study. This study aimed to investigate the interaction of URTIs with the pharmacokinetic (PK) and pharmacodynamic (PD) properties of insulin and FDKP (as administered in the form of Technosphere inhaled insulin) in patients with type 1 or type 2 diabetes during a URTI, and at least 2 weeks following full recovery from a URTI.

RESEARCH DESIGN AND METHODS
Study design and patients

This study (MKC-TI-112; ClinicalTrials.gov identifier: NCT00642681) included patients with type 1 and type 2 diabetes who developed a symptomatic URTI while being treated with Technosphere inhaled insulin using the MedTone inhaler in a phase 3 randomized controlled trial (MKC-TI-030 study; ClinicalTrials.gov Identifier: NCT00308737). The study took place between July 2005 and August 2008. URTI was defined as ≥3 URTI symptoms from a questionnaire with a list of symptoms (eg, runny nose, nasal stuffiness, sneezing, sore throat, scratchy throat, hoarseness, new-onset cough, sinus pain/pressure, head congestion/headache, and plugged ears/ear discomfort) in the 24 hours prior to and/or on the day of a clinic visit.

Patients were excluded from the study if there was evidence by medical history, physical examination, or laboratory findings of an acute bacterial infection, including but not limited to purulent sputum production, purulent nasal/eye/ear discharge, chest examination abnormalities on auscultation or percussion, throat exudates, or chest X-ray findings of pneumonia (if clinically indicated).

Each patient underwent two 4-hour meal challenges. The first 4-hour meal challenge was performed during the active phase of the URTI ('during URTI'). The second 4-hour meal challenge was performed after clinical resolution of URTI symptoms (≥15 days but ≤45 days; 'post-URTI'). Patients arrived in a fasting state and had not taken their morning dose of prandial Technosphere inhaled insulin; patients taking morning basal insulin or oral antidiabetes agents took them as usual. Following administration of a single dose of Technosphere inhaled insulin, patients ingested a standardized liquid meal of 540 kcal/67.5 g of carbohydrates (12 oz. Boost Plus, Novartis). Blood samples for measurement of serum FDKP, insulin, C-peptide, and plasma glucose were obtained 30 min before dosing, at dosing (0), and 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 min after insulin dose administration. Blood glucose was measured at a central laboratory (BARC-US, Lake Success, New York, USA). Patients received the same Technosphere inhaled insulin dose they were currently taking in the MKC-TI-030 study at the time of the meal challenge; that is, a standard insulin dose was not applied. It was intended that each patient served as his or her own control.

The study was conducted in accordance with the ethical principles of Good Clinical Practice as defined by the International Conference on Harmonization and Declaration of Helsinki.[12] Independent ethics committees or institutional review boards approved the protocol, and all participants gave written informed consent.

End points

The primary end point was the serum FDKP area under the concentration–time curve from 0 to 240 min ($AUC_{0-240\ min}$). Serum FDKP AUC and not the AUC under the serum insulin profile was used as the primary

end point to avoid interference from endogenously secreted insulin in patients with type 2 diabetes.

The primary outcome was the ratio of serum FDKP $AUC_{0-240\ min}$ during URTI and post-URTI. Other PK parameters assessed included insulin concentrations overtime ($AUC_{0-240\ min}$), maximum FDKP and insulin serum concentration (C_{max}), time to reach C_{max} (t_{max}), and FDKP half-life ($t_{1/2}$).

PD parameters assessed during URTI and post-URTI included plasma glucose concentrations, maximum and minimum plasma glucose (C_{max}, C_{min}), and baseline-corrected plasma glucose C_{max} and C_{min}.

Safety parameters assessed during URTI and post-URTI included vital signs, physical examination findings, and adverse events (AEs).

Statistical analyses

Descriptive statistics of the PK, PD, and safety parameters were calculated during URTI and post-URTI. Natural log transformation was performed on $AUC_{0-240\ min}$ and paired Student's t-tests were used to assess the between-period differences. The $p < 0.05$ was considered significant.

For five patients, Technosphere inhaled insulin doses during URTI and post-URTI were different, so AUC for FDKP and insulin was normalized for these patients to the lower of the two Technosphere inhaled insulin doses. The ratio was calculated on the log-transformed normalized AUC.

Efficacy analyses were performed on the intent-to-treat population, defined as all randomized patients who received ≥1 dose of trial medication and had values for the primary efficacy variables during URTI and post-URTI. Safety analyses were performed on the safety population, defined as all randomized patients who received ≥1 dose of trial medication during the study.

RESULTS
Patients

From 23 sites with a population of 283 individuals, a total of 20 patients were screened and enrolled in the study, six with type 1 and 14 with type 2 diabetes. All 20 patients received a single dose of Technosphere inhaled insulin at each of the two 4-hour meal challenges (during URTI and post-URTI) and all patients completed the study. Hence, the safety, intent-to-treat, and per protocol populations were identical. Of the 20 patients, 12 (60%) were men and eight (40%) were women; mean (SD) age was 49.8 (13.6) years (range 21–65 years). Three (15%) patients were aged 18–30 years, six (30%) were aged 31–49 years, 10 (50%) were aged 50–64 years, and one (5%) was aged ≥65 years.

During the study, Technosphere inhaled insulin doses were individualized and ranged from 15 to 90 units (corresponding to 4–24 units of subcutaneous rapid-acting insulin). Therefore, comparison of mean FDKP and insulin C_{max} and AUC is not meaningful. The variation in doses was addressed by normalizing within each patient and by using individual AUC ratios as the primary outcome.
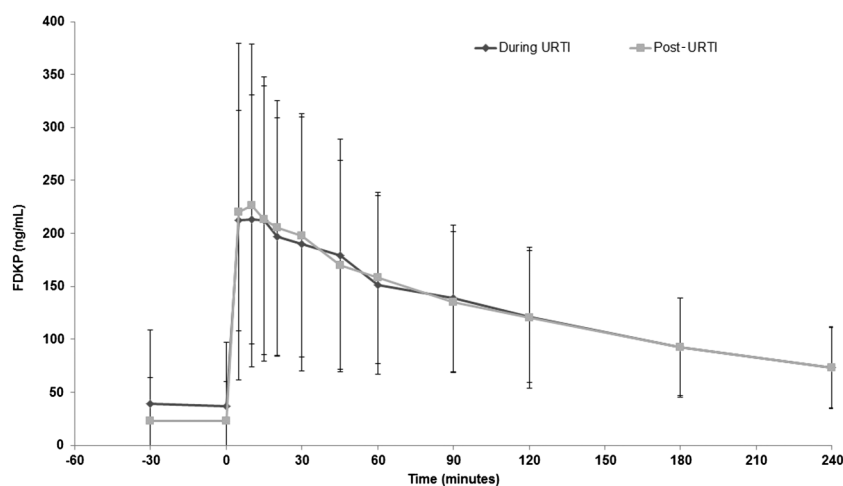
Pharmacokinetics
FDKP

The PK profile of FDKP measured by $AUC_{0-240\ min}$ after dosing was similar during URTI and post-URTI (figure 1). The dose-normalized mean (SD) FDKP $AUC_{0-240\ min}$ during URTI was 23 315 (12 586) ng min/mL and the post-URTI FDKP $AUC_{0-240\ min}$ was 26 763 (14 782) ng min/mL. The ratio (SD) was 1.1 (0.6) (p=0.4462; table 1). No significant differences were noted during URTI and post-URTI for t_{max} or $t_{1/2}$ (table 1).

Serum insulin

The serum insulin profile ($AUC_{0-240\ min}$) after dosing with Technosphere inhaled insulin was similar during URTI compared with post-URTI: the ratio was 0.9 (0.4) (p=0.1754) (table 1, figure 2). No significant differences were noted during URTI or post-URTI for t_{max} (25.5 (44.4) vs 21.3 (25.1) minutes, respectively; p=0.7194). The individualized dose administration precluded statistical comparison of insulin concentrations and C_{max} during URTI and post-URTI.

Figure 1 Fumaryl diketopiperazine (FKDP) concentrations over time during upper respiratory tract infection (URTI) and post-URTI. Data are mean±SD.

Table 1 FDKP and insulin pharmacokinetic parameters during URTI and post-URTI

Parameter, mean (SD)*	During URTI	Post-URTI	Comparison (during URTI −post-URTI)	p Value
FDKP $AUC_{0-240\ min}$, ng min/mL	23 315 (12 586)	26 763 (14 782)		
FDKP ratio $AUC_{0-240\ min}$ during URTI: $AUC_{0-240\ min}$ post-URTI	NA	NA	1.1 (0.63)†,‡	0.4462
FDKP t_{max}, min	15.8 (26.2)†	15.5 (14.8)†	−0.3 (31.98)†	0.9725
FDKP $t_{1/2}$, min	163.2 (35.5)†	174.8 (79.0)†	−15.4 (62.6)†	0.3105
Plasma glucose C_{max}, mg/dL	212.0 (65.6)	198.8 (69.7)	−13.2 (75.6)§	NA
Baseline-corrected plasma glucose C_{max}, mg/dL	81.0 (57.2)	69.7 (69.9)	−11.3 (72.7)§	NA
Plasma glucose C_{min}, mg/dL	116.7 (41.7)	111.1 (41.2)	−5.7 (57.8)§	NA
Baseline-corrected plasma glucose C_{min}, mg/dL	5.9 (14.6)	1.9 (7.9)	−4.0 (12.5)§	NA
Serum insulin ratio $AUC_{0-240\ min}$ during URTI: $AUC_{0-240\ min}$ post-URTI	NA	NA	0.9 (0.37)‡	0.1754
Serum insulin t_{max}, min	25.5 (44.42)	21.3 (25.12)	−4.3 (52.12)	0.7194

AUC was normalized for these participants to the lower of the two doses; the ratio was performed on the log-transformed normalized AUC.
*Across the study, insulin doses were individualized and ranged from 15 to 90 units; therefore, calculating mean FDKP and insulin AUC or mean insulin and C-peptide concentrations or PK parameters is not meaningful.
†n=19.
‡For five participants, doses between the two arms were different.
§Since differences were small and the variation was large, statistical analysis was limited.
AUC, area under the concentration; $AUC_{0-240\ min}$, area under the concentration–time curve from 0 to 240 min; FDKP, fumaryl diketopiperazine; NA, not applicable; PK, pharmacokinetic; URTI, upper respiratory tract infection.
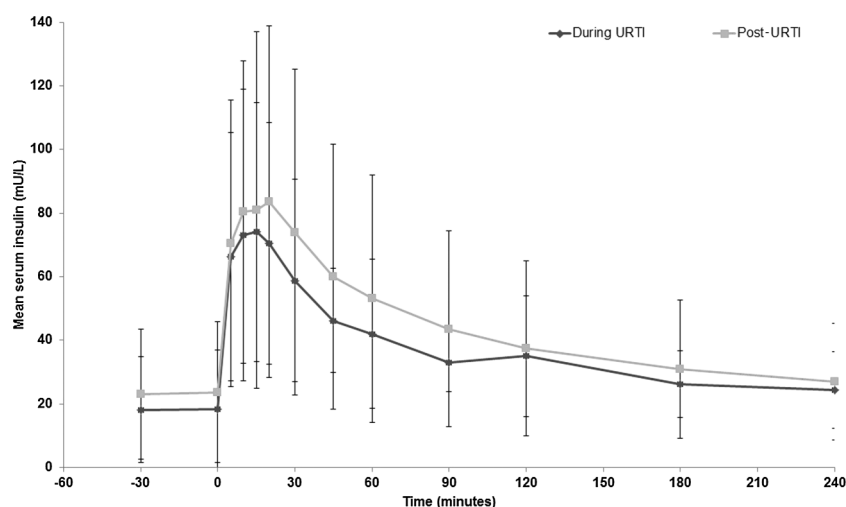
Pharmacodynamics

The maximal plasma glucose concentrations during each 4-hour meal challenge were similar during URTI and post-URTI (table 1, figure 3). Differences in plasma glucose parameters C_{max} and C_{min} (unadjusted and baseline corrected) during URTI and post-URTI were small. However, owing to the study design, statistical analysis of these data is not meaningful.

Safety

All 20 patients completed the MKC-TI-112 study; there were no premature discontinuations, no deaths, and no AEs (including hypoglycemia). No clinically relevant findings were reported for vital signs or physical examination.

CONCLUSIONS

Symptomatic URTIs, a common and frequent ailment among the general population as well as among those with diabetes, might cause concern for healthcare providers and patients with coincident use of Technosphere inhaled insulin. This study showed that active, symptomatic URTIs during treatment with Technosphere inhaled insulin had no impact on the PK and PD properties of Technosphere inhaled insulin, as assessed by the primary end point of FDKP $AUC_{0-240\ min}$. Furthermore, the other PK parameters of FDKP and insulin were found to be similar during URTI and following recovery from an URTI. The PD properties of Technosphere inhaled insulin, as assessed by unadjusted and baseline-corrected blood glucose C_{max} and C_{min}, were also similar during URTI and post-URTI. Moreover,

Figure 2 Serum insulin concentrations overtime with Technosphere inhaled insulin during upper respiratory tract infection (URTI) and post-URTI. Data are mean±SD.

Figure 3 Plasma glucose concentrations during a 4-hour meal challenge during upper respiratory tract infection (URTI) and post-URTI. Data are mean±SD.
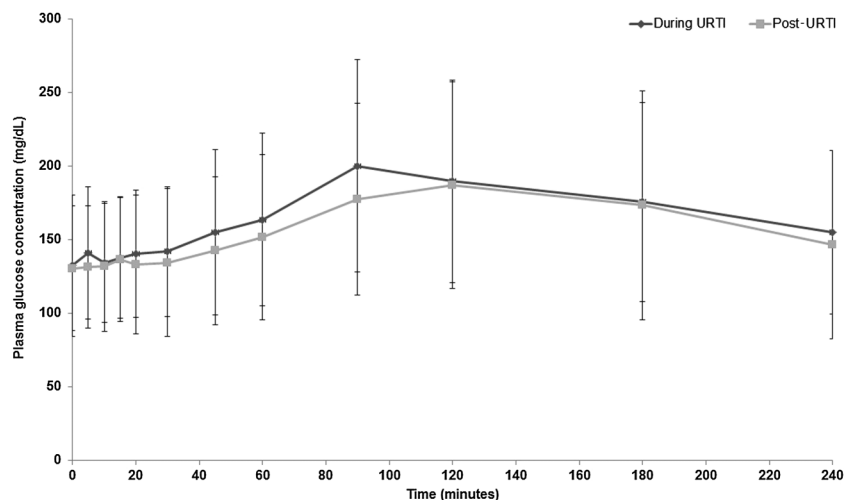
Technosphere inhaled insulin was well tolerated by participants in this study. Therefore, for individuals accustomed to using Technosphere inhaled insulin as a part of their insulin therapy who develop an active, symptomatic URTI, no difference in Technosphere inhaled insulin absorption is expected; that is, coverage of prandial insulin requirements should be identical. However, dose adjustments may be needed due to the infection itself; that is, the decreased insulin sensitivity seen with URTI might require higher insulin doses.

A limitation of this study is the small number of participants (N=20) enrolled. However, the data reported here are supportive of other studies that have been conducted to assess the suitability of using inhaled insulins during acute URTIs. The PK and PD properties of AERx insulin Diabetes Management System and AIR inhaled insulin have been assessed during URTI in normal individuals.[11][13] Both studies also suggested no significant differences in PK and PD properties of both inhaled insulins during a URTI. The incidence and clinical effect of intercurrent respiratory tract infections have also been investigated with Exubera. In a retrospective analysis of pooled data from 14 phase 2 and 3 clinical studies, no apparent changes in glycated hemoglobin (HbA1c) or in the rate of overall hypoglycemic events were observed with intercurrent respiratory tract infections in any treatment group.[14] Another limitation of our study is that patients with lower respiratory tract infections were not studied.

Given the route of delivery of Technosphere inhaled insulin, one question that may arise is whether the drug itself causes URTIs or their symptoms. Isolated and brief cough, categorized as mild, non-productive, and occurring within ≤10 min of inhalation of Technosphere inhaled insulin without other symptoms of URTI, is a commonly reported AE (frequency 25–29%).[6] However, when data from the phase 2 and 3 clinical studies of Technosphere inhaled insulin for all-cause respiratory treatment-emergent AEs are pooled, URTIs were reported more frequently with comparators than with Technosphere inhaled insulin (10.9% vs 9.4%,

respectively) (Data on file, MannKind Corporation). It is plausible that the slightly lower URTI incidence in Technosphere inhaled insulin-treated patients is due to cough being assigned as related to the drug, rather than as a symptom of URTIs. Bronchitis was reported in 3.0% of patients treated with Technosphere inhaled insulin and 2.6% of patients treated with comparators, suggesting no significant difference in the occurrence of lower respiratory tract infections.

In conclusion, the results of this study suggest that Technosphere inhaled insulin can be used successfully for prandial insulin coverage by patients with diabetes during an active, symptomatic URTI. However, it should be noted that if patients with type 1 or type 2 diabetes are unable to conduct proper inhalation during URTI, they should administer their insulin subcutaneously.

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