INHALATION OF INSULIN: EFFECT OF SYMPTOMATIC UPPER RESPIRATORY TRACT INFECTIONS ON PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) PROPERTIES

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ABSTRACT

Uncomplicated, acute upper respiratory tract infections (URTIs), i.e. common colds, occur in patients with diabetes at a similar frequency to the general population. We studied the effect of URTIs on the PK/PD properties of Technosphere® Insulin Inhalation Powder (TI) in patients with type 1 or type 2 diabetes (N = 20, mean age 50 years, 60% men).

The trial included patients who developed a URTI while treated with TI in a phase 3 study. Patients underwent two 4-hour meal challenges during which blood samples were drawn to measure serum FDKP (the dry powder excipient), serum insulin, serum C-peptide, and plasma glucose. The primary outcome was the ratio of serum FDKP $AUC_{0\text{-}4h}$ during URTI to after clinical resolution of URTI symptoms (≥ 15 to ≤ 45 days).

There were no significant differences in PK parameters during URTI versus after resolution of URTI. Plasma glucose concentrations (unadjusted and baseline-corrected) were similar during and after URTI resolution. No adverse events (including hypoglycemia) occurred during meal challenge visits.

URTIs had no impact on the PK/PD properties of TI. However, study observations are limited to patients with URTI, as individuals with lower respiratory tract infection were not studied. If a patient is unable to conduct proper inhalation, they should administer insulin subcutaneously.

INTRODUCTION

- Technosphere® Insulin Inhalation Powder (TI) is a dry powder formulation of recombinant human insulin adsorbed onto Technosphere microparticles for oral inhalation, via the Gen2 inhaler device (**Figure 1**), in patients with diabetes mellitus.
- TI consists of microparticles of fumaryl diketopiperazine (FDKP) to which insulin is adsorbed:
  - when the microparticles are exposed to physiological pH in the deep lung, they rapidly dissolve, allowing insulin and FDKP to be absorbed into the systemic circulation
  - FDKP is biologically inactive, is excreted unchanged in the urine, and has a clearance half-life from the lung of approximately 1 hour[1,2]
- It has been demonstrated that TI has rapid absorption and elimination profiles, approaching that of physiological early insulin release:[3]
  - regular human insulin has a time to maximum concentration of 80-120 minutes and a duration of action of 5-8 hours[4,5]
  - insulin analogs (e.g. insulin aspart, insulin lispro) have a time to maximum concentration of 40-50 minutes, and a duration of action of 3-5 hours[5,6]
  - TI has a time to maximum concentration of 12-17 minutes and has a duration of action of approximately 2-3 hours[3]
- In a study evaluating pulmonary function changes over 2 years in patients with type 1 (T1DM) or type 2 diabetes mellitus (T2DM) receiving TI or usual care, observed changes in lung function with TI were small, occurred early after treatment initiation, nonprogressive, resolved after discontinuation, and unlikely to be clinically meaningful.[6]
- Uncomplicated, acute upper respiratory tract infections (URTIs; i.e. common colds) are expected to occur in patients with diabetes at a similar frequency to the general population.[7]
- Due to the inhaled method of administration, it is clinically relevant to know if an URTI may have an effect on the pharmacokinetic/pharmacodynamic (PK/PD) properties of TI and thus impact glycemic control.

OBJECTIVES

- To study the effect of URTIs on the PK/PD properties of insulin and FDKP (as administered in the form of TI) in patients with T1DM or T2DM during and following recovery from an URTI.

METHODS

Study Design and Patients

- This study (ClinicalTrials.gov Identifier: NCT00642681) included patients with T1DM and T2DM who developed a symptomatic URTI while being treated with TI in a phase 3 randomized controlled trial (Study MKC-TI-030; ClinicalTrials.gov Identifier: NCT00308737).
  - URTI was defined as ≥ 3 URTI symptoms from a questionnaire with a list of symptoms (i.e. 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
- Each patient underwent two 4-hour meal challenges following administration of a single dose of TI:
  - 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)
- Blood samples for PK/PD were obtained 30 minutes before dosing, at dosing (0), and 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes after dose administration; patients received the same TI dose they had been titrated for Study MKC-TI-030 at the time of the meal challenge.
- Each patient served as his or her own control.

Endpoints

- The primary endpoint was serum FDKP area under the concentration–time curve (AUC) from 0 to 240 minutes ($AUC_{0\text{-}240\ min}$).
  - serum FDKP was used as the primary endpoint to avoid interference from endogenous insulin in patients with T2DM
- The primary outcome was the ratio of serum FDKP $AUC_{0\text{-}240\ min}$ during URTI and post-URTI.
- Other PK parameters assessed during the URTI and post-URTI included:
  - FDKP and insulin concentrations over time
  - FDKP and insulin maximum serum concentration (C_{max})
  - FDKP and insulin time to reach C_{max} (t_{max})
  - FDKP half-life ($t_{½}$)
    - insulin $t_{½}$ was not calculated because insulin is an endogenous compound
  - insulin $AUC_{0\text{-}240\ min}$
- PD parameters assessed during URTI and post-URTI included plasma glucose concentrations, plasma glucose C_{max} and minimum serum concentration (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 both during URTI and post-URTI.
- Natural log transformation was performed on $AUC_{0\text{-}240\ min}$ and paired t-tests were used to assess the between-period differences; $P < 0.05$ was considered significant.
  - for 5 patients, TI doses during URTI and post-URTI were different
    - AUC was normalized for these patients to the lower of the two TI 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 both 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

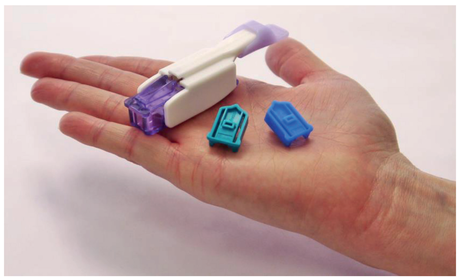
- A total of 20 patients with T1DM and T2DM were enrolled in the study; all 20 received a single dose of TI at each of the two 4-hour meal challenges (during URTI and post-URTI) and all 20 patients completed the study.
- Of the 20 patients: 12 (60%) were men and 8 (40%) were women; mean (standard deviation [SD]) age was 49.8 (13.6) years (range 21-65 years); and 3 (15%) patients were aged 18-30 years, 6 (30%) were aged 31-49 years, 10 (50%) were aged 50-64 years, and 1 (5%) was aged ≥ 65 years.
- During the study, TI doses were individualized and ranged from 15 to 90 U (corresponding to 4-24 U with current labeling); therefore, calculating mean FDKP and insulin PK parameters was not meaningful; the variation in doses was addressed by normalizing within each patient and by using individual ratios as the primary outcome.

Pharmacokinetics

FDKP

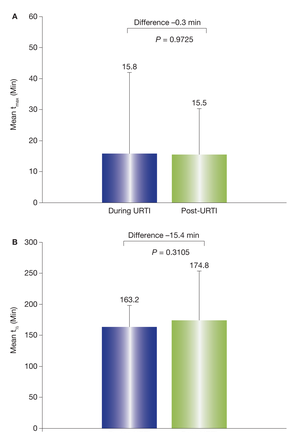
- The PK profile of FDKP measured by $AUC_{0\text{-}240\ min}$ after dosing with TI following the 4-hour meal challenge was similar during URTI compared with post-URTI.
  - the ratio (SD) of FDKP $AUC_{0\text{-}240\ min}$ during URTI to post-URTI was 1.1 (0.6) ng·min/mL ($P = 0.4462$)

Figure 1. Gen2 Inhaler Device.[a]



[a]In the study reported here, TI was administered via the MedTone inhaler device.

Figure 2. Mean (SD) FDKP PK Parameters During URTI and Post-URTI: t_{max} (A) and $t_{½}$ (B).



- No statistically significant differences were noted during URTI and post-URTI for t_{max} or $t_{½}$ (**Figure 2**).
- Mean FDKP concentrations over time during URTI and post-URTI are shown in **Figure 3**.
- The individualized dose administration precluded accurate comparisons of C_{max} during URTI and post-URTI.

Figure 3. Mean FDKP Concentrations Over Time During URTI and Post-URTI.

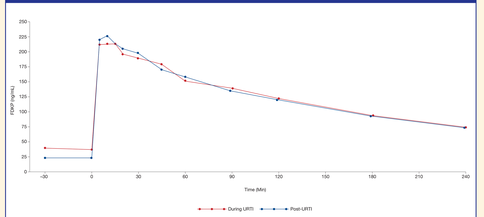


Figure 4. Mean Serum Insulin Concentrations Over Time With TI During URTI and Post-URTI.

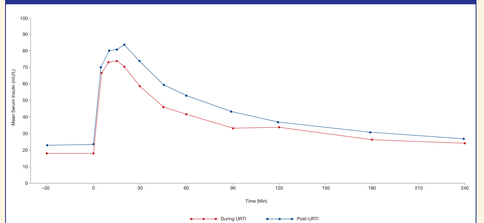
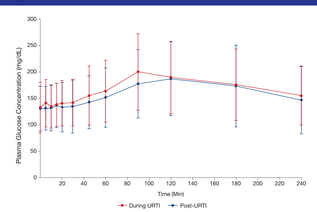


Figure 5. Mean (SD) Plasma Glucose Concentrations During each 4-Hour Meal Challenge During URTI and Post-URTI.



Serum Insulin

- The PK profile of serum insulin measured by $AUC_{0\text{-}240\ min}$ after dosing with TI following each 4-hour meal challenge was similar during URTI compared with post-URTI.
  - the ratio (SD) of insulin $AUC_{0\text{-}240\ min}$ during URTI to post-URTI was 0.9 (0.4) mU·min/L ($P = 0.1754$)
- No statistically significant differences were noted during URTI or post-URTI for t_{max} (mean [SD] 25.5 [44.4] minutes vs 21.3 [25.2] minutes, respectively; $P = 0.7194$).
- Mean insulin concentrations over time during URTI and post-URTI are shown in **Figure 4**.
- The individualized dose administration precluded accurate comparisons of insulin concentrations and C_{max} during URTI and post-URTI.

Pharmacodynamics

- The maximal blood glucose concentrations during each 4-hour meal challenge were similar during URTI and post-URTI (**Figure 5**).
- Differences in plasma glucose parameters C_{max} and C_{min} (unadjusted and baseline-corrected) during URTI and post-URTI were small and not likely to be clinically meaningful (**Table**).
  - differences post-URTI minus during URTI were small and variation was large, which limited statistical analysis of these data

Safety

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

Table. Plasma Glucose Parameters With TI During URTI and Post-URTI.

Parameter	During URTI (n = 20)	Post-URTI (n = 20)	Difference (Post-URTI – During URTI)
C_{max}, mg/dL	212.0 (65.6)	198.8 (69.7)	−13.2 (75.6)
C_{min}, mg/dL	116.7 (41.7)	111.1 (41.2)	−5.7 (57.8)
Baseline-corrected C_{max}, mg/dL	81.0 (57.2)	69.7 (69.9)	−11.3 (72.7)
Baseline-corrected C_{min}, mg/dL	5.9 (14.6)	1.9 (7.9)	−4.0 (12.5)

All values mean (SD).

CONCLUSIONS

- URTIs had no impact on the PK/PD properties of TI.
  - the PK properties of TI, as assessed by FDKP $AUC_{0\text{-}240\ min}$ (the primary endpoint), and the PK parameters of FDKP and insulin were similar during URTI and post-URTI
  - the PD properties of TI, as assessed by unadjusted and baseline-corrected blood glucose C_{max} and C_{min}, were similar during URTI and post-URTI
- In terms of safety and tolerability, there were no deaths, no premature discontinuations, and no AEs (including hypoglycemia), indicating that TI was well tolerated.
- However, these study findings are limited to diabetes patients with URTI, as patients with lower respiratory tract infection were not studied.
- If patients with T1DM or T2DM are unable to conduct proper inhalation, they should administer their insulin subcutaneously.

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DISCLOSURES

Levin: Novo Nordisk, Inc. – advisory panel, consultant, research support, speakers bureau; Sanofi US, Inc. – advisory panel, consultant, research support; Eli Lilly and Company – research support, speakers bureau; Amylin Pharmaceuticals, Inc. – research support, speakers bureau; GlaxoSmithKline – speakers bureau; Boehringer Ingelheim – speakers bureau.

Heinemann: Science & Co. – employment; Biodel, Eli Lilly, Halozyme, Novo Nordisk, Sanofi – advisory panel; Profil Institut für Stoffwechselforschung, Neuss, Germany – partner; Profil Institut for Clinical Research, San Diego, CA, USA – partner.

Boss: Sanofi US, Inc. – employment; MannKind – employment at the time the study was conducted.

Rosenblit: Abbott (AbbVie) – research support, speakers bureau; Lilly – research support, advisory board; Merck – research support, speakers bureau; Novo Nordisk – research support, speakers bureau; Janssen – speakers bureau, advisory board; Amgen, Dexcom, MannKind, Merck, Orexigen, Pfizer – research support; AstraZeneca, GSK, KOWA, Merck, Takeda, Pfizer – speakers bureau.