

A Phase 1, Open-Label Study of the Effect of Albuterol or Fluticasone on the Pharmacokinetics of Inhaled Technosphere® Insulin Inhalation Powder in Healthy Subjects

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ABSTRACT

The effects of acute albuterol or chronic fluticasone pre-treatment on the pharmacokinetics (PK) of Technosphere® Insulin (TI) Inhalation Powder were evaluated in nonasthmatic healthy subjects with normal lung function in a single-dose, 3-way crossover study. Eleven men and 2 women (43±10 years; 84±13 kg; and 27.2±3.1 BMI) received a single dose (45 U) of TI alone, after a single 180-µg dose of albuterol, and after fluticasone dosing for 7 days (440 µg twice daily for 6 days and 1 dose on Day 7). Twelve of the 13 subjects completed the study.

PK parameters were calculated from concentrations of C-peptide corrected insulin (see Figure) and fumaryl diketopiperazine (FDKP), the main TI powder component. The geometric mean insulin AUC₀₋₃₆₀ was not significantly different for TI alone (4820 µU•min/L) when compared to dosing after albuterol (4491 µU•min/L) or fluticasone (4415 µU•min/L). The similar range in the AUC₀₋₃₆₀ geometric mean %CV for the 3 treatment regimens (48.5% to 60.2%) indicated comparable insulin exposure. There were no statistically significant treatment differences in insulin AUC_{0-t}, AUC_{0-inf}, C_{max} or t_{1/2} between the 3 regimens. Fluticasone preadministration did not alter FDKP PK; however, albuterol pre dosing caused a slight, statistically significant increase in FDKP C_{max} and AUC; neither increase was clinically relevant.

The most frequent adverse event was cough, which was dry, mild in intensity, and occurred within 10 minutes of TI inhalation. No clinically relevant findings were observed in vital signs, clinical labs or physical examination.

Preadministration of albuterol or fluticasone did not affect the PK of insulin delivered via TI. Single doses of TI administered alone, or after albuterol or fluticasone, were well tolerated.

INTRODUCTION

MannKind Corporation is conducting a clinical development program with Technosphere® Insulin Inhalation Powder (AFREZZA™) for the treatment of hyperglycemia in adults with type 1 or type 2 diabetes mellitus. Because TI is delivered by the pulmonary route, other inhaled medications, if administered in succession, may affect the pharmacokinetic (PK) profile of insulin or the excipient FDKP. This study evaluated the effect of 2 frequently prescribed inhaled medications, albuterol and fluticasone, on the PK profiles of insulin and FDKP after administration of TI.

OBJECTIVES

The objectives of this trial were to investigate the effects of inhaled albuterol and inhaled fluticasone on the pharmacokinetics of TI in healthy volunteers with normal lung function when receiving: a single dose of inhaled albuterol 5 minutes before inhalation of TI; or, repeated dosing of inhaled fluticasone (twice daily for 1 week) with the last dose administered 5 minutes before inhalation of TI.

The primary objectives were to characterize the PK of inhaled TI as assessed by:

- Serum insulin area under the concentration-time curve from time 0 to 360 minutes after dosing (AUC₀₋₃₆₀)
- Serum fumaryl diketopiperazine (FDKP) area under the concentration-time curve from time 0 to 480 minutes after dosing (AUC₀₋₄₈₀)

The secondary objectives were to evaluate:

- Additional PK parameters of serum insulin and FDKP
- Safety parameters of TI

MATERIALS AND METHODS

This study was a prospective, controlled, open-label, 3-period trial utilizing a hyperinsulinemic-euglycemic clamp procedure in 13 healthy men and women with normal lung function (FEV₁ and FVC of ≥80% predicted value). Screening lab tests were within normal range.

Eleven men and 2 women were enrolled. Demographics included a mean age of 42.8 (± 9.7) years and a BMI of 27.2 (± 3.1) kg/m².

The clinical study consisted of 5 clinic visits:

- 1 screening visit (Visit 1)
- 3 treatment visits (Visits 2, 3, and 4)
- 1 follow-up visit (Visit 5)

The screening visit (Visit 1) occurred 1 to 21 days before the first treatment visit (Visit 2). Each treatment visit was separated by a period of at least 3 days. The follow-up visit (Visit 5) occurred 5 to 10 days after the last treatment visit (Visit 4).

MATERIALS AND METHODS (CONTINUED)

Each treatment visit had a 10- to 12-hour hyperinsulinemic (insulin lispro)-euglycemic clamp procedure to suppress endogenous insulin. Blood glucose (BG) was monitored to ensure subject safety and adjust the glucose infusion to maintain BG concentration at the clamp target of 5.0 mmol/L ± 0.6 mmol/L (90 ± 10 mg/dL). PK samples were collected to determine blood glucose (BG), serum insulin, insulin lispro, C-peptide, and FDKP concentrations.

At Treatment 1/Visit 2, subjects received 45 U of inhaled TI while undergoing a 10- to 12-hour hyperinsulinemic (insulin lispro)-euglycemic clamp.

At Treatment 2/Visit 3, while undergoing a 10- to 12-hour hyperinsulinemic (insulin lispro)-euglycemic clamp procedure, subjects received 180 µg of albuterol, followed approximately 5 minutes later by 45 U of inhaled TI.

Treatment 3/Visit 4 occurred over 7 days. On Days 1 through 6, the subjects were to take 440 µg dose of fluticasone BID. On Day 1, the first dose was administered at the clinic and the second dose at home. Subjects returned to the clinic once between Day 1 and Day 5 to review AEs, changes in concomitant medication, and the morning dose of fluticasone. On the nonclinic visit Days, subjects were contacted by telephone each day and changes in concomitant medication, adverse events (AEs), and instructions to take 1 dose of fluticasone were reviewed over the telephone. Subjects returned to the clinic on Day 6 and remained overnight until Day 7.

The evening dose of fluticasone was administered at the clinic on Day 6 and the final dose was administered on the morning of Day 7. The final dose was followed approximately 5 minutes later by administration of 45 U of inhaled TI while subjects were undergoing a 10- to 12-hour hyperinsulinemic (insulin lispro)-euglycemic clamp.

Primary PK Parameters: Insulin AUC₀₋₃₆₀, FDKP AUC₀₋₄₈₀

Secondary PK Parameters: Insulin and FDKP C_{max}, t_{max}, t_{1/2}

Other measurements included:

- Serum insulin lispro concentrations
- Insulin lispro infusion rates
- Glucose concentrations (for subject safety)
- C-peptide concentrations

Safety

- Adverse events (AEs)
- Serious AEs (SAEs)
- Cough
- Clinical laboratory tests

Statistical Methods

Pharmacokinetic parameters were determined by non-compartment methodology assuming a linear system using WinNonlin® v5.2. Between-visit differences (treatment differences) in C_{max} and AUC₀₋₃₆₀ of baseline corrected serum insulin and C_{max} and AUC₀₋₄₈₀ of serum FDKP were analyzed after log_e transformation of data via analysis of variance (ANOVA) with treatment included as fixed effect in the model and subject as random effect. All statistical analyses were performed using SAS® v8.2 (SAS® Institute, Cary, NC).

Primary Pharmacokinetic Analysis

Between-visit differences (treatment differences) in C_{max} and AUC₀₋₃₆₀ of C-peptide-corrected serum insulin and C_{max} and AUC₀₋₄₈₀ of serum FDKP were analyzed after log_e transformation of data using an ANOVA with treatment included as fixed effects in the model and subject as random effect.

The difference in least squares means between pairs of visits/treatments and associated 90% confidence interval (CI) were determined. Back-transformation provided a point estimate (geometric mean ratio) and conventional 90% CI and gave an indication of differences between pairs of visits/treatments.

Safety Analysis

For visit/treatment, the incidence (number and percentage of subjects) of TEAEs was summarized by system organ class (SOC), preferred term, and treatment; SOC, preferred term, treatment, and maximum severity; and SOC, preferred term, treatment, and causal relationship to the investigational medicinal product (IMP); and relationship to trial-related procedures and trial device.

RESULTS

Pharmacokinetic Results

After administration of 45 U of TI alone and after either albuterol or fluticasone, exposure to insulin as judged by AUC₀₋₃₆₀ was comparable following the 3 treatment regimens (Table 1, Figure 1). The geometric mean AUC₀₋₃₆₀ was slightly greater but not significantly different for subjects when TI was administered alone (4820 mU•min/L) compared to when it was administered after either albuterol (4491 mU•min/L) or fluticasone (4415 mU•min/L). Within the variability of this measurement, the 3 treatment regimens produced comparable insulin exposure.

Preadministration of albuterol or fluticasone did not affect the PK insulin when delivered using TI. There were no statistically significant treatment differences in AUC₀₋₃₆₀, C_{max}, or t_{1/2} for TI after albuterol and after fluticasone compared with TI alone.

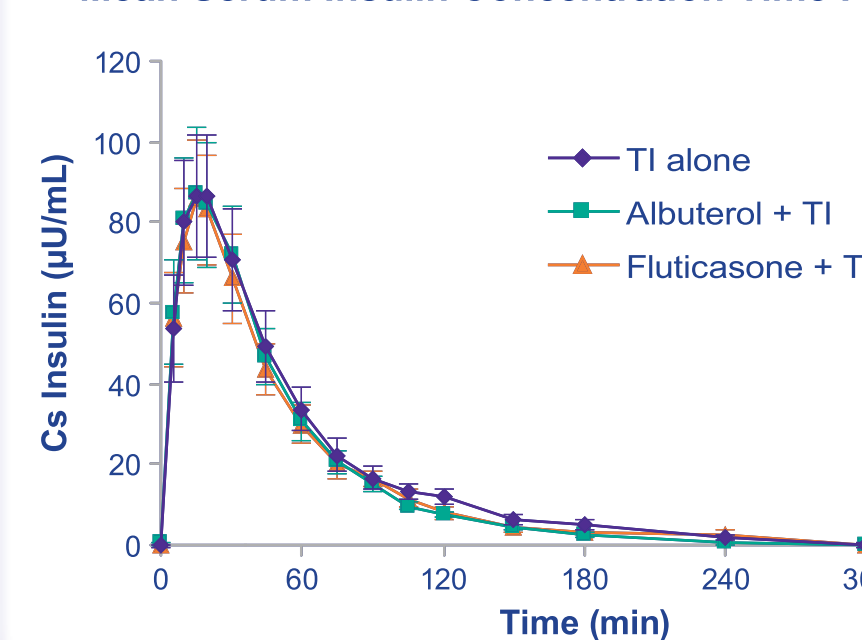
TABLE 1

Statistical Comparison of Insulin Pharmacokinetic Parameters (ANOVA Results; PK Population)					
Parameter	Treatment Regimen Comparison	Geometric Mean ^a		Geometric Mean Ratio (%) (90% CI)	p Value
		Test	Reference		
AUC ₀₋₃₆₀ (µU•min/L)	TI after albuterol : TI alone	4490.7	4819.8	93.17 (79.14 – 109.69)	0.4647
C _{max} (µU/L)	TI after albuterol : TI alone	78.562	77.746	101.05 (86.05 – 118.66)	0.9122
t _{1/2} (min)	TI after albuterol : TI alone	31.4	33.3 ^b	94.11 (78.45 – 112.90)	0.5721
AUC ₀₋₃₆₀ (µU•min/L)	TI after fluticasone : TI alone	4414.7	4819.8	91.59 (77.80 – 107.83)	0.3656
C _{max} (µU/L)	TI after fluticasone : TI alone	75.405	77.746	96.99 (82.60 – 113.89)	0.7469
t _{1/2} (min)	TI after fluticasone : TI alone	30.8	33.3 ^b	92.48 (77.09 – 110.94)	0.4677

^a n=12 unless stated
^b n=10

FIGURE 1

Mean Serum Insulin Concentration-Time Profiles



After administration of 45 U of TI alone and after either albuterol or fluticasone, exposure to the excipient (FDKP) as judged by AUC₀₋₄₈₀ was comparable after the 3 treatment regimens (Table 2, Figure 2). The geometric mean AUC₀₋₄₈₀ was numerically greater but not clinically different for subjects when TI was administered after albuterol — 42606 ng•min/mL compared with 37099 and 38291 ng•min/mL after TI alone and TI administered after fluticasone, respectively.

For AUC₀₋₄₈₀, a statistically significant difference was identified for TI after albuterol compared to TI alone (p = 0.0390). This difference was not viewed as being clinically significant.

Safety Results

At least 1 Treatment Emergent Adverse Event (TEAE) was experienced by each of the 13 subjects during the study. The most common TEAE was mild cough reported by 12 of the 13 subjects (92%). 6 subjects (46%) experienced headache. All other TEAEs were reported by 1 subject each.

No clinically relevant findings were observed for vital signs, laboratory parameters, or the physical examination. Most TEAEs were assessed as mild and the majority were considered certainly related to the IMP. None of the subjects had a study-device-related TEAE. Six subjects experienced 12 TEAEs related to study procedure. No deaths, SAEs or AEs leading to discontinuation occurred during the study.

RESULTS (CONTINUED)

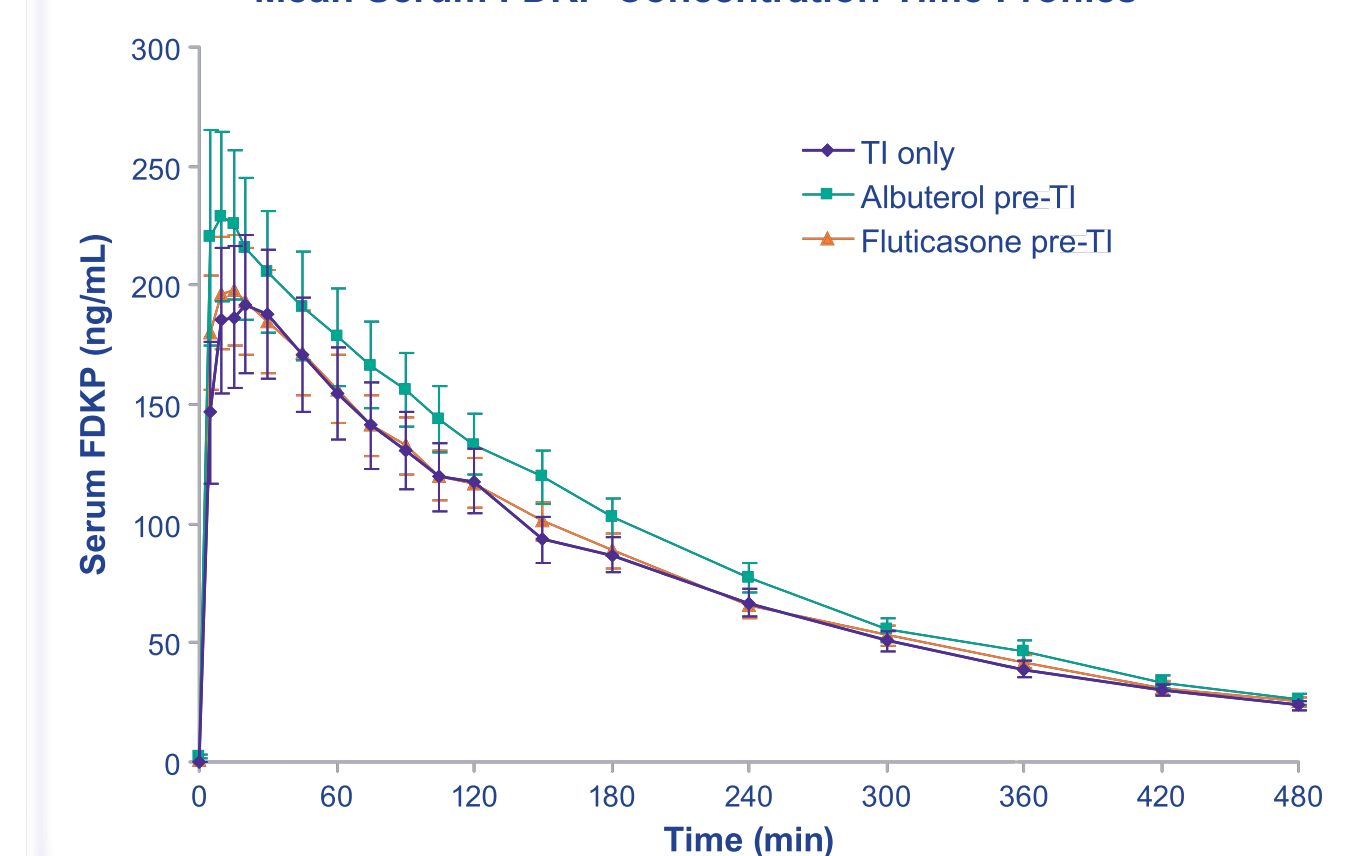
TABLE 2

Statistical Comparison of FDKP Pharmacokinetic Parameters (ANOVA Results; PK Population)					
Parameter	Treatment Regimen Comparison	Geometric Mean ^a		Geometric Mean Ratio (%) (90% CI)	p Value
		Test	Reference		
AUC ₀₋₄₈₀ (µU•min/L)	TI after albuterol : TI alone	42605.9	37099.4	114.84 (103.1 – 127.97)	0.0390
C _{max} (µU/L)	TI after albuterol : TI alone	232.556	191.459	121.47 (102.7 – 143.67)	0.0593
t _{1/2} (min)	TI after albuterol : TI alone	152.5	159.9	95.36 (88.91 – 102.27)	0.2559
AUC ₀₋₄₈₀ (µU•min/L)	TI after fluticasone : TI alone	38291.3	37099.4	103.21 (92.62 – 115.01)	0.6209
C _{max} (µU/L)	TI after fluticasone : TI alone	202.500	191.459	105.77 (89.42 – 125.10)	0.5722
t _{1/2} (min)	TI after fluticasone : TI alone	168.1	159.9	105.13 (98.03 – 112.75)	0.2321

^a n=12 unless stated
 ANOVA = Analysis of Variance

FIGURE 2

Mean Serum FDKP Concentration-Time Profiles



CONCLUSIONS

Pharmacokinetics

In normal healthy volunteers, preadministration of albuterol or fluticasone did not affect the PK of insulin when delivered using TI.

Preadministration of fluticasone did not affect the PK of FDKP when delivered using TI. However, preadministration of albuterol caused a slight increase in the FDKP C_{max} and AUC but did not affect the half life. The increase in AUC was statistically significant, but neither increase was clinically relevant.

While there was a slight decrease in mean insulin exposure after albuterol, there was a slight increase in mean FDKP exposure. This anomaly falls within the magnitude of the known variability of insulin and FDKP exposure after administration of TI. In another study with exactly the same design in healthy subjects (MKC-TI-113), the mean exposure to FDKP was essentially identical for both treatments (after-albuterol exposure was actually 2% lower, Poster 522-P).

Safety

Single doses of 45 U of TI administered alone, or after albuterol or fluticasone, were well tolerated. The most frequently reported TEAE was cough, which was mild in intensity and occurred within 10 minutes of inhalation; this is typical across all clinical studies using TI.

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