

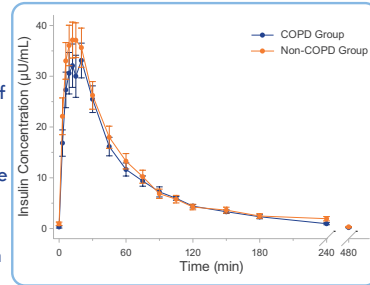
Pharmacokinetics of Technosphere® Insulin Unchanged in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background and aims: The rate and extent of insulin exposure have been shown to be decreased by approximately 20% to 50% in subjects with chronic obstructive pulmonary disease (COPD) with the use of inhaled insulin. **Materials and methods:** The pharmacokinetics (PK) of Technosphere® Insulin (TI), a rapid-acting insulin for pulmonary delivery, was evaluated in an open-label, single-dose, euglycemic glucose clamp study in 37 non-diabetic, non-smoking healthy subjects (n = 19; Baseline mean ± SD aged 51 ± 14 years; BMI 29 ± 3 kg/m²; forced expiratory volume in 1 second [FEV₁] 3.5 ± 1 L) and subjects with COPD (n = 17; aged 60 ± 9 years; BMI 29 ± 5 kg/m²; FEV₁ 2.6 ± 0.8 L). **Results:** Thirty-four subjects were age-, gender-, and BMI-matched. One COPD subject was excluded. Each subject received a single dose of 30 U of TI via inhalation. Serial blood samples were drawn for insulin and C-peptide concentration determination until 480 minutes post-dose. Insulin concentrations were C-peptide corrected to account for endogenous insulin, and C-peptide corrected values were used for PK parameter estimation. There was no statistically significant difference in absorption in the two groups. Mean peak insulin was 34.7 and 39.5 µU/mL (p = 0.285) with a median time to maximum insulin concentration of 15 and 12 minutes (p = 0.241) in the COPD and non-COPD groups, respectively. Mean insulin exposure from time 0 to 240 minutes post-dose (AUC₀₋₂₄₀) was 2037 and 2270 µU/mL·min (p = 0.469) for the COPD and non-COPD groups, respectively. Dosing was well tolerated. **Conclusion:** These results indicate that the characteristic absorption pattern of TI is not significantly altered in the COPD population.



BACKGROUND AND AIMS

The rate and extent of insulin exposure has been shown to be decreased by approximately 20% to 50% in subjects with COPD, with the use of inhaled insulin.¹ The relatively high prevalence of COPD in subjects with diabetes, combined with evidence that such patients may develop underlying lung disease related to chronic hyperglycemia,^{2,3} warrants that the effect of COPD on insulin PK be examined when insulin is administered via the lung. This study was conducted to compare insulin PK in subjects with and without COPD following administration of TI, a novel, inhaled, regular human insulin for pulmonary delivery.

MATERIALS AND METHODS

Study Population

This was a single-dose, open-label, parallel, controlled, euglycemic glucose clamp trial of TI in age, gender, and BMI-matched, nondiabetic, nonsmoking subjects with and without COPD. COPD criteria included: diagnosis of COPD (emphysema or chronic bronchitis); prebronchodilator: FEV₁ ≥ 50% of predicted (National Health and Nutrition Examination Survey [NHANES] III), TLC ≥ 80% of predicted (Intermountain Thoracic Society [ITS]), and DL_{CO} (uncorrected) > 50% (Miller); postbronchodilator: FEV₁/FVC < 70%; and one or more of the following: 1) smoking history ≥ 10 years, 2) chronic cough present intermittently or daily, with or without sputum production, and not attributable to a known cause, 3) dyspnea on exertion. Criteria for subjects without COPD included: pre-bronchodilator FEV₁ ≥ 70% of predicted (NHANES III), TLC ≥ 80% of predicted (ITS), and DL_{CO} (uncorrected) > 80% (Miller). The study was approved by the local ethics committee, and all subjects gave their written informed consent prior to starting the study.

Study Procedures

The trial was comprised of 3 clinic visits: Screening, Treatment, and Follow-up. Following an overnight fast, the subjects received an intravenous infusion of insulin lispro to suppress endogenous insulin production. This infusion was continued until the end of the study. A variable dextrose infusion was administered to regulate blood glucose (BG) and to keep subjects BG levels at target range (100 ± 18 mg/dL for the first 5 subjects and 80 ± 15 mg/dL for the remainder of the subjects). During a run-in period, subjects were stabilized at the target glycemic range. Blood glucose was monitored every 10 minutes from 2 hours prior to drug administration until the end of the clamp procedure. Following the run-in period, each subject received a single dose of 30 U of TI. The clamp procedure lasted approximately 10 hours, from 2 hours before to 8 hours after dosing.

MATERIALS AND METHODS (CONT'D)

Pharmacokinetic Sampling

Serial blood samples were drawn for insulin and C-peptide concentration assay at 180 to 121, 20, and 10 minutes before dosing, at time 0, and 3, 6, 9, 12, 15, 20, 30, 45, 60, 75, 90, 105, 120, 150, 180, 240, 300, 360, 420, and 480 minutes post-dose. Samples were obtained from an indwelling catheter or venous puncture in the vein not receiving the glucose and insulin infusions. Insulin concentrations were determined using an RIA method which did not cross-react with insulin lispro.

Baseline Correction Methodology

Insulin concentrations were C-peptide-corrected to account for incomplete suppression of endogenous insulin. A mixed effect linear regression model (NONMEM, version VI, Icon Development Solutions, Ellicott City, MD) was used to determine the slope and intercept for each individual's C-peptide-insulin relationship, using C-peptide and serum insulin concentrations collected predose and ≥ 6 hours post-dose. The following equation was used:

$$Insulin_{i,j} = Intercept_i + Slope_i \times C-peptide_{i,j}$$

where *i* corresponds to the *i*th individual, and *j* corresponds to the *j*th measurement within that subject. The slope and intercept estimates were used to predict endogenous insulin concentrations for each subject at each timepoint. The predicted endogenous insulin concentration was then subtracted from the measured serum insulin concentration. All resulting negative concentrations were set to 0.

Pharmacokinetic Model and Data Analysis

All insulin concentrations used for the PK analysis were C-peptide-corrected. The following PK parameters were derived using noncompartmental analysis using WinNonlin v 5.2 (Pharsight Corporation, Mountain View, CA): observed peak insulin concentration (C_{max}), time to peak insulin (t_{max}), and insulin exposure as measured by the area under the insulin concentration-time curve from time 0 until *t* minutes post-dose (AUC_{0,t}), calculated by the linear-trapezoidal method.

RESULTS

Study Population

Thirty-nine subjects were enrolled in the study. One enrolled subject was not successfully cannulated for the clamp procedure and never received TI; therefore, the Safety Population contains 38 subjects. Of these subjects, 36 had measurable insulin concentrations at the treatment visit. Summary demographics, other baseline characteristics, and pulmonary function test (PFT) results are presented in Tables 1 and 2.

Table 1. Demographics and Other Baseline Characteristics

Baseline Characteristics	Category/Statistics	COPD (n = 18)	Non-COPD (n = 20)
Age (years)	Mean ± SD	60.2 ± 8.8	51.5 ± 14
Age group (years), n (%)	18-40	1 (5.6)	3 (15.0)
	41-60	5 (27.8)	9 (45.0)
	> 60	12 (66.7)	8 (40.0)
Gender, n (%)	Male	11 (61.1)	13 (65.0)
	Female	7 (38.9)	7 (35.0)
Race, n (%)	Caucasian	14 (77.8)	11 (55.0)
	Black of African Heritage	0	2 (10.0)
	Hispanic	3 (16.7)	7 (35.0)
	Other	1 (5.6)	0
Weight (kg)	Mean ± SD	82.6 ± 15.8	86.9 ± 14.6
Height (cm)	Mean ± SD	170.8 ± 11.4	173.2 ± 11.4
BMI (kg/m ²)	Mean ± SD	28.4 ± 4.9	28.8 ± 3.6

SD = standard deviation
 Note: Percentages are based on the number of subjects in each treatment group in the Safety Population

RESULTS (CONT'D)

Table 2. Baseline Pulmonary Function Test Results (mean ± SD)

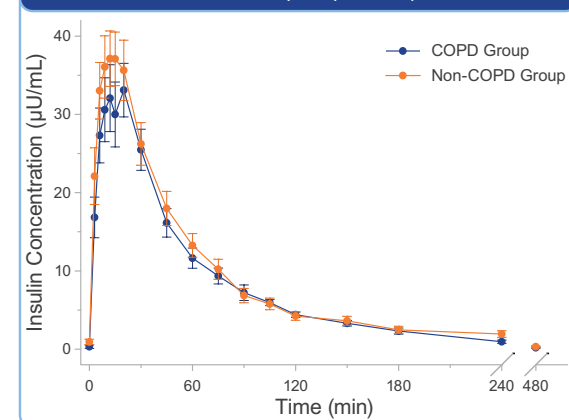
PFT	COPD (n = 18)	Non-COPD (n = 20)
FEV ₁ (L)	2.6 ± 0.8	3.6 ± 1.0
FVC (L)	4.2 ± 1.4	4.6 ± 1.4
FEV ₁ /FVC (%)	62.7 ± 9.7	77.4 ± 4.2
TLC (L)	6.5 ± 1.6	6.3 ± 1.6
Hb-corrected DL _{CO} (mL/min/mm Hg)	24.4 ± 7.0	28.1 ± 7.3

SD = standard deviation
 Note: Percentages are based on the number of subjects in each treatment group in the Safety Population

Insulin Concentrations

The mean insulin concentration-time profiles are shown in Figure 1. On average, the PK profiles of the COPD population were slightly lower around the peak when compared to the non-COPD group; however, within the variability observed, the difference was not considered meaningful.

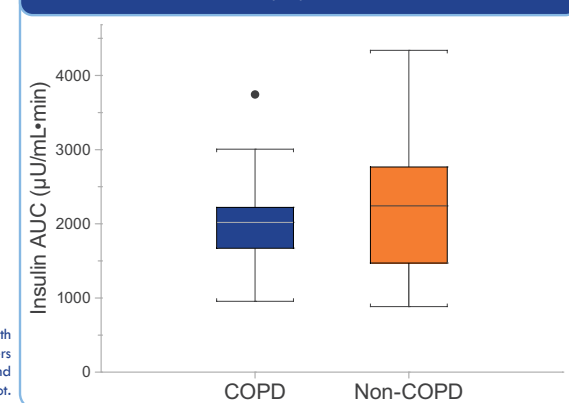
Figure 1. Mean (± SE) Insulin Concentration-Time Profiles by Subject Group



Pharmacokinetic Parameters

The mean insulin C_{max} (Figure 1) and AUC₀₋₂₄₀ (Figure 2) were slightly higher for subjects without COPD compared to subjects with COPD. However, the similar range of parameter values between the groups indicated comparable exposure to TI. The insulin t_{max} was comparable when TI was administered to both groups. The associated variability (%CV) was between 33% and 39% for both parameters in these populations. Insulin pharmacokinetic parameters are presented in Table 3.

Figure 2. Box and Whiskers Plot of Insulin AUC₀₋₂₄₀ by Subject Type



The top and bottom of each box represent the 25th and 75th percentiles of the data. The whiskers extend to 1.5 of the interquartile range, and outlying points are represented by a single dot.

Table 3. Insulin Pharmacokinetic Parameters

Parameter	Statistic	COPD (n = 17)	Non-COPD (n = 19)	Ratio (Non-COPD: COPD)	p Value
C _{max} (µU/mL)	Mean (%CV)	34.7 (39.4)	39.5 (37.4)	1.14	0.285 ^a
t _{max} (min)	Median	15.0	12.0	0.8	0.241 ^b
AUC ₀₋₂₄₀ (µU/mL·min)	Mean (%CV)	2037 (33.6)	2279 (39)	1.12	0.4689 ^a

%CV = percent coefficient of variation
^a 2-sample t test on the natural log transformed insulin C_{max} and AUC₀₋₂₄₀
^b Wilcoxon Rank sum test

RESULTS (CONT'D)

Statistical Analysis

A between-group comparison was performed using a 2-sample *t* test on the natural log transformed insulin C_{max} and AUC₀₋₂₄₀. A between-group comparison of t_{max} was performed using the Wilcoxon Rank Sum test. No statistically significant differences were found between the COPD and non-COPD groups for insulin AUC₀₋₂₄₀ (p = 0.4688), C_{max} (p = 0.285), and t_{max} (p = 0.241).

Subgroup Analysis

Three subjects classified as having COPD did not meet the protocol criteria for FEV₁/FVC ratio. The subjects were granted exemptions based on their histories. A subanalysis performed without these 3 subjects did not alter the PK findings. The parameter estimates based on the subpopulation analysis are presented in Table 4.

Table 4. Insulin Pharmacokinetic Parameters

Parameter	Statistic	COPD (n = 14)	Non-COPD (n = 19)	Ratio (Non-COPD: COPD)
C _{max} (µU/mL)	Mean (%CV)	35.8 (41.4)	39.5 (37.5)	1.1
t _{max} (min)	Median	15	12	0.8
AUC ₀₋₂₄₀ (µU/mL·min)	Mean (%CV)	2079 (34)	2279 (39)	1.1

%CV = percent coefficient of variation

Safety

Fourteen of 18 subjects with COPD and 15 of 20 subjects without COPD reported AEs during the study. The most common TEAE in both groups was mild cough, reported by 12 of 18 subjects with COPD and 14 of 20 subjects without COPD. The cough episodes were typical of those seen after inhalation of a dry powder.

Changes observed from Baseline to Visit 3 in mean FEV₁, FVC, DL_{CO}, and TLC were small and comparable between the subjects with and without COPD (maximum change of 2.7% and 1.4% in the COPD and non-COPD groups, respectively). Unlike subjects without COPD, subjects with COPD had a small decline in FEV₁ immediately (at 18 minutes) after inhalation of TI followed by gradual, spontaneous improvement over the next 8 hours.

No clinically meaningful changes or notable differences in any pre- or post-dose laboratory values in either the COPD or non-COPD groups were observed.

CONCLUSIONS

In this study, insulin pharmacokinetics following administration of Technosphere® Insulin were similar in subjects with and without COPD. A slightly lower insulin exposure, as determined by C_{max} and AUC₀₋₂₄₀, was observed in the COPD group. However, the associated variability of these values and the similar range of values between the two groups indicated comparable insulin exposure. There were no statistically significant differences between the pharmacokinetic parameters for the two groups. This finding is unique for an inhaled insulin product.

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