

ABSTRACT

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Lung Deposition and Absorption of Insulin from Technosphere® Insulin

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Background and aims: A clinical trial in 12 healthy subjects determined the pulmonary concentrations of insulin and fumaryl diketopiperazine (FDKP) using bronchoalveolar lavage (BAL) before and after administration of a rapid-acting insulin, Technosphere® Insulin (TI) Inhalation Powder.

Materials and methods: Each subject received a 60 U dose and had two bronchoscopies at 0.5 and 6 h, or 4 and 8 h, or 0.5 h before dosing and 12 h after dosing. At each bronchoscopy, two independent BAL samples were collected. Serum samples for serum insulin, FDKP, and serum C-peptide were collected at baseline and up to 475 minutes post-dose. Urea concentrations in BAL samples and blood urea nitrogen were measured and used for correcting BAL concentrations (see figure below).

Results: We previously reported a phase 1 trial using ^{99m}Tc-labeled TI inhalation particles. These particles were evenly distributed with approximately 28% to 48% (mean 39.4%) of the ^{99m}Tc TI delivered to the deep lung. In this study, subjects were dosed with 60 U of TI. Concentrations of insulin and FDKP in BAL fluid were corrected for urea BAL to serum concentration ratios. The amount of insulin and FDKP remaining in the lung epithelial lining fluid was highest (21.5 mIU/mL) in the first post-dose BAL samples (0.5 h). By 4 h, levels were 31% of maximum; at 12 h, insulin and FDKP values in BAL were 0.3% and 0.4% of maximum, respectively. Accumulation of insulin and FDKP in the lungs after chronic dosing is unlikely.

Conclusion: Preliminary pharmacokinetic modeling of insulin (see solid line figure below) suggests a two-compartment lung absorption model, one with fast absorption reflected in the plasma profile of insulin. The other compartment reflects reduced absorption, which is presumably due to proteolysis and mucociliary clearance of insulin.

