

A Pharmacokinetic/Pharmacodynamic Model of Inhaled Insulin with Application to Clinical Trial Simulation

Mark T. Marino, MD, Mannkind Corporation

Inhaled Technosphere® Insulin, when delivered via the NexGen device, produces peak levels of insulin within 14 minutes and insulin levels return back toward baseline in 2 hours. To understand the pharmacokinetic and pharmacodynamic relationship of this novel ultra rapid-acting insulin, a model was developed to explain the glucose and insulin kinetics from a study in healthy normal volunteers.

The model was developed in 2 software packages: Berkeley Madonna® and NONMEM®. Berkeley Madonna® was used to develop the components of the model and initial parameter estimates for the differential equations and NONMEM® (Nonlinear Mixed Effects Modeling Software) was used to optimize the model as well as provide population mean predictions and individual parameters. Two different dosing regimens were used to develop the model, one a meal challenge without insulin administration and the other with different doses of inhaled Technosphere® Insulin. The model in NONMEM® contained parameters for meal absorption (0.036 min^{-1}), insulin suppression of hepatic glucose production ($90 \pm 5 \text{ mg/dl/min}$), glucose-stimulated insulin secretion ($8.4 \pm 5.2 \text{ } \mu\text{U/ml/min}$), glucose elimination (0.03 min^{-1}), and insulin elimination (0.2 min^{-1}).

The model was able to describe both the mean individual glucose and insulin concentration time curves for the meals and the meal challenges administered with insulin as shown below. This model can be used to simulate large-scale clinical trials with different doses and dose regimens of Technosphere® Insulin.

