Enhancing Clinical Utility of Model-based Pharmacokinetic Profiles of Subcutaneous Insulin Through Interactive Visualization

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Objectives: Optimal insulin therapy in diabetics delivers higher insulin concentration when glucose is elevated around mealtimes and lower insulin concentration between meals and during nighttime. The goal was to integrate pharmacokinetic (PK) models of insulin formulations with diverse onset and duration of action characteristics to enable simulation of insulin concentration-time profiles following subcutaneous administration of insulin. An interactive tool was applied to provide easily accessible visualization.

Methods: A PK model was developed using clinical studies with healthy volunteers or diabetics and implemented in a nonlinear mixed effects modeling program (NONMEM 7.3). The model was parameterized to reflect the absorption of rapid-, short-, and long-acting formulations, including insulin lispro, regular insulin, insulin isophane (NPH), and pre-mixed preparations (NPH with regular insulin (Mix 70/30), and lispro protamine with insulin lispro (Mix 50/50, Mix 75/25)). Influences on the concentration-time profile, including weight-based dosing, the effect of body weight (WT) on volume of distribution, and time of insulin administration relative to meal were incorporated into the model. Simulations were generated using differential equations solved in R and accessed through a customized web browser interface built with the Shiny package [1].

Results: The interactive tool displayed predicted insulin concentration-time profiles that reacted to changing user specified values for model variables such as formulation, dose, daily administration frequency, WT, concomitant insulin therapy, observation period, and number of doses. PK profiles were simulated for typical insulin regimens, single and multiple doses, and weight distributions representative of Asian and Western populations.

Conclusions: Modeling enabled informative visualization of the concentration-time profiles of multiple insulin formulations. A customized web browser interface tool was an efficient way to quickly convey and interactively explore many insulin PK simulations.

References: