A PKPD Model-Based Meta-Analysis of Subcutaneously Administered Insulins in Clinical Glucose Clamp Studies

Craig Fancourt, Jos Lommerse, Bhargava Kandala, Thomas Kerbusch, Sandra A.G. Visser

1Certara Strategic Consulting, Oss, The Netherlands; 2Merck & Co. Inc., Kenilworth, NJ, USA

Objectives: A model-based meta-analysis (MBMA) of subcutaneously (SC) administered insulins in clinical glucose clamp studies was conducted to develop pharmacokinetic (PK) and glucose metabolism (PD) models to support systems pharmacology model development and clamp trial design.

Methods: Insulin concentration and glucose infusion rate time-action profiles were digitized for 3 to 15 published trial arms per Standard of Care insulin (lispro, RHI, glargine, and degludec) and patient population (Type 1/2 diabetics (T1DM/T2DM), and non-diabetics (ND)).

A one-compartment PK model (Figure) with two sequential absorption compartments and constant endogenous infusion was applied to estimate apparent absorption rate, elimination rate, and volume. A second parameterization used clearance and volume from IV clamp studies [1,2], allowing estimation of SC bioavailability (ex-degludec). Both non-linear mixed effects models implemented variability as inter-trial baseline, and inter-arm absorption rate and bioavailability. The PD model (Figure) utilized an insulin effect compartment (for time-delay), which acts on a Hill function predicting GIR [1].

Results: Both PK models adequately described the database. Across patient populations, absorption half-life was 1.4–2.5 hr (lispro), 2.7–4.0 hr (RHI), 10.7–14.7 hr (glargine), and 21.5–25.4 hr (degludec). The half-life for insulin effect delay was 33 min, and for elimination was 5 min (ex-degludec). The PD model EC50 in ND/T1DM/T2DM was 210, 270, 480 pM (ex-degludec), and 9.0, 14.7, 38.8 nM (degludec), respectively, using GIRmax 900 mg/min (ND) and 750 mg/min (T1/2DM) from IV clamp studies [1].

Conclusions: A curated database of SC insulins in clinical glucose clamp studies was modeled, affirming that lispro, RHI, and glargine time-action profiles can be explained by the same structural PKPD model with differences in bioavailability and absorption. The models are useful both as comparators and hypothetical backbones for novel insulins.

References:
2. Kandala et al., ACOP 2015.

Figure: PKPD structure for SC Insulin Glucose Clamp MBMA.