A Model-Based Meta-Analysis of Insulin PK-PD in Glucose Clamp Studies of Diabetes Mellitus Type 1 and Non-Diabetic Human Subjects

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Objectives: A model-based meta-analysis (MBMA) of hyperinsulinemic glucose clamp clinical data was conducted to quantitatively characterize differences in standard insulin pharmacokinetics (PK) and glucose metabolism (PD) in Type 1 diabetics (T1DM) compared to non-diabetics (ND).

Methods: A literature search identified 21 clinical study publications examining glucose disposal rates (GDR) under different insulin infusion rates (IIR) and steady-state insulin ([INS]) and glucose ([GLC]) concentrations among T1DMs, with or without ND control groups (two seminal ND-only studies were included to support ND modeling). The relationship between [INS] and IIR and GDR was described by a steady-state mechanistic PK-PD clamp model [1]. Parameters were estimated by fitting the literature data using non-linear mixed effects techniques. Models were explored using different random (study) and population effects (ND vs. T1DM). Visual predictive check simulations ensured central tendencies and variability in the relationships were captured.

Results: The PK model’s insulin clearance was saturable, resulting in total clearance declining with increasing [INS]. The non-specific clearance mechanism was dominant under high [INS] conditions. No population differences in insulin PK were identified.

A population difference was estimated for the PD model’s maximum insulin-dependent glucose clearance and half-maximal insulin-mediated disposition. Compared to NDs, the [INS] required to maintain a given GDR was increased 1.5-fold among T1DMs, and the maximum GDR for a given fixed [GLC] target level was reduced 13% among T1DM subjects. As shown in Figure 1, together these effects result in slightly higher GDR among NDs than in T1DM, with the difference depending on both [GLC] and [INS].

Conclusions: The clamp PK-PD model successfully described the relationship between IIR and [INS] and between GDR and [INS] and [GLC] for T1DM and ND populations. Simulations based on the final model were used to plan, and were ultimately in agreement with, a clinical clamp study of T1DM subjects [2].

References:
Figure 1: Visual Predictive Check of GDR vs IIR for Final PD Model. Observed data are grouped into four panels by population type and if the glucose goal was above or below 100mg/dL; the mean projection is shown as a black line bounded by a grey polygon representing the 90% prediction interval; the size of the symbols are proportional to the relative number of subjects in a particular trial arm while the color of the symbols indicate glucose target levels.