A Dynamic Model-Based Analysis of a Multi-Level Glycemic Clamp Study of Regular Human Insulin in T1DM Subjects

Bhargava Kandala*, Craig Fancourt, Kuenhi Tsai, Marian Iwamoto, Christina Canales, Amy Cheng, Michael Crutchlow, David E. Kelley, Sandra A.G. Visser

Merck & Co., Inc., Kenilworth, NJ USA

Objective: Hyperinsulinemic clamp studies assess non-linear insulin pharmacokinetics (PK) and pharmacodynamics (PD) during steady-state conditions. This investigation aimed to determine if a well-sampled clamp experiment can be used to identify dynamic insulin PK-PD parameters by utilizing the entire clamp study time-course.

Methods: 12 T1DM subjects received infusions of regular human insulin (RHI) and glucose during a 3-period multi-glycemic (200, 75, and 300 mg/dL) 9-hr clamp study. During period one, the insulin infusion rate (IIR) was varied to achieve a target glucose infusion rate (GIR) of 5 mg/kg/min. During periods 2-3, IIR was fixed at steady state IIR from period one, and GIR was varied to achieve the set glucose target. Two dynamic insulin-glucose models were fit using nonlinear mixed effects (NONMEM) to the PK-PD data: a) a “dynamic” steady-state (DSS) model based on a PK-PD model-based meta-analysis (MBMA) of the T1DM clamp literature [1]; b) a modified integrated glucose-insulin (IGI) model [2] with insulin secretion removed for T1DM, and peripheral glucose removed for improved fit.

Results: Statistical analysis of (GIR) and glucose revealed that steady-state was achieved during the final 30 minutes of each 3-hr clamp period. The mean steady-state RHI clearance and GIR were in agreement with the literature T1DM model [1]. Comparing the DSS and IGI model fits, both models yielded reasonable and comparable estimates of key insulin and glucose PK-PD parameters.

Conclusions: Both the DSS and IGI models could describe the RHI clamp data well and provided distinct advantages in the quantification of RHI PK-PD. These models provide a modeling platform to analyze and simulate future trials under both clamp and non-steady state conditions in the development of novel insulins.

References:
[1] Burroughs et al., ACOP 2015