Development of a Joint PKPD Model of the Hyperinsulinemic Glucose Clamp

Craig Fancourt*, Chandni Valiathan, Dan Tatosian, Carolyn Cho, Sandra A.G. Visser
Merck & Co., Inc., Kenilworth, NJ USA

Objectives: The hyperinsulinemic glucose clamp is an experimental platform to measure insulin sensitivity by infusing exogenous insulin and glucose to measure insulin effect on whole-body glucose disposal rate (GDR) during homeostasis. We developed a pharmacokinetic (PK) - pharmacodynamic (PD) model of the hyperinsulinemic clamp that is physiologically plausible and can fit clinical data.

Methods: The PK model consisted of saturable binding of insulin to the insulin receptor, expressed as target-mediated drug disposition, which at steady-state results in Michaelis-Menten saturable clearance, plus a non-specific linear first-order clearance. The PD model consisted of (1) non-insulin mediated glucose disposal (constant glucose clearance); (2) non-linear and saturable insulin mediated glucose uptake (an insulin Emax model with Hill coefficient); and (3) glucose auto-inhibition of glucose uptake (a glucose Emax model, which modulates the sum of (1) and (2)).

This PKPD model was simultaneously fitted to data from [1], which studied 22 healthy male subjects at four porcine insulin infusion rates (0, 20, 60, 400 mU/min/m²) and four glucose clamp levels (90, 160, 250, 400 mg/dL), using non-linear least-squares on log-transformed steady state insulin concentrations and GDR measurements.

Results: The model fit (Figure) was good and all parameters could be estimated. For the PK model, non-specific insulin clearance was 5.1 mL/kg/min, maximum IR clearance was 11.2 mL/kg/min, and Kd of insulin for its receptor was 716 pM. For the PD model, maximum non-insulin mediated clearance was 2.8 mL/kg/min, maximum insulin-mediated clearance was 11.1 mL/kg/min, insulin concentration at half-maximal GDR was 552 pM with a Hill coefficient of 2.0, and glucose concentration at half-maximal GDR was 353 mg/dL.

Conclusions: A joint PKPD mechanistic model can describe and explain insulin PK and action during the hyperinsulinemic clamp. This model was successfully applied to investigate differences in PKPD between healthy and T1DM subjects [2].

References:
Figure. PK (top) and PD (bottom) model fit to clinical clamp data. Open circles are data, closed circles are model predictions at measured values, and lines are model predictions at nominal values.

PK Model:
- $HR = [INS] \cdot CL_{INS}$
- $CL_{INS} = CL_{INS0} + \frac{CL_{INS0}}{1 + [INS]}$
- $GDR = (GLC) \cdot CL_{GLC}$
- $CL_{GLC} = \frac{CL_{GLC0} \cdot [INS]^m}{INS0 + [INS]^m}$

PD Model:
- Glucose Disposal Rate
- Insulin Clearance