Semi-mechanistic modeling of dog tracer study data to quantify insulin action on glucose disposal rate and inhibition of lipolysis

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Objectives: To quantify insulin action on glucose disposal and inhibition of lipolysis for Regular Human Insulin (RHI), using euglycemic clamp data combined with glucose tracer in healthy dogs.

Methods: Time-course insulin concentration, labeled glucose and non-esterified fatty acid (NEFA) data were available from healthy dogs undergoing a euglycemic clamp with continuous IV infusion of regular human insulin (RHI) at 7 dose levels (0.6 – 12 pmol/kg/min, n=8 per arm). A semi-mechanistic PKPD model was developed describing the effects of insulin on labeled glucose and NEFA over time. Steady state PKPD relationships were predicted for the glucose disposal rate (GDR) and effect on lipolysis.

Results: The PK was described with a 1-compartment model (CL= 0.2 L/min, V=6.8 L) and was used as input to the PD model. The model consisted of insulin receptor binding (RO), stimulation of GDR, and inhibition of NEFA production, followed by release of NEFA inhibition of GDR. All endpoints were modeled simultaneously over time and did not demonstrate significant bias. Predictions were made for endpoints at end of infusion and time to steady state was assessed. It was demonstrated that suppression of lipolysis by 80% increases GDR twofold.

Conclusions: This analysis provides novel insights in the insulin PKPD relationship in adipose tissue and skeletal muscle in dogs. Further analysis of hepatic glucose production will enable comparisons of tissue selectivity of standard vs. novel insulin therapies.


Figure: A) PKPD model and B) predictions of clamp readouts over a range of RHI concentrations.