Modeling Pharmacokinetics and Pharmacodynamics of Glucagon for Simulation of the Glucometabolic System in Patients with Type 1 Diabetes.

The goal of this thesis was to develop a pharmacokinetics/pharmacodynamics (PK/PD) model for glucagon. The proposed PD model included multiplication of the stimulating glucagon effect and inhibiting insulin effect on the endogenous glucose production (EGP). Moreover, the concentration-response relationship of glucagon and EGP was characterized by a non-linear function, where the response saturated for high concentrations of glucagon. The novel EGP model extended Hovorka's glucoregulatory model to include the effect of glucagon. The PK/PD model described both regular glucagon and a novel glucagon analogue in healthy dogs. The extended glucoregulatory model translated to the human species and described glucose-insulin-glucagon dynamics in healthy subjects and patients with type 1 diabetes (T1D). The extended glucoregulatory model was successfully validated by leave-one-out cross-validation in seven T1D patients which justified its use for simulations. The final model parameters were estimated from three to four datasets from each patient. The validated extended glucoregulatory model was used for in silico studies. The model replicated a clinical study of the effect of glucagon at varying insulin levels. The simulations also suggested new glucagon doses to be tested in a similar in vivo study to provide new insight to the relationship between insulin, glucagon, and EGP. Finally, the model was used to conduct a large original simulation study investigating an insulin dependent glucagon dosing regimen for treatment of insulin-induced mild hypoglycemia.