Modelling the glucose-insulin-glucagon dynamics after subcutaneous administration of native glucagon and a novel glucagon analogue in dogs

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MODELLING THE GLUCOSE-INSULIN-GLUCAGON DYNAMICS AFTER SUBCUTANEOUS ADMINISTRATION OF NATIVE GLUCAGON AND A NOVEL GLUCAGON ANALOGUE IN DOGS

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Background

Zealand Pharma has invented a glucagon analogue, ZP-GA-1, with increased stability in liquid formulation for treatment of hypoglycemia. A pharmacodynamic (PD) model is needed to compare ZP-GA-1 with marketed glucagon. We aim to develop a model of the complex glucose-insulin-glucagon dynamics based on physiology and data.

Discussion

Profile likelihood analysis revealed that some model parameters were unidentifiable (dark grey) due to limitations in the dynamics of the datasets. Model parameters describing the glucose response due to glucagon at concentrations below saturation ($E_0$, $EC_{50}$, $\gamma$) could not be estimated from the datasets since plasma glucagon concentrations were high during the entire sampling period.

Zealand’s novel glucagon analogue, ZP-GA-1, shows PD characteristics similar to marketed glucagon. The new model enables simulations of the glucose-insulin-glucagon dynamics.

Results

For each identifiable model parameter, posterior probability distributions (teal and blue) are listed along with p-values (red) of two-tailed paired t-tests comparing glucagon and ZP-GA-1 model parameter values.