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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.

Methods

Five dogs were included in a randomized cross-over study. At four dosing occasions each dog received a SC bolus injection of 20 or 120 nmol/kg glucagon (GlucaGen ®) or ZP-GA-1. Blood samples were collected at 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 110, 140, and 180 minutes after dose administration.

We adopted a physiological model of endogenous glucose production with multiplicative effects of insulin and glucagon and combined it with the Hovorka model of glucose and insulin. The model was fitted to each individual dataset by Maximum a Posteriori (MAP) estimation of model parameters given priors reported in literature using the CTSM package in R (version 3.1.0). Profile likelihood analysis was used to fixate unidentifiable parameters at prior mean values.

$$\frac{\mathrm{d}Q_1(t)}{\mathrm{d}t} = -F_{01} - S_T x_1(t) Q_1(t) + k_{12} Q_2(t) + EGP(t) \qquad Q_1(0) = Q_{10}$$

$$\frac{\mathrm{d}Q_2(t)}{\mathrm{d}t} = S_T x_1(t) Q_1(t) - [k_{12} + S_D x_2(t)] Q_2(t) \qquad Q_2(0) = Q_1(0)\frac{x_1(0)}{x_2(0) + k_{12}}$$

$$EGP(t) = \frac{(1 - S_E x_3(t))}{(1 - S_E I_b)} \cdot \left((E_{max} - E_0) \frac{C(t)^\gamma}{EC_{50}^\gamma + C(t)^\gamma} \right) \quad \text{where } (1 - S_E x_3(t)) \geq 0$$

$$G(t) = \frac{Q_1(t)}{\mathrm{V}}$$

$$\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} = k_{a1}[I(t) - x_1(t)] \qquad x_1(0) = \mathrm{I}_b$$

$$\frac{\mathrm{d}x_2(t)}{\mathrm{d}t} = k_{a2}[I(t) - x_2(t)] \qquad x_2(0) = \mathrm{I}_b$$

$$\frac{\mathrm{d}x_3(t)}{\mathrm{d}t} = k_{a3}[I(t) - x_3(t)] \qquad x_3(0) = \mathrm{I}_b$$

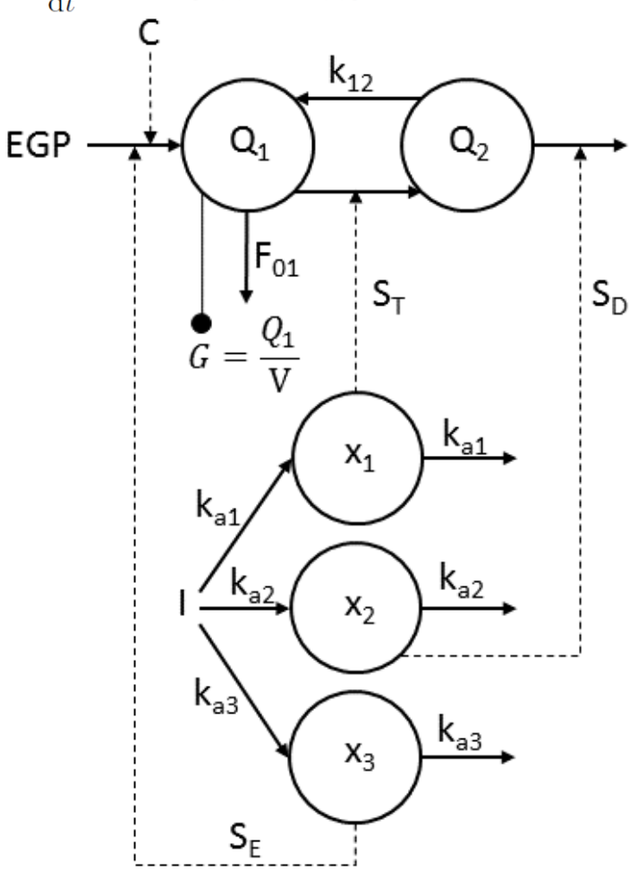

Figure 1: Diagram of the PD model with glucagon or analogue (C), and insulin (I) concentrations as inputs and glucose (G) concentration as output.

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.

	Glucagon	ZP-GA-1	P-value
E_0 (µmol/kg/min)	8		-
E_{max} (µmol/kg/min)	(50.1, 13.7)	(53.8, 16.5)	0.51
EC_{50} (pg/mL)	337.8		-
γ (-)	1		-
F_{01} (µmol/kg/min)	(9.8, 1.5)	(9.6, 2.0)	0.81
Log-distributions			
k_{12} (1/min)	(-2.87, 0.27)	(-3.02, 0.23)	0.29
k_{a1} (1/min)	(-5.19, 0.86)	(-5.90, 0.83)	0.09
k_{a2} (1/min)	-2.89		-
k_{a3} (1/min)	(-4.88, 0.73)	(-4.70, 0.98)	0.42
S_D (L/mIU/min)	(-9.11, 0.93)	(-8.72, 1.15)	0.42
S_E (L/mIU)	(-2.71, 0.57)	(-2.95, 0.43)	0.14
S_T (L/mIU/min)	(-5.65, 0.86)	(-5.35, 0.50)	0.19

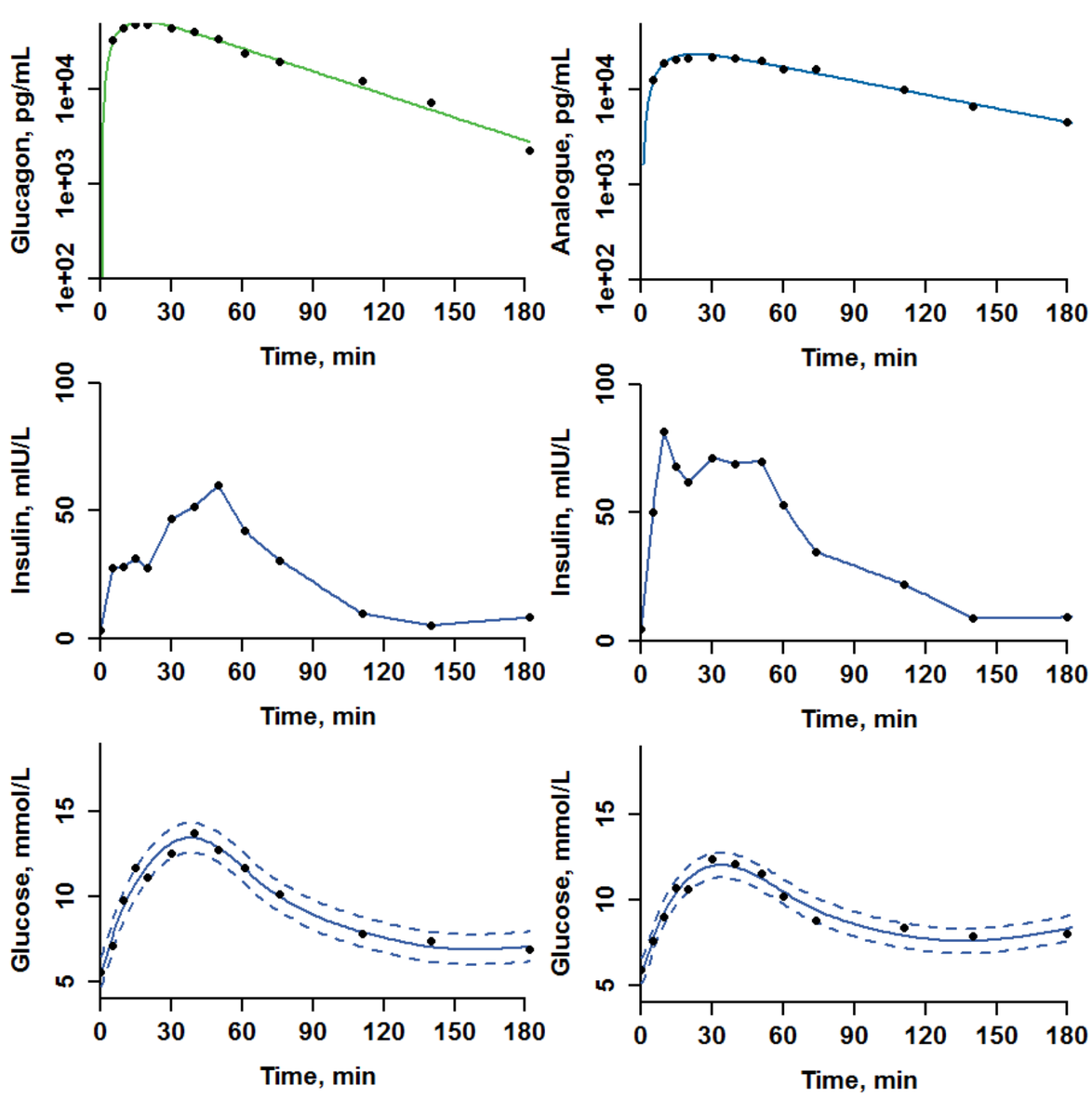

Figure 2: PK profiles and PD responses after a bolus of glucagon (left) or ZP-GA-1 (right) in one dog. Fit and 95% confidence limits are shown.

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}, γ) could not be estimated from the datasets since plasma glucagon concentrations were high during the entire sampling period.

Conclusions

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.