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Model of the Glucose-Insulin-Glucagon Dynamics after Subcutaneous Administration of a Glucagon Rescue Bolus in Healthy Humans

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Abstract

In healthy individuals, insulin and glucagon work in a complex fashion to maintain blood glucose levels within a narrow range. This regulation is distorted in patients with diabetes. The hepatic glucose response due to an elevated glucagon level depends on the current insulin concentration and thus endogenous glucose production (EGP) can not be modelled without knowledge of the concentration of both hormones in plasma. Furthermore, literature suggests an upper limit to EGP irrespective of glucagon levels. We build a simulation model of the glucose-insulin-glucagon dynamics in man including saturation effect of EGP.

Ten healthy subjects received a 1 mg subcutaneous (SC) glucagon bolus (GlucaGen®). Plasma samples were collected until 300 minutes post dose and analyzed for glucagon, insulin, and glucose concentrations. All observations were used to fit a physiological model of the glucose-insulin-glucagon dynamics using the Hovorka model with a novel multiplicative description of the effects of insulin and of glucagon on EGP.

Bayesian estimation by Maximum a Posteriori using prior knowledge reported in literature was used to estimate the model parameters for each subject. Profile likelihood plots were used to investigate parameter identifiability. Unidentifiable parameters were fixed at their prior mean values.

The new model enables simulations of the glucose-insulin-glucagon dynamics in humans at both low and high glucagon concentrations (180-8000 pg/mL) and physiologic insulin concentrations (1.2-81.9 mIU/L). The model can be used for simulation of glucagon bolus strategies for treatment of hypoglycemia and for *in silico* simulation of dual-hormone artificial pancreas algorithms.

1 Background

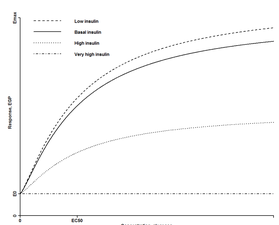

Figure 1: EGP as modeled by the PD model.

There is currently no consensus on a model describing the endogenous glucose production (EGP) as a function of glucagon.
Recent studies suggest a multiplicative effect of insulin and of glucagon on EGP [1].
The pharmacodynamics (PD) model used in this study is mainly described by *Hovorka et al.* [2].
In a previous study, we extended the PD model to include the effects of insulin and of glucagon on EGP based on physiology and pre-clinical data [3].
Figure 1 shows examples of modelled EGP in response to varying glucagon concentrations and constant insulin concentrations at various levels.

2 Data

Ten healthy male subjects weighing 84.5±7.4 kg (mean±2SD) received a 1 mg subcutaneous (SC) glucagon bolus (GlucaGen®). Plasma samples were collected pre dose and at nominal times 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 180, 240, and 300 minutes post dose. Samples were analyzed for their concentrations of glucagon, insulin, and glucose using RIA test kit for glucagon (Euro Diagnostica), MSD human insulin kit (Meso Scale Diagnostics), and Hexokinase/glucose-6-P-dehydrogenase test kit for glucose (Roche Diagnostics), respectively.

3 Methods

The pharmacokinetics (PK) model is a one-compartment model with first order absorption.

$$\frac{dq_1(t)}{dt} = u(t) - k_1 q_1(t)$$
$$\frac{dq_2(t)}{dt} = k_1 q_1(t) - k_2 q_2(t)$$

$q_1(t)$ and $q_2(t)$ are the masses of glucagon (pg) in the non-accessible and accessible compartments. k_1 and k_2 are transfer rate constants with k_2 being greater than k_1 since data demonstrate absorption limited elimination (flip-flop kinetics). Glucagon concentration in the accessible compartment is $k_2 q_2/Cl_F+C_b$ (pg/mL) where Cl_F is clearance uncorrected for bioavailability and C_b is basal plasma glucagon concentration. u(t) is the glucagon bolus (pg/min). The PD model by Hovorka *et al.* [2] and our extension $F_{IC}(t)$ of the insulin and glucagon dependent EGP [3].

$$\frac{dQ_1(t)}{dt} = -F_{01} - S_T x_1(t) Q_1(t) + k_{12} Q_2(t) + F_{IC}(t)$$
$$\frac{dQ_2(t)}{dt} = S_T x_1(t) Q_1(t) - \left(k_{12} + S_D x_2(t)\right) Q_2(t)$$
$$\frac{dx_{ai}(t)}{dt} = k_{ai}\left(I(t) - x_{ai}(t)\right) \qquad i = 1, 2, 3$$
$$F_{IC}(t) = \frac{1 - S_E x_3(t)}{1 - S_E I_{b,y}}\left((E_{max} - E_0)\frac{C(t)}{C_{E50} + C(t)}\right)$$

$Q_1(t)$ and $Q_2(t)$ are the masses of glucose per bodyweight (µmol/kg) in the accessible and non-accessible compartments. Glucose concentration (mmol/L) in the accessible compartment is Q_1/V with V fixed at 160 mL/kg. I(t) is the insulin concentration (mIU/L) in the accessible compartment. $x_i(t)$ are remote effects of insulin (mIU/L). F_{01} is the non-insulin-dependent glucose flux. k_{12} and k_{ai} are transfer rate constants.
S_D, S_E, and S_T are insulin sensitivities.
C(t) if the glucagon concentration (pg/mL) in the accessible compartment. $I_{b,y}$ is the fixed basal insulin concentration (mIU/L) for subject y, and E_0 is the minimum EGP fixed at 8 µmol/(kg·min). E_{max} is the maximum EGP at $I_{b,y}$. C_{E50} is the glucagon concentration at half maximum EGP.

We used a maximum likelihood method to estimate individual PK model parameters, while a maximum a posteriori method with prior information [2, 3] was used to estimate individual PD model parameters [4]. Finally, we used profile likelihood analysis to find unidentifiable variables in the PD model and in the case of identifiability issues the parameters were fixed at their prior mean values.

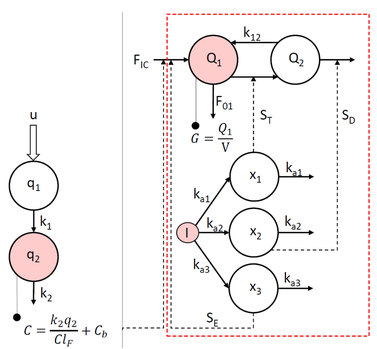

Figure 1: Full PK/PD model. The open arrow symbolizes SC input of glucagon. Solid arrows indicate mass transfer. Dashed arrows indicate effect without mass transfer. Solid lines with dot endings indicate how concentrations are calculated. Plasma compartments are colored. A red dashed line surrounds the Hovorka *et al.* model [2].

4 Results

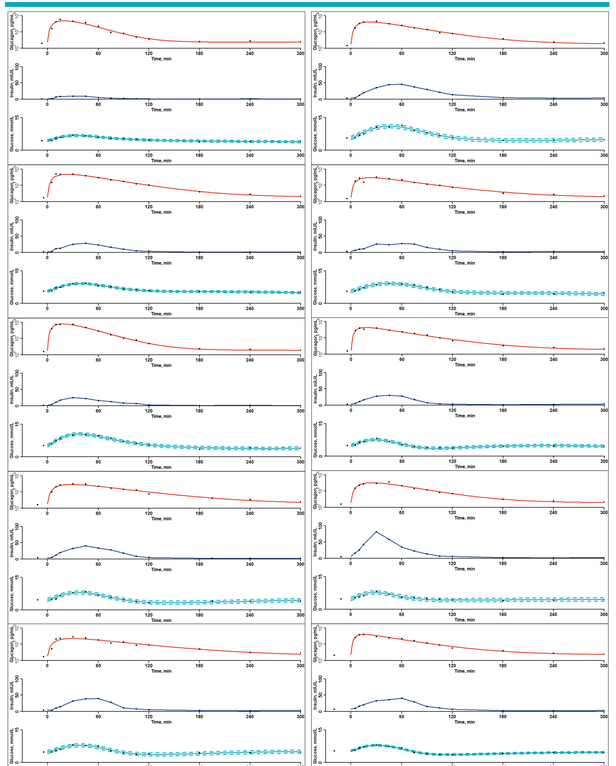

Figure 2: PK model fit of glucagon (red), interpolated endogenous insulin (blue), and PD model fit of glucose with 95% confidence interval (teal) for each of the ten subjects.

Table 1: Average PK and PD parameter estimates and 95% confidence intervals. *Fixed parameter.

Parameter	Unit	Mean	95% Confidence Interval
C_b	pg/mL	197	[155-239]
Cl_F	mL/min	3689	[2343-5035]
k_1	min^{-1}	0.023	[0.010-0.049]
k_2	min^{-1}	0.082	[0.043-0.155]
C_{E50}	pg/mL	407	[329-485]
E_{max}	µmol/(kg·min)	38.8	[28.9-48.7]
F_{01}	µmol/(kg·min)	10.5	[8.6-12.4]
k_{12}	min^{-1}	0.031	[0.018-0.052]
k_{a1}	min^{-1}	0.0034	*
k_{a2}	min^{-1}	0.12	[0.11-0.13]
k_{a3}	min^{-1}	0.015	[0.003-0.066]
S_D	min^{-1} per mIU/L	0.0005	*
S_E	per mIU/L	0.04	[0.01-0.16]
S_T	min^{-1} per mIU/L	0.0033	[0.0011-0.0096]

5 Conclusions

The PK model and the parameter distributions enable simulations of glucagon kinetics in healthy males weighing 77-92 kg. In the same population, the PD model and the parameter distributions enable simulations of the glucose-insulin-glucagon dynamics at the following plasma concentrations: glucagon (180-8000 pg/mL), insulin (1.2-81.9 mIU/L), and glucose (3.3-11.5 mmol/L). The models can be used for simulation of glucagon bolus strategies for treatment of hypoglycemia and for *in silico* simulation of dual-hormone artificial pancreas algorithms.

References

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