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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 disturbed in patients with diabetes. The hepatic glucose response due to an increased glucagon level depends on the current insulin concentration and thus endogenous glucose production (EGP) can be modified without knowledge of the concentrations of both hormones in plasma. In this study, we present a model of the glucagon-insulin-glucagon dynamics in men including estimation of EGP.

Ten healthy subjects received a 1 mg subcutaneous (SC) glucagon bolus (Glucagon®). 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 glucagon-insulin-glucagon dynamics using the nonlocal model with a novel multiplicative description of the effects of insulin and of glucagon on EGP.

Baysian 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. Uncertain parameters were fixed at their prior mean values.

The new model enables simulation of the glucagon-insulin-glucagon dynamics in humans at both low and high glucagon concentrations (100-1000 mIU/mL), and physiologic insulin concentrations (0.003-0.0034 mIU/mL). It is suitable for simulation of glucagon and glucagon mimetic induced hypoglycemia and for in silico simulation of dual-hormone artificial pancreas algorithms.

1 Background

There is currently no censensus 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 pharmacokineti-pharmacodynamic model used in this study is mainly described by Hovorka et al. [2], in a previous study, we collected the PK data to estimate the nonlocal PK model of glucagon in silico based on physiology and pre-clinical data [3]. Figure 1 shows examples of modified EGP in response to varying glucagon concentrations and constant insulin concentrations at various levels.

2 Data

The ten main subjects weighing 81.9 ± 8.7 kg (mean ± standard deviation) received a 1 mg subcutaneous (SC) glucagon bolus in their dominant arm. Glucose and insulin steady state kinetics were used to estimate the model parameters. Simulations are done using the PK module of the simulation software (Astra Zeneca, Macclesfield, UK).

3 Methods

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

\[ \frac{dC(t)}{dt} = -k_d C(t) + k_{inj} \]

where \( C(t) \) is concentration of glucagon, \( k_d \) is the elimination rate constant, \( k_{inj} \) is the injection rate constant.

The PK model is used to estimate individual PK model parameters, while a maximum a posteriori method with prior information [2] was used to estimate individual PD model parameters. Finally, we used profile likelihood analysis to find unidentifiable parameters in the PD model. Uncertain parameters in the PD model cause identifiability issues in the parameters area and are fixed at their prior mean values.

4 Results

In the next figures, solid and dashed lines indicate mean fit and 1 standard deviation, respectively.

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

5 Conclusions

The PK model and the parameter distributions enable simulations of glucagon kinetics in healthy males weighing 79.2 kg. In the same population, the PD model and the parameter distributions enables glucagon-insulin-glucagon simulations at normal and high glucagon concentrations (100-1000 mIU/mL). The models can be used for simulation of glucagon kinetics for estimation of glucose levels in clinical and artificial pancreas algorithms.

References

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