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) cannot be modulated without knowledge of these concentrations of both hormones. In this pilot study, we investigated a new model of the glucose-insulin-glucagon dynamics in men including satiation effect of EGP.

Ten healthy subjects received a 1 mg subcutaneous (SC) glucagon bolus (Glucagen®, Pharma Nord A/S, Hørsholm, Denmark). Inulin, insulin, and glucagon concentrations. All observations were used to fit a physiological model of the glucose-insulin-glucagon-dynamics using the Egervej 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 (10-9000 pg/mL), and physiological insulin concentrations (0.01-0.08 mIU/mL). This model may enable new approaches to control the concentration of both hormones in plasma. Furthermore, literature suggests an upper limit to EGP (EGP ≈ 3.5 mg/min/m²) depends on the current insulin concentration, and thus glucagon dynamics as a function of glucagon.

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

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Abstract

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 pharmacokinetics (PK) model is a one-compartment model with first-order elimination of glucagon (kG) and endogenous glucagon concentration (50% being greater than kG) and accounting for f≤0.5% of the glucagon bolus.

The PK model is of the form:

\[ \frac{\text{d} [G]}{\text{d} t} = -k_G [G] \]

where [G] is the glucagon concentration, kG is the first-order elimination rate constant, and C0 is the glucagon bolus.

The PK model is then 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 individual PK parameters:

\[ \text{PD model:} \frac{\text{d} [G]}{\text{d} t} = -k_G [G] + k_{EI} \cdot \text{insulin} \left( \frac{[G]}{E50} \right) \]

The PD model is used to estimate individual PD model parameters:

\[ \text{PD model:} \frac{\text{d} [G]}{\text{d} t} = -k_G [G] + k_{EI} \cdot \text{insulin} \left( \frac{[G]}{E50} \right) \]

where [G] is the glucagon concentration, kG is the first-order elimination rate constant, kEI is the insulin sensitivity, and E50 is the half-maximal effective concentration for the insulin-glucagon interaction.

5 Conclusions

The PK parameters and the parameter distributions enable simulations of glucagon kinetics in healthy male subjects with glucagon bolus protocols. The PK parameters and the parameter distributions enable simulations of glucagon kinetics in healthy male subjects with glucagon bolus protocols.

References


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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>kG</td>
<td>0.034</td>
<td>(0.013, 0.055)</td>
</tr>
<tr>
<td>kEI</td>
<td>0.003</td>
<td>(0.002, 0.004)</td>
</tr>
<tr>
<td>E50</td>
<td>5035</td>
<td>(4750, 5320)</td>
</tr>
</tbody>
</table>

Figure 1: PK model fit of glucagons (red). Corresponding author: SL Wendt, slw@zealandpharma.com or slwe@dtu.dk

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