Validation of a Simulation Model Describing the Glucose-Insulin-Glucagon Pharmacodynamics in Patients with Type 1 Diabetes

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Introduction

Currently, no consensus exists on a model describing endogenous glucose production (EGP) as a function of glucagon concentrations. Reliable simulations to determine the glucagon dose preventing or treating hypoglycemia or to tune a dual-hormone artificial pancreas control algorithm need a validated glucoregulatory model including the effect of glucagon.

This poster presents the results from the leave-one-out cross-validation of a glucoregulatory model with interacting effects of insulin and glucagon [1]. We present model fits to data, and simulations with the model showing the glucagon dose-response relationship at varying insulin levels [2].

Materials and Methods

Eight type 1 diabetes patients received a subcutaneous (SC) bolus of insulin (NovoRapid®) on four study days to induce mild hypoglycemia followed by a SC bolus of saline (A) or 100 (B), 200 (C) or 300 (D) µg glucagon (GlucaGen®). Samples were analyzed for concentrations of glucagon, insulin, and glucose.

The PD model is mainly inspired by Hovorka et al. [3].

\[
\frac{dC(t)}{dt} = k_i(t) - x_i(t)
\]

where: 
- \(C(t)\) and \(Q(t)\) are the masses of glucose per BW (µmol/kg) in the accessible and non-accessible compartments.
- Glucose concentration (mmol/L) in the accessible compartment is \(Q/V\) with \(V\) fixed at 160 mL/kg.
- \(x_i(t)\) are remote effects on insulin (µIU/mL) or glucagon.

The model is modified so \(G_{GNG} = G_i\) the insulin and glucagon dependent EGP corresponding to glycogenolysis and \(G_{EGP}\) is the constant EGP contribution from gluconeogenesis [1].

\[
G_{EGP}(t) = \frac{1}{\bar{S}_i} S_x(t) T_\gamma + E_{max}\frac{C(t)}{C_\gamma + C(t)}
\]

\(C(t)\) is the glucagon concentration (pg/mL) in the accessible compartment.

\(T_\gamma\) is the fixed basal insulin concentration (µIU/mL) for subject \(y\), and \(E_{max}\) is the minimum EGP at \(E_{max}\). \(C_{EGP}\) is the glucagon concentration at half maximum EGP.

The PD model validation was carried out as a 4-fold leave-one-out cross-validation leaving all data from one visit out per fold. We used patient specific parameter sets to establish a glucoregulatory system:

Table 1: Result of leave-one-out cross-validation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Accepted Test-visit fits (Training-visits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (BCD), 3 (AB)</td>
<td>1 (BD), 4 (ABC)</td>
</tr>
<tr>
<td>2 (BCD), 3 (ABCD)</td>
<td>1 (BD), 4 (ABC)</td>
</tr>
<tr>
<td>2 (BCD)</td>
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<td>2 (BCD), 3 (ABCD)</td>
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<tr>
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<td>1 (BD), 4 (ABC)</td>
</tr>
<tr>
<td>None</td>
<td>1 (BD), 4 (ABC)</td>
</tr>
</tbody>
</table>

Figure 1: Data and model fits of patient 7. Insulin PK (top), glucagon PK (middle), glucose PD (bottom) during visits A-D (left to right).

Figure 2: Simulation of glucagon dose-response relationship at varying insulin levels.

Conclusions

We successfully validated a model describing the glucose-insulin-glucagon dynamics by leave-one-out cross-validation in seven type 1 diabetes patients. We used patient specific parameter sets to establish a virtual population. Simulations with the virtual patients showed that the ambient insulin level affects the maximum EGP response to glucagon, but has little influence on the dose yielding half maximum response.

References

