Application of an integrated glucose-insulin model to investigate the effects of glibenclamide and its active metabolites on postprandial glucose and insulin concentrations in healthy volunteers

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Background and Objectives

The sulphonylurea drug glibenclamide (Gb) is an insulin secretagogue used in the treatment of type 2 diabetes [1]. Previous PKPD modeling showed that both Gb and its active metabolites (M1 and M2) decrease postprandial glucose in man [2]. To investigate pathways predictive to be affected by Gb and its metabolites, we applied an existing semi-mechanistic integrated glucose-insulin (IGI) model [3] to clinical trial data.

Methods and Materials

Rich glucose and insulin concentration-time data (Fig 1) from 8 healthy volunteers enrolled in a 5-way crossover study were analyzed using NONMEM7. The drug arms were: Gb, M1 and M2 intravenously; Gb oral tablet; and placebo intravenously, all receiving a 3.5mg dose [3]. Flexible input stepwise absorption functions [4] were estimated using placebo arm data. Drug effect was simultaneously estimated with the three active intravenous arms using a competitive agonistic Emax function [2] on either glucose production (A), insulin elimination (B), insulin-dependent glucose elimination (C), or insulin production (D) (Fig 2). Models were estimated using intravenous data only. Data from the oral Gb drug arm were used as an external validation.

Results

Stimulation of insulin secretion via incretin as a drug effect showed by far the largest drop in objective function value (~ΔOFV) compared to the baseline model in the active intravenous arms of the study (Table 1). Similarly, this was also found in the external validation (without parameter re-estimation) on oral Gb data. Moving drug effect further downstream to affect total insulin secretion improved the model further with a ~ΔOFV of 11 units. There were no further improvement in ~ΔOFV after the primary drug effect was identified. The Emax and EC50s of glibenclamide and its metabolites indicate a linear drug effect in the observed range of concentrations.

Table 1. Change in objective function value of the drug effect pathways for glibenclamide and its metabolites, relative to base model (no drug effect).

<table>
<thead>
<tr>
<th>Pathways</th>
<th>Drug arms</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gb, iv</td>
<td>-15</td>
<td>15</td>
<td>-14</td>
<td>-228</td>
<td></td>
</tr>
<tr>
<td>M1</td>
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<td>-1</td>
<td>-4</td>
<td>-91</td>
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</tr>
<tr>
<td>M2</td>
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<td>-3</td>
<td>-1</td>
<td>-122</td>
<td></td>
</tr>
<tr>
<td>All iv arms</td>
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<td>-1</td>
<td>-42</td>
<td>-387</td>
<td></td>
</tr>
<tr>
<td>Gb, po (external)</td>
<td>-0.3</td>
<td>-2</td>
<td>-121</td>
<td>-337</td>
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</tr>
</tbody>
</table>

Conclusions

- The IGI model could be successfully applied to meal test data.
- The effect of glibenclamide and its active metabolites on the effect on insulin production provided the best description and prediction of the glucose and insulin data in healthy volunteers.
- As in a previous example [5], this illustrates that the correct mechanism of action can be identified when the IGI model is applied to PKPD data.

References