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 function parameters [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.

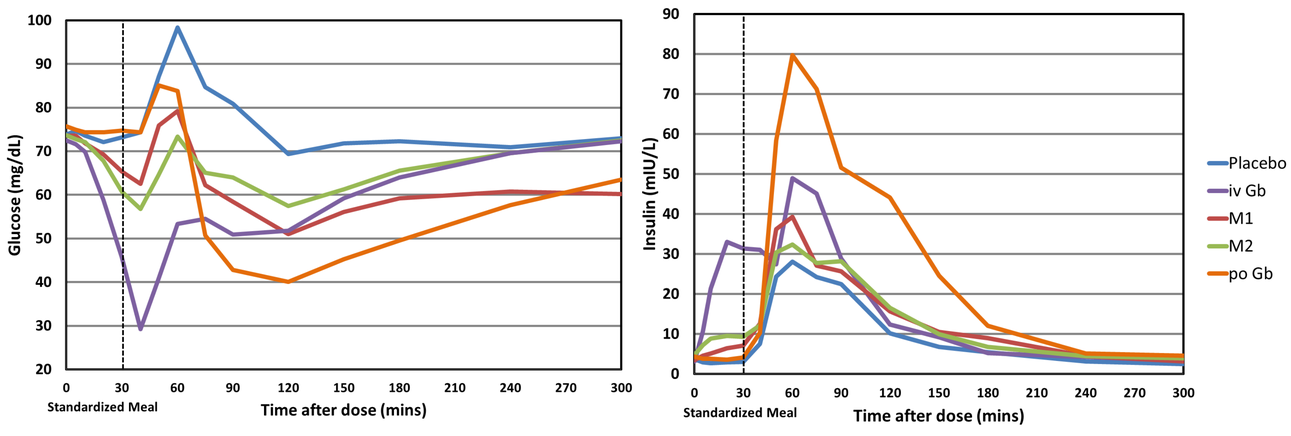

Figure 1. Average concentration-time profile for glucose and insulin observations. The drug is given at 0 minutes, and the standardized meal was give at 30 minutes post-dose. The three intravenous drug arms were glibenclamide (parent) and the metabolites M1 and M2.

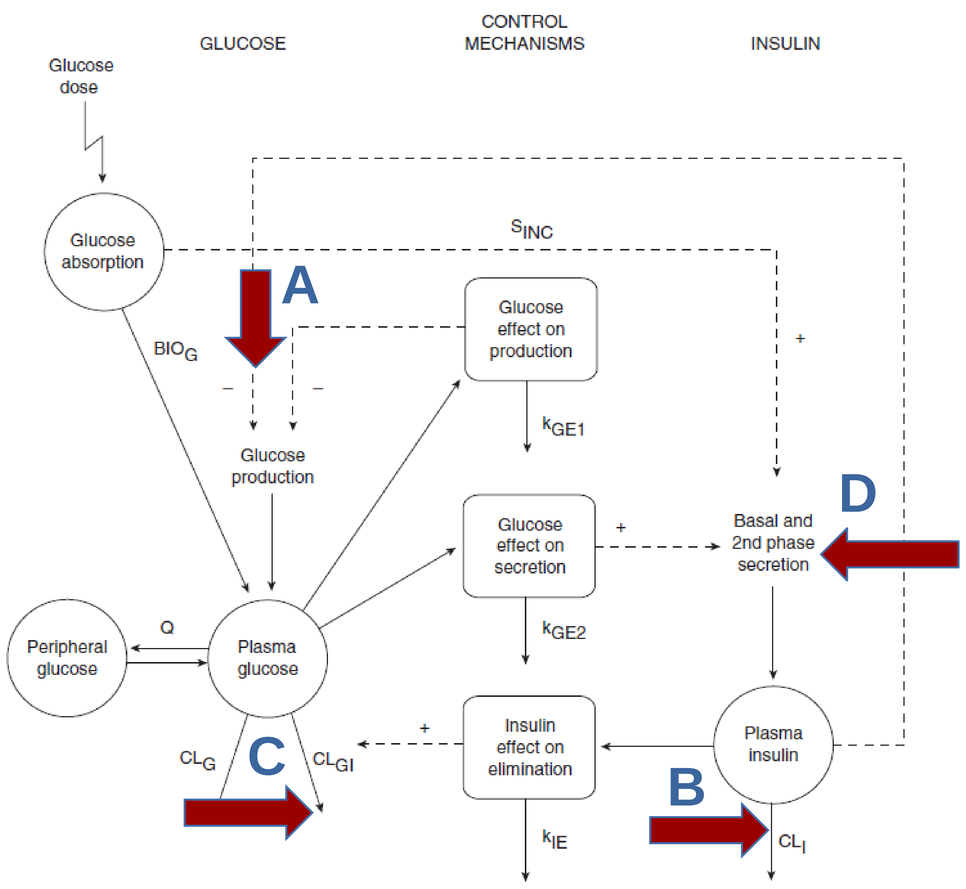

Figure 2. The semi-mechanistic, integrated insulin-glucose model. Drug effect of glibenclamide and its metabolites were investigated on several pathways indicated by the arrows, where A= inhibitory effect on glucose production; B = inhibitory effect on insulin elimination; C = stimulatory effect on insulin-dependent glucose elimination, and D = stimulatory effect on insulin production. Diagram adapted from Silber et al [3].

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). A= inhibitory effect on glucose production; B = inhibitory effect on insulin elimination; C = stimulatory effect on insulin-dependent glucose elimination, and D = stimulatory effect on insulin production.

Pathways / Drug arms	A	B	C	D
Gb, iv	-15	15	-14	**-228**
M1	-0.0	-1	-4	**-91**
M2	-0.0	-3	-1	**-122**
All iv arms	22	-1	-42	**-387**
Gb, po (external)	-0.3	-2	-121	**-337**

Drug effect **(D)** was then expressed as the increase in total insulin secretion relative to baseline (no drug effect). Gb exerts up to a 7-fold effect in insulin production, while its metabolites have less impact (Fig 3). Visual predictive checks (VPC) of the IGI model demonstrated its effectiveness in capturing the glucose-lowering effects of Gb (Fig 4; middle panels).

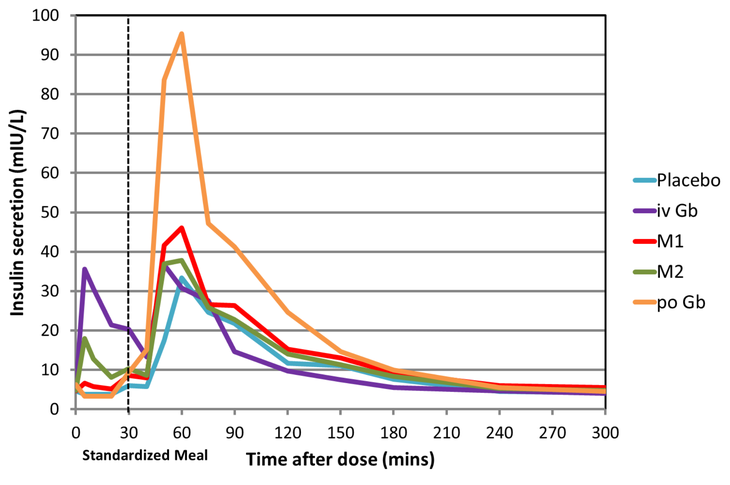

Figure 3. Average insulin secretion following dose from the predictions.

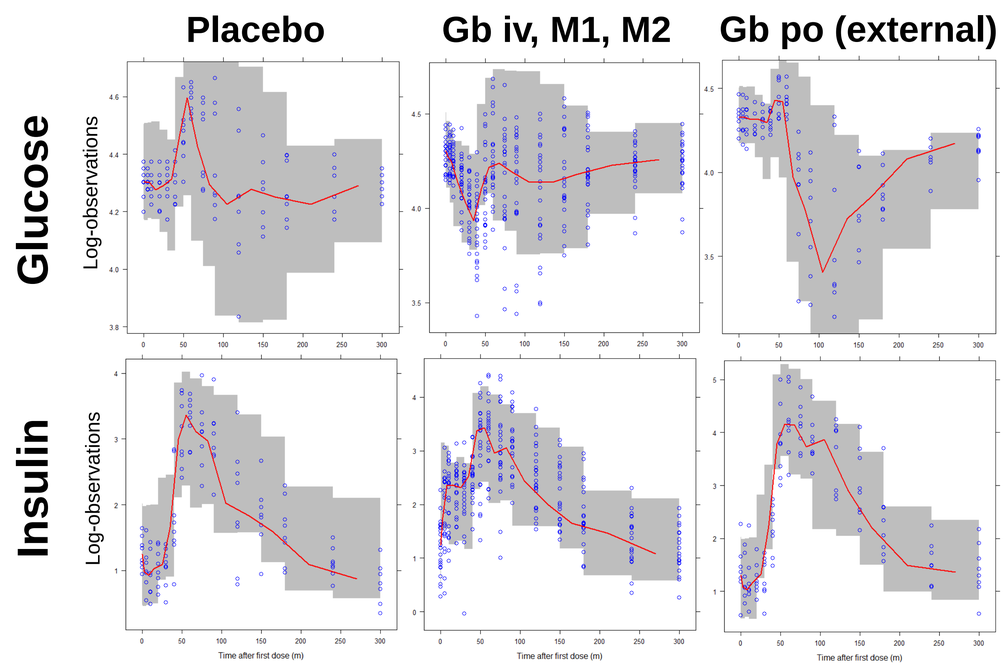

Figure 4. Prediction- and variance-corrected VPC of the IGI model. Blue circles indicate observations; red lines indicate the median observations; grey bands indicate the 90% prediction intervals.

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

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