

Assessment of Mechanism of Action and Drug Effects in Early Signal of Efficacy Trials Using Integrated Glucose-Insulin Modeling: A Simulation-Estimation Approach

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INTRODUCTION

- Standard oral glucose tolerance tests (OGTT) are increasingly used for the early assessment of the pharmacodynamic (PD) effect of new anti-diabetic agents on glucose excursion and insulin secretion in type 2 diabetes (T2DM) subjects [1].
- A physiology based integrated glucose-insulin (IGI) model describing glucose and insulin regulation during OGTT was recently proposed [2-4].
- Such mechanistic PK/PD model can be ideally applied to quantify the magnitude and mechanism of drug effects in small and short duration studies focusing on glucose-insulin endpoints after OGTT and then integrated to simulate the outcome of longer duration trials providing translation of OGTT results to 24-hour glucose and ultimately HbA1c [5-6].

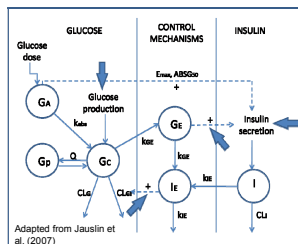
OBJECTIVES

- 1) to understand if the IGI model can be used to gain insight in the main mechanism of action (MOA) of a test anti-diabetic agent.
- 2) to assess the precision and bias of the IGI model in estimating quantitatively the main drug effects.

METHODS

Model:

Schematic representation of the IGI model with point of perturbation for 4 main MOAs of anti-diabetic treatments and typical structural model parameters for baseline or placebo effect:



Simulated Study Design:

- N=12 T2DM received an OGTT at baseline and at steady state of drug effect (assumed constant during the glucose test).

Simulation Data:

- The simulated steady state drug effects aimed at achieving an average 20% glucose lowering during the OGTT were:
 - 1) 65% hepatic glucose production lowering (HGP)
 - 2) 300% glucose dependent insulin secretion increase (IPRG)
 - 3) 130% overall insulin secretion increase (ISEC)
 - 4) 200% insulin sensitivity increase (ISEN)
- For each MOA, 50 trials were simulated employing intensive (every 10 min) glucose and insulin sampling over 180 min.

MOA Identification & Drug Effect Estimation:

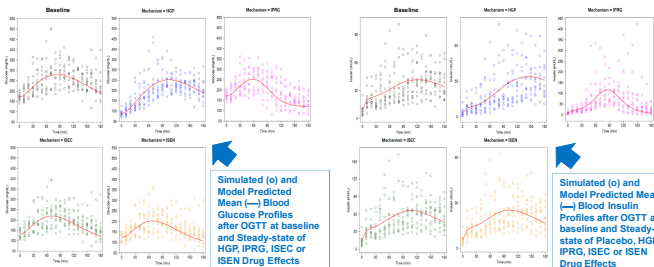
- Part 1 - identifying correct MOA:** Inclusion of different MOA factor in the model was applied to the baseline and post drug data simultaneously in a one-by-one manner. Goodness-of-fit plots and the Objective Function Value (OFV) provided by NONMEM (v7.1.2) were used for selecting the correct MOA.
- Part 2 - quantifying drug effects:** Percent Relative Estimation Error (REE%) for the specific MOA factor was determined.

RESULTS

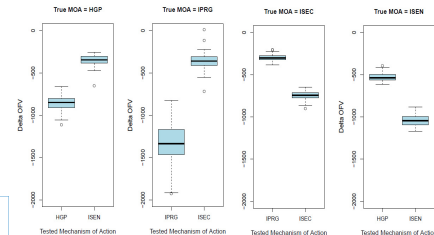
Part 1 - Identifying Correct MOA

Simulated Data & Model Diagnostics:

All the data were simulated and fitted by NONMEM® 7.1.2 with FOCEI.



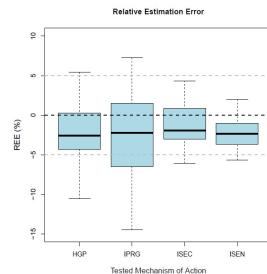
Delta OFV for Identifying the Best (and 2nd best) MOAs:



- The IGI model without incorporation of drug effect was used as the reference run for the calculation of delta OFV.
- For each of the 4 MOA categories, the model incorporating the correct drug effect generated the lowest OFV (typically a delta OFV of 750-1300).
- The difference of OFV to the second best MOA model was generally 300-500.
- Goodness-of-fits plots also supported correct model selection.

Part 2 - Quantifying Drug Effects:

Relative Estimation Error (REE) for the Drug Effect Factor:



- The correct model consistently provided accurate estimation of the drug effect with the median REE < 5% (90% CI < 15%) for each MOA factor

CONCLUSION

The mechanistic integrated glucose-insulin model was able to both correctly categorize and quantify the MOA responsible for the glucose and insulin response following simulated small size OGTT protocols in T2DM patients.

References:

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