Using T1DMS Simulation for the Conceptualization and Design of Clinical Clamp Studies in the Development of Modified Insulin Therapeutic Agents: Part II – MK-2640

**Synopsis**

Background:
- Simulations of glucose-responsive insulin (GRI) MK-2640 were used to design in-clinic glucose clamp study.
- The University of Virginia/Patrick University Type 1 diabetes mellitus human metabolic simulation platform (T1DMS) is validated and demonstrated to be useful in designing a multiphasic clamp clinical study with regular human insulin (RHI).
- Predicting quantitative impact of a modified insulin on clinically meaningful outcomes is necessary to successfully develop a novel insulin.

Objective:
- To evaluate the pharmacology of MK-2640, relative to RHI

**Methods**

- Simulations were generated to predict therapeutic index of GRI.
- In order to interpret the clinical observations and inform ongoing strategy, it is important to determine optimal dose regimen.

**Results and Conclusions:**
- Systemic glycemic control by MK-2640 was predicted to be improved over RHI given similar absorption rate. Observed response was less than predicted, indicating that mechanism of action was not fully described.
- Details of local hepatic pharmacokinetics/pharmacodynamics may be implemented to explore future clinical design for GRI.

**This work lays the foundation for model-informed testing of modified insulins or insulin-mimetic therapeutic agents and mechanistic hypothesis-generating interpretation of their clinical effects.**

**OBJECTIVE**

- To identify glycemic control and PK of a GRI and predict optimal glucose control for a variety of possible GRI characteristics.

**METHODS**

Modeling GRI Using the T1DMS

- GRI action was simulated as glucose-dependent CL decreasing by 30% (left, top); observed prediction: mean plasma glucose range from 75 to 300 mg/dL. Some individuals (15%, 30%, 50%, 70%) explored.
- Scenarios explored to identify stigmas influences on GRI action: differing GPCL sensitivity relative to RHI, prandial and/or basal use, differing GRI potency relative to RHI, prandial and/or basal use, differing GPCL sensitivity relative to RHI, prandial and/or basal use, differing GPCL sensitivity relative to RHI, prandial and/or basal use.

**Results**

**RESULTS**

- GRI with 15% to 50% glucose-dependent CL is predicted in <2% of simulated patients, versus 15% of patients treated with RHI.

- Predictions are made from literature-based meta-analysis together with clinical data of euglycemic clamp (EGC) = 75 mg/dL.

**Figure 1. T1DMS**

**Figure 2. Plasma Glucose Summary Predictions for Hypoglycemia Defined as <70 mg/dL.**

**Figure 3. Simulated Prandial Hypoglycemia (<70 mg/dL) Following Administration of a 30% Glucose-Dependent CL GRI with Varying Time of Administration.**

**Figure 4. Predicted vs Observed PK-PD**

**CONCLUSIONS AND DISCUSSION**

- In-silico simulation, successfully being applied in closed-loop controllers, has demonstrated utility in setting therapeutic index objectives for GRI proof-of-concept. T1DMS allows simulations of tissue-based CL and site of insulin action for mechanistic hypothesis generation.

- The model assumptions, particularly systemic action and passive hepatic clearance, are not consistent with evidence for a hepatic site of action and fraction hepatic CL. 4. The likelihood that this modified mechanism of action explains current inconsistency between predicted and observed GRI PK should be simulated with an updated T1DMS model in order to support the next clinical study design.

**REFERENCES**


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