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

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Synopsis

Background:

- Simulations of glucose-responsive insulin (GRI) MK-2640[1] were used to design a clinical glucose clamp study.[2] The University of Virginia/Padova University Type 1 diabetes mellitus human metabolic simulation platform (T1DMS)[3] demonstrated successful utility in designing a multiglycemic clamp clinical study with regular human insulin (RHI)[4]
- Predicting quantitative impact of a modified insulin on clinically meaningful outcome would greatly improve the success of developing modified insulin or insulin-mimetic therapeutic agents

Objectives:

- 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 to determine optimal dose regimen

Results and Conclusions:

- Systemic glucose 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. Description of local hepatic pharmacodynamics may be implemented to explore future clinical design for a 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

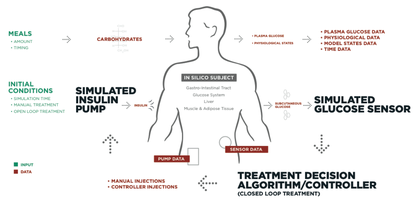
- To identify glucose-responsive PK and PD of a GRI and predict optimal glucose control for a variety of possible GRI characteristics

METHODS

Modeling GRI Using the T1DMS

- GRI action was simulated as glucose-dependent CL decreasing linearly by 30% (ΔCL observed preclinically) over plasma glucose range from 75 to 300 mg/dL. Alternative ΔCL = 0%, 15%, 30%, 50%, 70% explored
- Scenarios explored to identify strongest influences on GRI action: differing GRI potency relative to RHI, prandial and/or basal use, duration and size of meals, optimized dose and absorption kinetics
- Outcomes were generated including: %Time within range (ranges 50, 60, 70, 75 mg/dL to 180, 250, 300 mg/dL plasma glucose were studied); %Time hypoglycemic; %Subjects experiencing hypoglycemia; postprandial insulin. Control variability grid analysis (CVGA) used to visually summarize glucose excursions

Figure 1. T1DMS



https://tegvirginia.com/software/t1dms/

The model[3] is qualified with a reference population cohort of T1DM patients, accepted by the FDA as a substitute for preclinical trials. A subgroup population software (N=10 subjects) is licensed to Merck. http://Tegvirginia.com.

Final simulations: s.c. bolus dose optimized per virtual patient. 24-hour simulation of 3 meals:

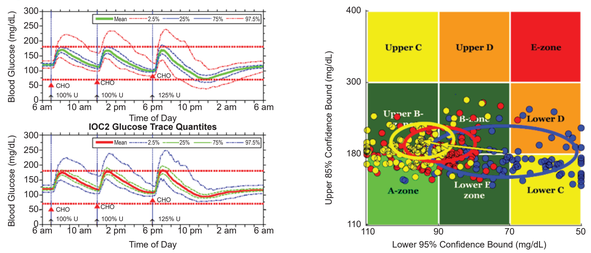
- 7:00 AM 50 g meal with optimal dose
- Noon 80 g meal with optimal dose
- 6:00 PM 80 g meal with 125% dose

Full simulations run using 100 adult cohort similar but not identical to the FDA cohort.

RESULTS

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

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



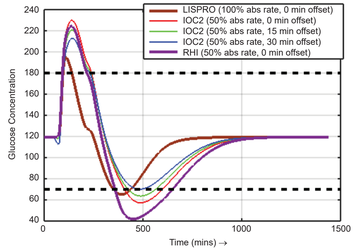
In order to evaluate GRI therapeutic index relative to RHI, a simulated supper meal overcorrection of RHI (**left, top**) was chosen to have 50% of individuals experience hypoglycemia. The mean glucose (green line) remains above 70 mg/dL plasma glucose with 95% confidence interval (red dashed curve) dropping below. The same regimen with a 30% glucose-dependent CL GRI (**left, bottom**) is predicted to prevent hypoglycemic excursions for all subjects.

CVGA (**right**) for the simulation shows individuals treated with RHI (blue) experience overcorrection or failure to deal with hypoglycemia (zones lower C and D, respectively) whereas individuals treated with a 30% glucose-dependent CL GRI (red) stay within accurate control (zone A) or benign deviations of control (zone B). GRI-treated individuals trend to higher glycemia than RHI-treated individuals.

Glycemic control using a GRI with absorption rate similar to RHI is predicted to be improved over RHI if given 15-30 minutes prior to a meal

Of the investigated determinants of insulin action, absorption rate was identified to impact GRI action in addition to other known characteristics of GRIs. RHI and Lispro are both benchmarked in the T1DMS and represent a 2-fold difference in absorption. Absorption rates of 25%, 35%, 50%, 75%, and 100% of Lispro were simulated, administered 0 min, 30 min, and 60 min prior to a meal in order to predict the balance between the two factors

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



The N=10 subject subgroup simulator was used simulate the glucose control of 30% and 50% glucose-dependent CL GRIs, at an optimal (calculated per subject) and 135% overcorrection dose given prior to a single 80 g meal.

For a GRI with the same absorption as RHI (**above**), the prandial glucose excursion below 70 mg/dL is reduced depending on the time of administration (0, 15, and 30 min; red, green, and blue lines, respectively). The hypoglycemia is reduced compared to RHI (heavy purple line) and similar to Lispro (heavy red line).

Observed MK-2640 PD was consistent with predictions including glucose responsiveness. PK was higher than predicted

Table 1. Summary of Predicted and Observed PK and PD for RHI and MK-2640 in T1DM Patients

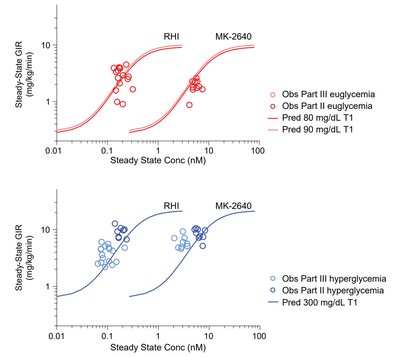
Multiglycemic Clamp Study Predictions	Steady-State Predictions	Predicted from Minipig (EGC = 75 mg/dL)	Predicted from Dog (EGC = 75 mg/dL)	Predicted from Meta-analysis (EGC = 75 mg/dL)	Predicted from T1DMS (EGC = 75 mg/dL)	Observed MK-2640 FIH (EGC = 90 mg/dL)
Interval 1: Euglycemic glucose clamp with MK-2640 infusion rate @ 81 pmol/kg/min	Insulin conc (pM)	2,900	4,700	4,800	5100 (3300, 9100)[b,d]	2,900 (2,700, 3,100)[b]
	Insulin clearance (mL/min/kg)	8.3	6.2	4.9-17	18 ± 4[a]	13.94 (13.03, 14.92)[b]
	GIR (mg/kg/min) Euglycemic clamp	1.6	2.1	1.8	3 (1, 9)[b,d]	1.47 ± 0.79[a]
Interval 2: Glucose clamp @ 300 mg/dL with MK-2640 infusion rate @ 81 pmol/kg/min	Insulin conc (pM)	2,900	4,700	4,800	6600 (4300, 11800)[b]	3,000 (2,800, 3,300)[b]
	Insulin clearance[c] (mL/min/kg)	5.7	4.4	3.4-12	13 ± 3[a]	13.13 (11.99, 14.37)[b]
	GIR (mg/kg/min) @ 300 mg/dL clamp	8.3	7.0	6.9	9 (4, 17)[b]	5.50 ± 1.59[a]
Interval 1: Euglycemic glucose clamp with RHI infusion rate @ 3 pmol/kg/min	Insulin conc (pM)	170	112	195 (169, 226)[b]	206 (109, 529)[b]	101 (87, 117)[b]
	Insulin clearance (mL/min/kg)	11.1	19.9	15.1	16.5	13.68 (11.81, 15.84)[b]
	GIR (mg/kg/min) @ Euglycemic clamp	1.9	2.4	2.6 (2.2, 3.0)[b]	2.1 (0.0, 5.6)[b]	1.11 ± 0.42[a]
Interval 2: Glucose clamp @ 300 mg/dL with RHI infusion rate @ 3 pmol/kg/min	Insulin conc (pM)	170	112	195 (169, 226)[b]	206 (109, 529)[b]	98 (83, 115)[b]
	Insulin clearance (mL/min/kg)	11.1	19.9	15.1	16.5	14.13 (12.05, 16.57)[b]
	GIR (mg/kg/min) @ 300 mg/dL clamp	7.5	6.4	6.4 (5.4, 7.5)[b]	6.6 (2.6, 8.8)[b]	3.89 ± 1.23[a]

[a]Mean ± SD; [b]Geometric Mean (90% CI); [c]Glucose-responsive CL is assumed to be 30% lower at hyperglycemic clamp based on preclinical observations; [d]EGC = 80 mg/dL.

Euglycemic clamp (EGC) predictions reported for EGC = 75 mg/dL except where noted; observations reported for EGC = 90 mg/dL. Pharmacodynamics measure is glucose infusion rate (GIR) or glucose disposal.

Figure 4. Predicted vs Observed PK-PD

Predicted T1DM subject PK-PD (lines) are overlaid with observed (circles) for euglycemic clamp (EGC, red) and clamp at 300 mg/cL (blue). Predictions are made from literature-based meta-analysis together with the observed 27x potency reduction in Parts I and II of the clinical study. Observations are consistent with predicted 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 fractional hepatic CL.[2,5] 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

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