

Alteration of glucose and insulin regulatory networks for the treatment of type 2 diabetes mellitus

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Abstract

A quantitative framework for the (patho)physiological mechanisms and pathways that underlie type 2 diabetes mellitus (T2D) is needed in order to characterize the pharmacological and toxicological attributes of single or multiple compound/target pairs. The objective of this work was to develop an integrated pharmacokinetic and (patho)physiological based model that links relevant information from *in vitro* experiments, evaluations in non-clinical studies, and results from clinical studies. In particular, a network of interactions that represents key attributes of T2DM was generated and relevant parameter values were identified from literature and non-clinical assessments. Virtual patients based on the disease state of the patients enrolled in Phase I studies were created with the goal of assessing the performance of altered glucose metabolism in late-stage clinical studies through trial simulation. In conclusion, this model may serve as a basis to identify the impact of altered pharmacokinetics and the pharmacokinetic/pharmacodynamic relationship to identify target populations for therapy and for lead optimization.

Background

Type 2 diabetes mellitus (T2D) accounts for more than 90% of all types of diabetes. This disorder afflicts an estimated 6% of the adult population in Western society and over 2% of the population worldwide. The worldwide prevalence of T2D is increasing and is expected to grow by 3% per annum, reaching an expected total of 210 million cases by 2010. While advances in the management of T2D have been made in recent years, many patients still remain inadequately treated. Development of novel therapeutics and/or use of combinations of novel and existing therapeutics will continue to aid advancements in the management of T2D. This poster presents a modeling and simulation framework that makes use of existing data to aid in the development of novel and combination therapeutics.

Methods

Virtual Patients

Approximately 150 virtual patients with T2D were defined by physiologically validated parameter sets that resulted in a fit of glucose and, if available, insulin concentration time profiles obtained from patients with T2D enrolled in several Merck & Co. Inc clinical studies and data reported in literature. All pathophysiological changes associated with the development of diabetes were considered. Often, multiple metabolic changes were needed to fit the parameters to the data, though those changes typically clustered within a metabolic pathway.

Regulatory Networks

Glucose and insulin regulatory networks were generated on the basis of several models available in the literature. Parameters for these networks were based on values reported in the literature (using more than 300 references), and nonclinical and clinical assessments. The regulatory networks implemented in this model include:

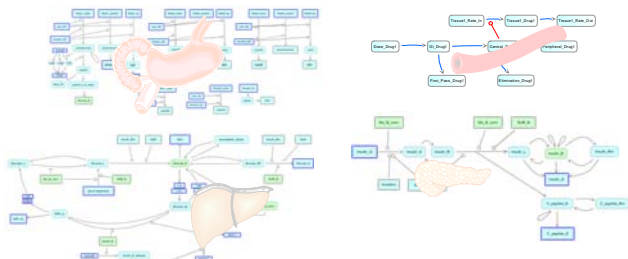
Glucose Inputs – IVGTT, OGTT, MTT

Drug Pharmacokinetics – two compartment model with effect compartment for two drugs: one to increase glucose metabolism and the second to increase insulin secretion/production

Glucose Regulation – first pass metabolism, glucose absorption rate, effect of dietary components, hepatic metabolism, peripheral tissue glucose metabolism

Insulin Regulation – production, release, metabolism

Figure 1 – Graphical depiction of the regulatory networks included in the model



Simulation Method

JDesigner was used to generate the reaction networks. A JDesigner export to MATLAB function was used to generate a MATLAB script with the ordinary differential equations (ODEs) from the JDesigner reaction networks. A wrapper that invoked the JDesigner derived script and parameter sets that defined the virtual diabetic patients was scripted in MATLAB for such larger scale computations as clinical trial simulation.

Clinical Study Simulation Method

Virtual patients were randomly sampled from a distribution representative of the target population and were administered a MTT 30 minutes post-dose with placebo (Figure 2), a drug to stimulate insulin production and secretion (Figure 3), a drug to stimulate glucose metabolism in tissue (Figure 4), or both drugs (Figure 5). The pharmacokinetics of the two drugs were altered by increasing the half-life to determine the effect of controlled-release (Figure 6).

Results

Figure 2

Baseline (placebo) glucose and insulin plots based on a MTT administered to virtual patients

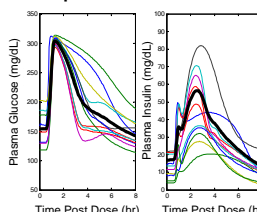


Figure 3

Effect of altered insulin regulatory networks by stimulation of insulin release and production

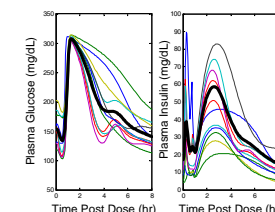


Figure 4

Effect of altered glucose regulatory networks by increasing glucose metabolism in tissue

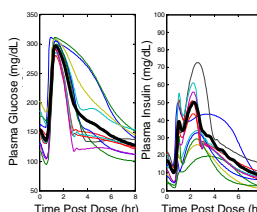


Figure 5

Effect of altered insulin and glucose regulatory networks

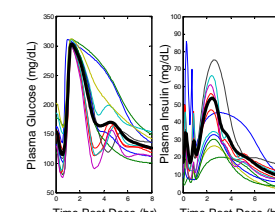


Figure 6

Effect of altered pharmacokinetics – controlled release formulation

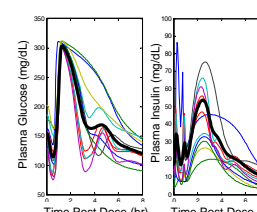


Table 1

Effect of altered glucose and insulin regulatory networks and pharmacokinetics on the mean 8-hr weighted mean glucose following a meal tolerance test

Modeling Scenario	Mean 8 hr WGMG (mg/dL)
Baseline	197.5
Increased Insulin Release or Production Alone	196.4
Increased Glucose Metabolism Alone	178.4
Increased Insulin Release or Production and Increased Glucose Metabolism	176.4
Increased Drug Half-life and Increased Insulin Release or Production and Increased Glucose Metabolism	174.6

Discussion and Conclusions

Alteration of key components of the glucose-insulin regulatory network can aid in the identification of targets to treat T2D. Using virtual patients based on subjects enrolled in clinical studies (Figure 2), clinical studies were simulated to identify the effect of different pharmacological interventions following a MTT. Increasing insulin release and/or production resulted in a minimal effect on the mean 8 hr-WGMG (Figure 3), suggesting that in this population of virtual patients, that therapies that target insulin release and/or production may be ineffective due to the disease state. On the other hand, increasing glucose metabolism was shown to be effective in reducing blood glucose levels (Figure 4). Combining both alterations in insulin and glucose regulatory networks resulted in approximately additive decreases in the mean 8 hr-WGMG (Figure 5). In addition, doubling the half-life of both drugs resulted in a mild reduction in the mean 8-hr WGMG (Figure 6).

In conclusion, the effect of altered PK and the PK/PD relationship can be explored, *in silico*, to identify key target(s) and to optimize the design of clinical studies.

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