Leveraging a Quantitative Systems Pharmacology Model to Explore the Mechanism of Action of a Novel Basal Insulin Analog

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Objectives: To mechanistically evaluate, using a Quantitative Systems Pharmacology [QSP] model, the plausible range of differential tissue distribution and insulin receptor binding of novel basal insulin analog [BIL] and its impact on glucose metabolism (endogenous glucose production [EGP] and glucose disposal rate [GDR]) in healthy subjects [HV] and patients with type 1 diabetes [T1DM].

Methods: A QSP model of glucose regulation was developed previously [1]. Data from a clinical euglycemic clamp study [2, 3] that evaluated EGP and GDR in HV and T1DM receiving intravenous infusion of Glargine [GL] for 8 hours was used to incorporate study design in the model. A range of values for two important mechanistic parameters that differentiated BIL from GL: tissue distribution (periphery:liver, [P:L]) and insulin binding affinity relative to GL (relative potency, [RP]) were used to simultaneously simulate the observed EGP and GDR of BIL.

Results: Plausible range of tissue distribution of BIL (P:L from 0.1 to 1) and relative potency (RP between 0.01 to 0.5) were used to simulate the clamp experiment in HV and T1DM subjects [2, 3]. Simulated EGP and GDR profiles were in agreement with clinical data for a select combinations of the 2 parameters – P:L ratio was estimated to be lower than 0.5 and RP between 0.05 and 0.1, based on simulating GDR and EGP data in HV simultaneously. Estimates from HV were confirmed in T1DM subjects. Additional hypotheses (e.g. different potency at liver and muscle, dose dependent tissue distribution etc.) were also examined. The estimated differential tissue distribution and relative potency of BIL was used to predict glucose responses for BIL in long term trials in T1DM subjects.

Figure: Basal insulin concentration vs. GDR and EGP relationships for BIL and GL in HV after 8 hours of primed intravenous infusion.

Conclusions: A QSP model with physiological parameters that can be modulated is a useful tool to aide the understanding of the mechanisms of action of a novel therapeutic agent. Attenuated peripheral activity of BIL with approximately 3-fold lower activity than in liver and potency relative to GL of 0.06, described the clinical data well.

References: