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

Parag Garhyan*[1], Rukmini Kumar[2], Jeanne Geiser[1]

[1] Global PK/PD/Pharmacometrics, Eli Lilly and Company, Indianapolis, USA. [2] Vantage Research, Chennai, India

ABSTRACT

Objective: 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 previously1. Data from a clinical euglycemic clamp study2, 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.

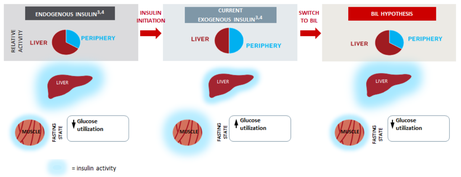
Results: Plausible range of tissue distribution of BIL (P:L from 0.1 to 1) and relative potency (RP between 0.01 to 0.5) were used to simulate the clamp experiment in HV and T1DM subjects2, 3. Simulated EGP and GDR profiles were in agreement with clinical data for a select combinations of the 2 parameters – 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.

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.

BACKGROUND

- Basal insulin peglispro (BIL) is a novel, PEGylated basal insulin with a large hydrodynamic size[4] and reduced insulin receptor binding affinity in comparison to human insulin5.
- The half-life of BIL is between 2-3 days and the peak-to-trough ratio is less than 1.5[6].
- BIL is distinguished from existing basal insulins by a peripheral-to-hepatic action more like that of endogenous insulin (Figure 1).
- Euglycemic clamp using tritiated glucose (D-[3-3H] glucose) is a standard method to estimate endogenous glucose production (EGP) and glucose disposal rate (GDR)[7].
- Based on euglycemic clamp studies in healthy subjects[2] and patients with Type 1 Diabetes (T1DM)[3], we used a Quantitative Systems Pharmacology (QSP) model of diabetes to estimate plausible ranges of relative potency and tissue distribution of BIL in comparison to insulin glargine.

Figure 1. Hepatic and Peripheral Activity of BIL Compared to Endogenous and Exogenous Insulin



METHODS

- The Lilly Metabolism Model was developed to describe the glucose metabolism and flux in key tissues/organs[1] (Figure 2).
- Insulin dependent rates of hepatic glucose output (EGP) and muscle glucose uptake (GDR) were calibrated using euglycemic clamp (with glucose tracer) and meal tolerance studies in healthy subjects and T1D virtual patients using published data (not shown here).
- Simulations were performed using virtual patients (healthy subjects and T1DM) for glargine and BIL.
- Observed data at the end of 8h or 10h of infusion indicating 'steady state' of EGP and GDR were compared over a range of glargine and BIL doses.
- Two important mechanistic parameters for BIL representing its reduced potency (relative potency with human insulin, RP) and hepato-preferential activity (periphery to liver distribution, P:L) were varied simultaneously to simulate the EGP and GDR profiles in healthy subjects and T1DM patients.

Figure 2. An Overview of QSP Model Structure Depicting Key Glucose Pathways (top panel) and Basal Insulin Specific Glucose Fluxes (bottom panel)

Abbreviations: G6P: Glucose 6 Phosphate; G6Pase: Glucose 6 Phosphatase
(M): mass flux

SIMULATION SETUP

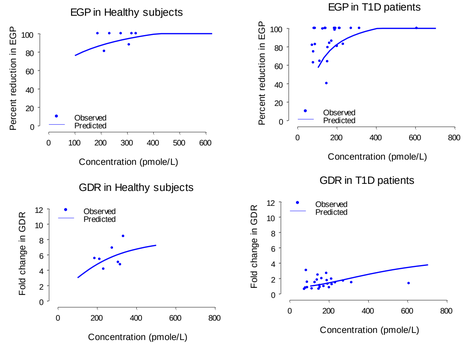
- Virtual Patients (VPs) were created to match the baseline characteristics of the healthy subjects and T1DM patients in the clinical study. Simulations were carried out to re-create the euglycemic clamp procedures.
- Healthy Subjects:
  - Mean HbA1c = 5%, mean fasting plasma glucose (FPG) = 90mg/dL.
- T1DM Patients:
  - Mean HbA1c = 7.7%, mean FPG = 180mg/dL (baseline in clinical trial: mean HbA1c = 7.6% and mean FPG = 181 mg/dL).
  - Physiological changes were implemented that distinguish T1DM patients from healthy subjects:
    - No endogenous production of insulin
    - Decreased insulin sensitivity in muscle and liver

RESULTS

Glargine (EGP and GDR)

- Simulations were consistent with EGP and GDR data in healthy subjects and T1DM patients in response to glargine infusion (Figure 3).
- A range of EGP suppression and GDR increase were observed, but the magnitude of GDR increase in T1DM patients was lower than healthy subjects.
- Simulated glucose infusion rates and EGP were also compared to published reports of glargine euglycemic clamp studies and found to be consistent (not shown)

Figure 3. Simulations (lines) Described the Observed EGP and GDR Data (points) Reasonably Well in Healthy Subjects and T1DM patients with Glargine Across a Range of Concentrations

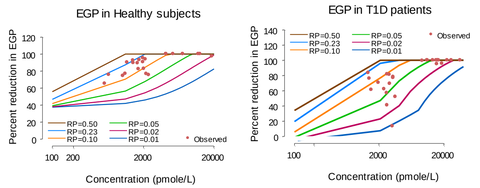


RESULTS

BIL (EGP and GDR)

- BIL suppressed EGP in a dose (concentration)-dependent manner.
- Increase in EGP suppression was simulated with higher RP values (RP=0.01 to 0.5, Figure 4).
- Varying P:L ratio did not affect the EGP values because the concentration of BIL in liver is assumed to be identical to that in the blood. Varying P:L impacts the peripheral activity of insulin, not the activity in the liver.

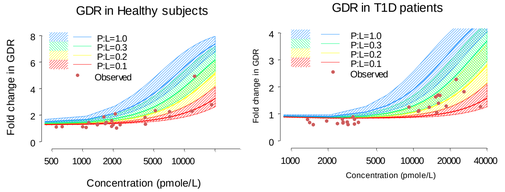
Figure 4. Simulations (lines) Show That a Range of RP Values Can Potentially Describe the Change in EGP Observed in Healthy Subjects and T1DM patients



BIL (GDR)

- Magnitude of increase in GDR with BIL was smaller than glargine.
- The differential effect on GDR at similar EGP suppression (indicative of reduced peripheral glucose uptake by BIL) was implemented in the QSP model using a range of P:L ratio for BIL.
- Simulated profiles of GDR at various BIL concentrations with combinations of P:L ratio (between 0.1 - 1) and RP (between 0.05 - 1) overlaid with the observed data are presented in Figure 5.
- In healthy subjects, 100% suppression of EGP was achieved at ~2000 pmol/L, the GDR increased by ~2 fold. Magnitudes of EGP suppression and GDR increase were lower in T1DM patients at similar concentrations.

Figure 5. Simulated Change in GDR (lines and shaded regions) in Healthy Subjects and T1DM patients for a Range of RP and P:L Values



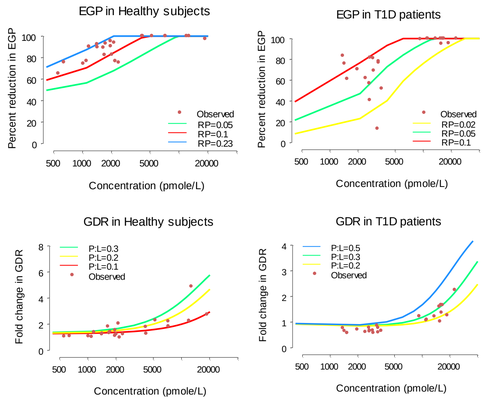
RP values ranged from 0.05 to 1.0. The solid line within each shaded area represents RP=0.07.

RESULTS

BIL (EGP and GDR)

- Simulated EGP and GDR with a combination of P:L < 0.3 and RP = 0.06 appear more consistent with observed data for BIL in healthy subjects and T1DM patients (Figure 6).

Figure 6. Simulated EGP and GDR (lines) versus Concentration Overlaid with Observed Data (points) for BIL in Healthy Subjects and T1DM Patients



CONCLUSIONS

- Attenuated peripheral activity of BIL with approximately 2 - 5-fold lower activity than in liver (P:L ratio = 0.2 - 0.5) and reduced potency relative to human insulin (RP = 0.06), described the mechanistic clinical data well in healthy subjects and T1DM patients across a wide range of doses.
- A QSP model with physiological parameters that can be modulated within a reasonable range is a useful tool to aide the understanding of the mechanisms of action of a novel therapeutic agent.

References:

1. Kumar R et al, JPKPD, M-028, Volume 41, Issue 1 Supplement, October 2014.
2. Henry, RR et al, Diabetes. 63(Suppl 1):A226, 2014 (note for Libra reviewers: this is ADA abstract reference, not the publication).
3. Mudaliar S et al, Diabetologia, 58: S1 2015.
4. Hansen RJ et al, Diabetes. 61: A228, 2012.
5. Owens RA et al, J Pharmacol Exp Ther. 357(3):459-65, 2016.
6. Sinha VP et al, Diabetes Obes Metab. 16: 344-350, 2014.
7. Mudaliar S et al, Diabetes Care. 25:1597–1602, 2002.

* Parag Garhyan, PhD, Eli Lilly and Company, Indianapolis, IN, 46285
Phone: 37-276-0963, Email: PGarhyan@lilly.com

Sponsored by Eli Lilly and Company