M-028

Designing Optimal Basal Insulin Analogs Using a Quantitative Systems Pharmacology Model

Rukmini Kumar[1], Jeanne Geiser[2], Jennifer Leohr[2], Derek Leishman[2], Brian Topp[2]
[1]Vantage Research, Chennai, INDIA, [2]Eli Lilly and Company, Indianapolis, IN, USA

ABSTRACT

Objectives: To identify optimal PK/PD characteristics for a next generation basal insulin analog that maximize efficacy and minimize hypoglycemic risk. Here we focus on quantifying the relationship between the rate of insulin absorption from the subcutaneous space into plasma (Ka) and clinical outcomes (HbA1c, Fasting Plasma Glucose and rates of hypoglycemia).
Methods: A systems pharmacology model of plasma glucose regulation was developed (Lilly Metabolism Model) and calibrated to clinical data on existing insulin therapies. Virtual patients (250) were developed and calibrated to baseline characteristics and response to basal insulin treatment (Glargine) from Zinman et al. 2012 [1]. Five theoretical insulin analogs were created with a wide range of Ka values, but identical values for clearance, bioavailability, and volume of distribution. Chronic dosing for 26 weeks was simulated for each analog in each virtual patient
Results: Ka was increased to achieve a Tmax of 6, 9, 12, 24 and 48 hr resulting in a peak to trough ratio of 5.3, 2.0, 1.6, 1.1, and 1.05 and reduced hypoglycemia (23, 14, 10, 9, 9 events < 70mg/dL per patient year) in a moderately severe Type 2 diabetic population (Initial HbA1c = 8.2%) when predicted efficacy was similar for all insulin analogs. Similar results were obtained when titrating to various Plasma Glucose targets.
Conclusions: Simulation results presented here suggest that slowing absorption is a promising strategy for decreasing hypoglycemic risk with insulin treatment, however, this relationship appears to saturate at a Tmax of about 24 hours. Since insulin analogs presently in development are approaching optimal Ka values, other characteristics, such as tissue distribution will need to be manipulated to see further reductions in hypoglycemic risk. Quantitative Systems Pharmacology models of relevant physiology can be used to visualize clinical outcomes of novel therapies and provide direction to drug development.

BACKGROUND

- Insulin was first commercialized in 1923 dramatically improving morbidity and mortality in patients with diabetes.
- However, insulin Rx does not match normal plasma insulin profiles.
- As a result insulin treated patients display elevated glucose levels and increased risk of hypoglycemia
- Several generations of basal insulin analogs have been developed
- Each generation has reduced hypoglycemic risk by displaying longer and flatter PK profiles.
- It is unclear if the development of ultra-long basal insulin analogs will continue to reduce hypoglycemic risk or if present basal insulin analogs are “flat-enough” to minimize hypoglycemic risk.

METHODS

- The Lily Metabolism Model was adapted from the Entelos Metabolism PhysioLab[2] and simplified to facilitate the target selection for next generation basal insulin analogs.

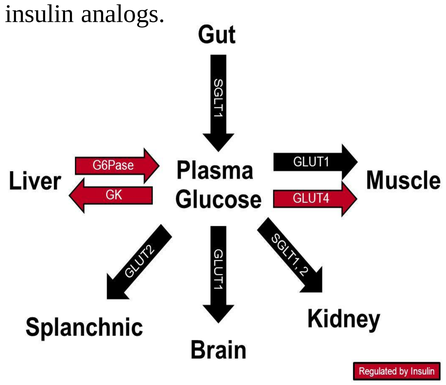

Figure 1. Schematic of Lilly Metabolism model

- Population of Virtual Patients with varying disease parameters were developed and response to exemplar basal insulin Glargine was used to calibrate insulin sensitivity of population and frequency of hypoglycemic events

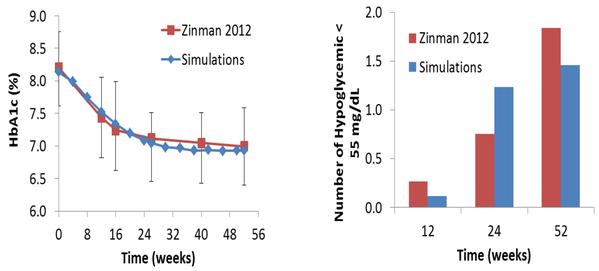

Figure 2. Model matches clinical safety and efficacy data

- Virtual clinical trials were simulated with 250 insulin naïve virtual patients with type 2 diabetes
- 52 weeks of chronic dosing with insulin dosing titrated to meet targets of HbA1c reduction (Fig. 4a) or dosing adjusted for individual patient insulin sensitivity to achieve similar HbA1c drop (Fig. 4b)

RESULTS

- Five theoretical insulin analogs were created by varying the absorption rate, but keeping all other PK parameters constant

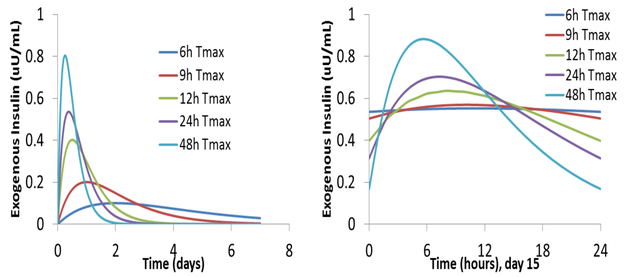

Figure 3. PK profiles of theoretical insulin after a single (left) and multiple doses (right).

- These theoretical insulin analogs displayed a Tmax of 6, 12, 18, 24, and 48 hours respectively (Fig. 3, left)
- The Peak to Trough ratios with daily dosing at steady state are 5.3, 2.0, 1.6, 1.1, and 1.05 respectively (Fig 3, right)

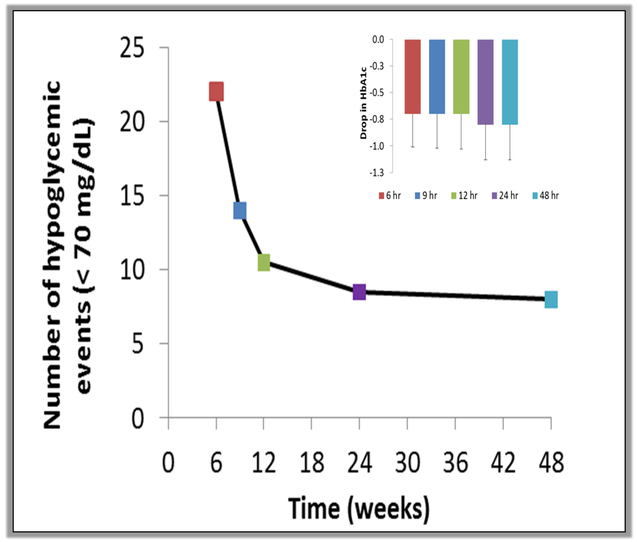

Figure 4. For a given efficacy, hypoglycemia reduces for flatter insulin PK profiles

- In a virtual clinical trial of 250 patients given a daily fixed dose (38 U/d) of a theoretical insulin (adjusted for variability in virtual patient insulin sensitivity), the decrease in HbA1c over 52 weeks is similar (~1%) (Figure 4 insert) but the number of hypoglycemic events are reduced with flatter insulin profiles - 23, 14, 10, 9, 9 events (< 70mg/dL) per patient year. (Fig. 4)
- At a standard efficacy, hypo is projected to display a nonlinear relationship with Ka

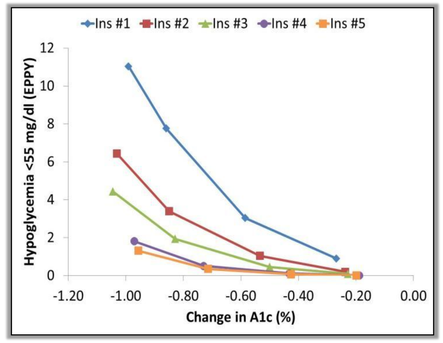

Figure 5. Hypoglycemia increases with increasing dose (and increasing efficacy) for all theoretical insulins

- Hypoglycemic risk increased with dose and efficacy
- Flatter PK profiles showed a flatter relationship between hypo and A1c

CONCLUSION

- QSP models used to visualize outcomes early in drug design and provide guidance to project teams on advantages and disadvantages of strategy employed
- 5 different theoretical insulin PK profiles were developed by adjusting rate of absorption from the injection site
  - Peak to Trough ratio at steady-state ranges from ~5 to 1; Time to peak ranges from 6-24 hours
  - Drop in HbA1c and hypoglycemic events were simulated
- Slowing absorption is a promising strategy for decreasing hypoglycemic risk with insulin treatment
- However, this relationship appears to saturate at a Tmax of about 24 hours

References

1. Zinman, B et al, on behalf of the NN1250-3579 (BEGIN Once Long) Trial Investigators, 2012. Insulin Degludec Versus Insulin Glargine in Insulin-Naïve Patients with Type 2 Diabetes. Diabetes Care December 2012 Vol. 35 no. 12 2464-2471
2. David J. Klinke. 2008. Integrating Epidemiological Data into a Mechanistic Model of Type 2 Diabetes: Validating the Prevalence of Virtual Patients. *Annals of Biomedical Engineering* **36**:2, 321-334.

For questions related to this presentation, please contact Dr. Rukmini Kumar, Vantage Research
Email: rukmini@vantage-research.net

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- A Quantitative Systems Pharmacology models was developed in order to predict responses to basal insulin treatments