MODELLING SUBCUTANEOUS ABSORPTION OF U100 AND U300 INSULIN GLARGINE IN TYPE 1 DIABETES

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BACKGROUND AND AIM

Subcutaneous administration of long-acting insulin analogues are often employed in multiple daily injection (MDI) therapy of type 1 diabetes (T1D) to cover patient's basal insulin needs. Among these, insulin glargine 100 U/mL (Gla-100) and 300 U/mL (Gla-300) are formulations indicated for once daily subcutaneous administration in MDI therapy of T1D. Some models of subcutaneous insulin absorption of insulin glargine have already been proposed but were not assessed under controlled experimental conditions for both formulations. The aim here is to develop a **model of subcutaneous absorption** of both **Gla-100** and **Gla-300** formulations in **T1D**.

DATABASE & PROTOCOL

Subjects

A total of **54 T1D** subjects from 2 different datasets:

- *Dataset 1*: N=24 (age 43±10 y, body weight 79±10 kg, BMI 25±2 kg/m^2)
- *Dataset 2*: N=30 (age 43±9 y, body weight 79±12 kg, BMI 25±3 kg/m^2)

Protocol

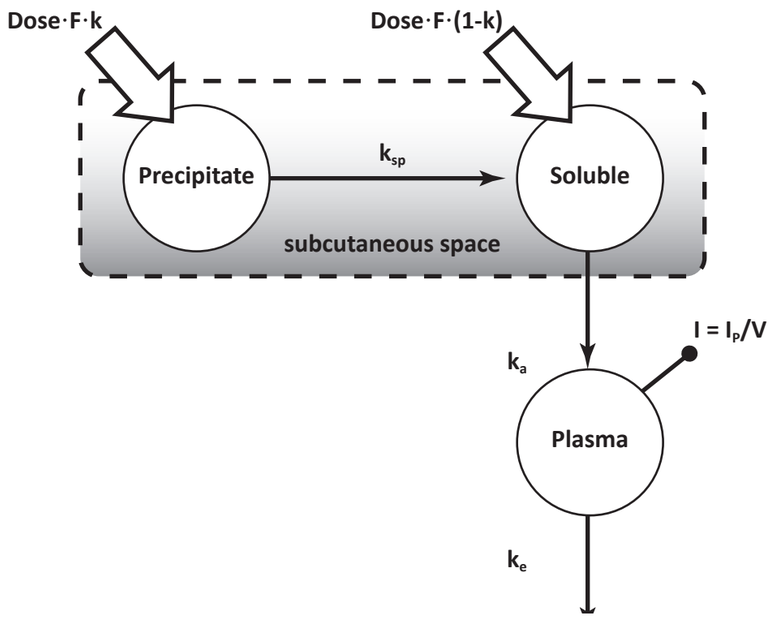
- *Dataset 1*: a randomized, 4-sequence, cross-over, double-blind, dose-response **euglycaemic** clamp study of **single-dose** subcutaneous administration of 0.4, 0.6 and 0.9 U/kg Gla-300 and 0.4 U/kg Gla-100 (NCT01195454) [1].
- *Dataset 2*: a randomized, cross-over, double-blind, two-treatment, two-period, two-sequence in **two parallel cohorts euglycaemic clamp** study after **8-day once-daily** subcutaneous administration of 0.4 (cohort 1) or 0.6 (cohort 2) U/kg Gla-300 in one treatment vs. 0.4 U/kg Gla-100 in the other (NCT01349855) [2].

Plasma insulin concentrations were measured for 36 h using a validated radioimmunoassay (LLOQ: 5.02 μU/mL).

METHODS

Model:

The subcutaneous absorption of Gla-100 and Gla-300 is described as a two-compartment model coupled with a single compartment for plasma insulin kinetics [3].



where

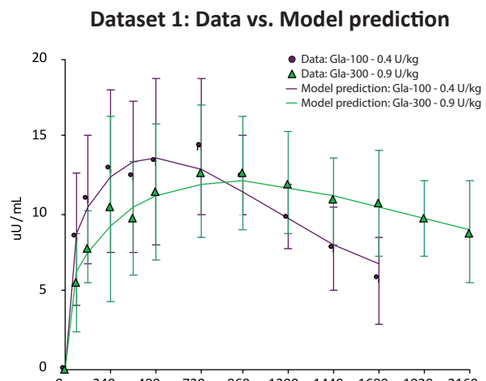
- **Dose** is the subcutaneous insulin dose administered
- **F** is the bioavailability
- **k** is the precipitate fraction of the administered dose
- k_{sp} is the rate constant of dissolution from precipitate to soluble state
- k_a is the rate constant of insulin absorption to plasma
- k_e is the fractional rate of plasma insulin clearance
- **V** is the insulin distribution volume

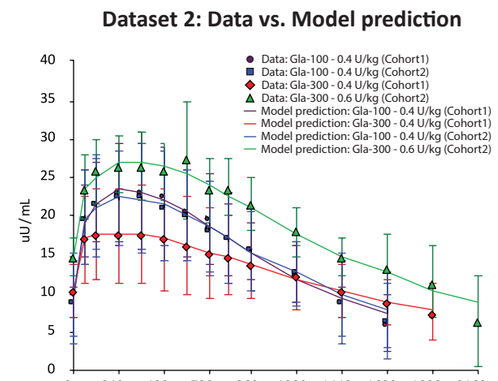
Identification strategy:

- Model parameters are estimated with a Bayesian Maximum a Posteriori identification technique since the model is a non-uniquely a priori identifiable.
- Measurement error on insulin concentration is assumed to be uncorrelated, Gaussian, with zero mean and variance defined in [4], while values at insulin concentration below LLOQ are fixed to zero with infinite variance.

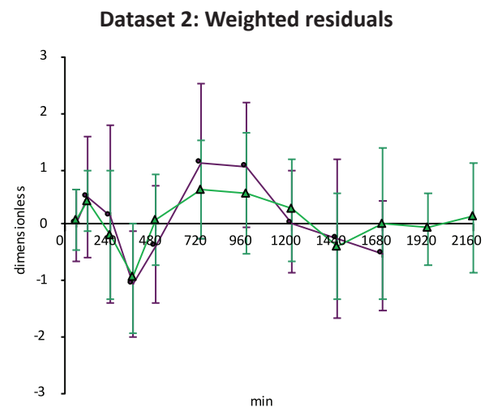
RESULTS

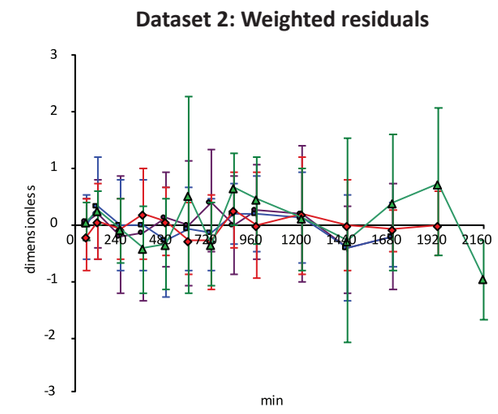
Data vs. Model prediction:



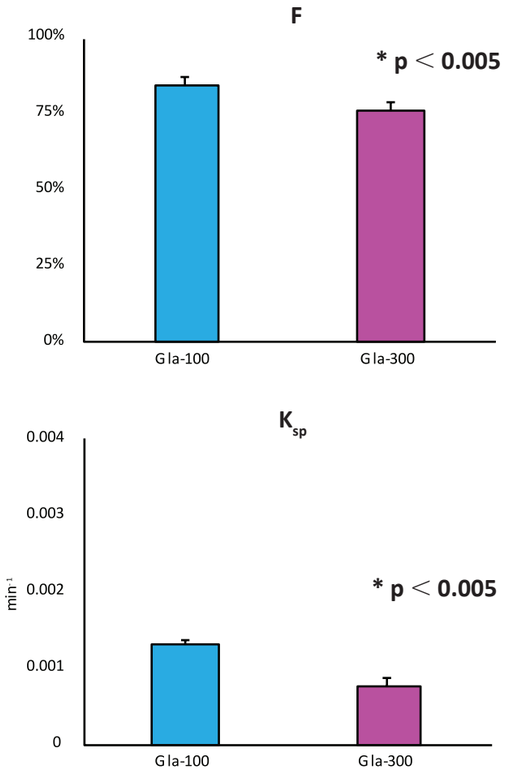


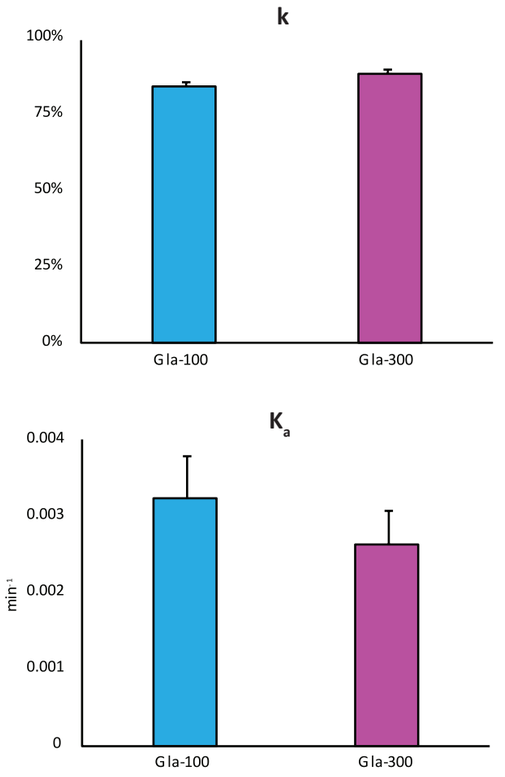
Weighted residuals:





Model parameters of subcutaneous absorption:





CONCLUSIONS

- A new model of subcutaneous insulin absorption of Gla-100 and Gla-300 is developed describing the gradual dissolution from the precipitate to soluble state for both insulin formulations.
- The model well predicts the data and provides precise parameter estimates characterizing the different rates of subcutaneous absorption into plasma between Gla-100 and Gla-300 formulations.
- The model will be then incorporated into the UVA/Padova T1D Simulator together with the joint parameter distribution. This will open the door to perform in silico clinical trials for testing novel up-titration and insulin glargine switching rules.

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