Introduction

The Integrated Glucose-Insulin (IGI) model [1] is widely used to characterize the effects of antidiabetics. It captures various major metabolic functions involved in the glucose homeostasis, such as:

- First-phase insulin secretion,
- Second-phase insulin secretion,
- Insulin mediated glucose clearance (CLGI),
- Non-insulin mediated glucose clearance (CLG), and
- Endogenous glucose production (glucose-inhibited).

The IGI model has been applied to describe several challenge tests, such as the intravenous glucose tolerance test (IVGTT), oral glucose tolerance tests (OGTT), mixed meal tolerance tests (MMTT) and clamp studies. An important aspect in the development of antidiabetic drugs is to translate the effects of treatment from preclinical species into the clinic. The IGI model has been used for this purpose to translate the clinical glycemic response into human volunteers [3]. This is the first inclusion of GGI data into the IGI concept, with inclusion of scaling to a new species: NHP.

Objectives

To develop a foundational framework to extrapolate novel drug effects observed in non-human primates (NHP) to healthy volunteers, utilizing the Graded Glucose Infusion (GGI) study paradigm. The GGI is a simpler method than the hyperglycemic clamp (HGC) for measurement of glucose-dependent insulin secretion (GDS).

Methods

- Placebo glucose and insulin full profile data from three healthy subject GGI studies (N=47) and one NHP GGI study (N=11) were included for an analysis using NONMEM.
- The IGI model developed by Silber et al [1] was the starting point. The need for adjusting parameters to fit the GGI data was assessed (2). Translation to NHP was done by allometric scaling of the human GGI model [3]. Subsequently the need for parameter adjustments was assessed.
- The model was evaluated using VPCs and was externally qualified on human GGI data from a separate study.

For the estimation of Insulin secretion (Isec) and beta-cell sensitivity (IIS), slope of insulin secretion vs glucose concentration, the GGI protocol was simulated using the population parameter from the IGI model. The steady state solution was used to calculate Isec [2].

Study design

Human data:

- Placebo glucose and insulin data from three placebo groups of a randomized, 4-period study using a graded intravenous administration of glucose (N=26).
- A stepwise graded infusion was initiated (t=0) with a stable rate of infusion maintained for 40 minutes at each of 5 steps: 2-, 4-, 6-, 8-, and 12 mg/kg/min. Blood samples for glucose, insulin, and C-peptide were collected every 10 minutes during each glucose infusion step.
- For external qualification insulin and glucose data from another GGI study was used (N=21).

NHP data:

- For the NHP part of the model, the data included observations of glucose and insulin from the placebo groups of a NHP GGI study (N=11).

Results

- First-phase insulin secretion was absent in GGI, which is anticipated as the glucose levels are slowly increasing.
- The CLGI and IPRG were estimated in combination with GSS and IIS and residual RESG and RESI for both NHP and human data.
- Based on the VPC and external qualification the final IGI model for each species adequately described the human and NHP GGI data.
- Species differences between NHP and humans were observed for CLGI, IPRG and GPMG estimates. The GPMG is much stronger in NHP compared to human (-19.9 vs. -2.97, respectively). IPRG seems to be comparable, although insulin levels in NHP reach much higher levels after glucose infusions. This may effect of IPRG was estimated modeled for 6-min infusion for CLGI could be the model compartmentizing for the absence of an insulin effect on the glucose production (IPRG) (5).
- ISR and BCS are in line with observed data. Differences observed in AICON paper [2] using the Silber model data (Fig. 3a) are not visible any more after model update (Fig. 3B).

Conclusions & Perspectives

- The IGI was optimized to human GGI placebo data and allometrically scaled and optimized to the NHP GGI placebo data. The presented model is also an extension of the IGI model to NHPs and to a GGI application.
- This foundational framework for interspecies translation of placebo GGI data can be used as a starting point in the drug discovery setting, to explore the effect of novel diabetes treatments on GDS and ISR from animal to human.