Application of a Semi-Mechanistic, Integrated Glucose-Insulin Model to Graded Glucose Infusion Placebo Data to translate Glucose Insulin dynamics between Healthy Humans and Non-Human Primates

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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 homeo-stasis, 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 GGI procedure has been used to estimate beta-cell sensitivity, as the slope of insulin secretion versus glucose at steady-state during a stepped glucose infusion.

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 Han Wistar rats [3]. This is the 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 (GDIS).

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 (BCS, 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).

Species	Nr of subjects in placebo group	BW range (kg)	Glucose Dose (mg/kg/min)	Time (min)	Glucose range (mg/dL)	Insulin Range (mg/dL)	comment
Human	26	65 - 99	2, 4, 6, 12, 6, 4	0–270	79 - 325	1.9 - 335	Obese subjects ignored
Human	21	63 - 94	2, 4, 6, 12, 6, 4	0-250	78 - 342	1.8 - 220	Used for external validation
NHP	11	8.4 - 16	2, 4, 8, 16	30-180	47-209	2.6-1997	

Table 1: Overview of data used for modeling

Model

Allometric Scaling and Estimation of parameters for the healthy subjects IVGTT model

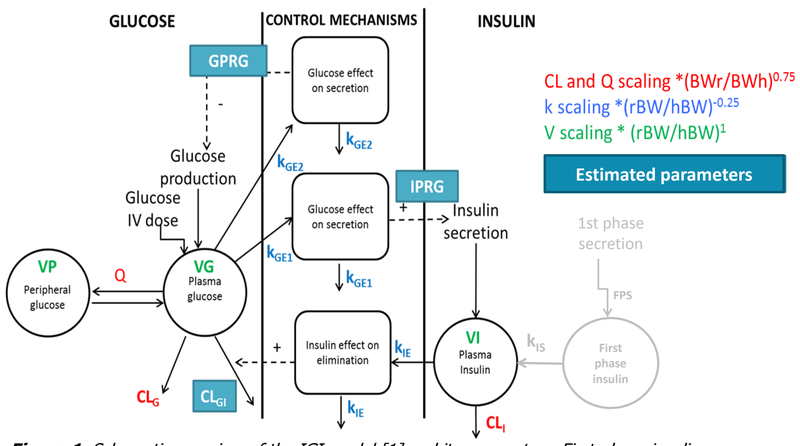

Figure 1. *Schematic overview of the IGI model [1] and its parameters. First-phase insulin secretion was not observed in the GGI data and was omited from the model.*

Model Parameters

- CLG, insulin-independent glucose clearance; pat, patient-specific parameter;
- CLGI, insulin-dependent glucose clearance;
- CLI, insulin clearance;
- GPRG, control parameter for glucose effect on glucose production;
- IPRG, control parameter for the effect of glucose on insulin secretion;
- kGE1, kGE2, and kIE, rate constants of the effect compartments;
- Q, intercompartmental clearance of glucose;
- RESG, and RESI, residual errors for total glucose, and insulin;
- VI, volume of distribution of insulin;
- (–), parameter has no unit
- Estimated parameters are in Table 2, other parameters are fixed to the final estimates determined based on intravenous provocations by Silber et al. [1].

	Human		NHP	
Parameter	Final Model	90% CI from bootstrap N=500	Final Model	90% CI from bootstrap N=500
CLGI (L/min (mU/L))	0.0038	0.00318 - 0.00448	0.0003	0.00019 – 0.00033
IIV	24%			
IPRG (–)	2.98	2.71 - 3.25	2.94	2.27 – 3.61
IIV	26%			
GPRG (–)			-19.9	-44.2 - -13.6
GSS (mU/L)	92.0	89.8 - 94.2	66.5	64.2 – 68.6
IIV	6%		6%	
ISS	5.09	4.48 - 5.69	24.1	17.9 – 34.5
IIV	35%		15%	
RESG	0.056	0.044 - 0.068	0.0577	0.040 – 0.0761
RESI	0.300	0.225 - 0.375	0.654	0.409 – 0.806

Table 2. * RSE, relative standard error in % calculated from Bootstrap results; IIV, inter-individual variability.

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 ISS 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 NPH and humans were observed for CLGI, IPRG and GPRG estimates. The GPRG 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 infusion. The high effect of GPRG estimated for NHP could be the model compensating for the absence of an insulin effect on the glucose production (GPRI) [5].
- ISR and BCS are in line with observed data. Differences observed in ACoP poster [2] using the Silber model parameters (Fig. 3A) are not visible any more after model update (Fig. 3B).

Visual Predictive checks

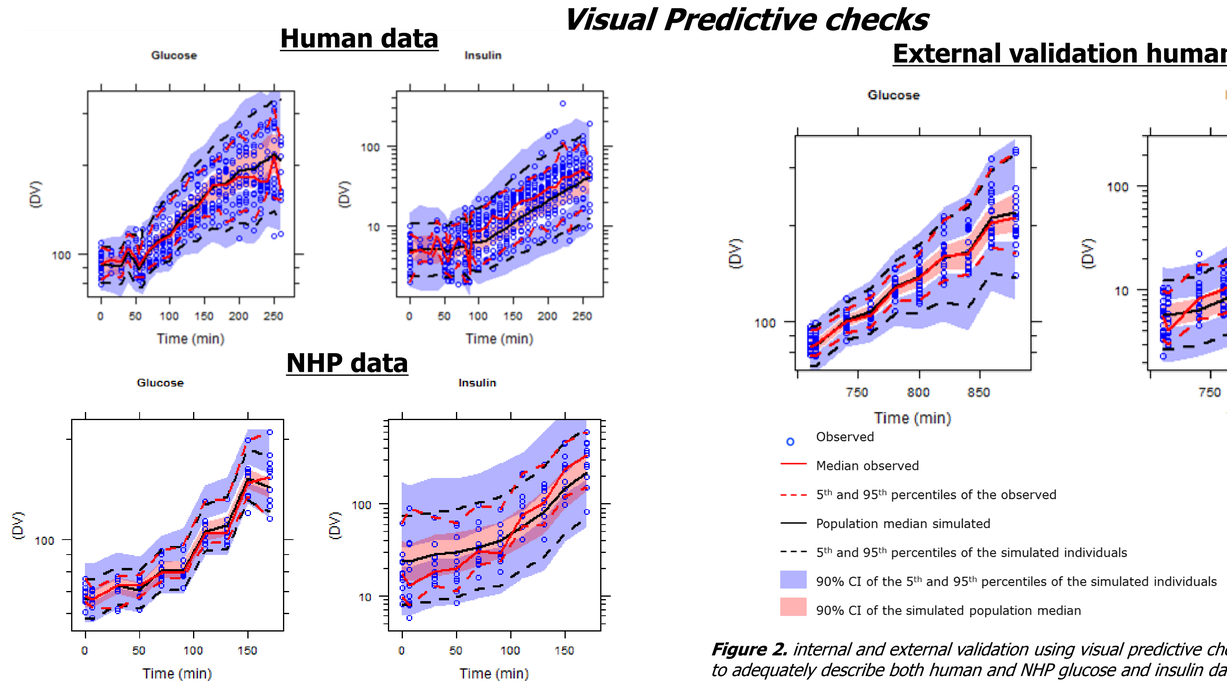

Figure 2. *internal and external validation using visual predictive checks (VPCs). Model is able to adequately describe both human and NHP glucose and insulin data.*

Calculation of ISR and BCS

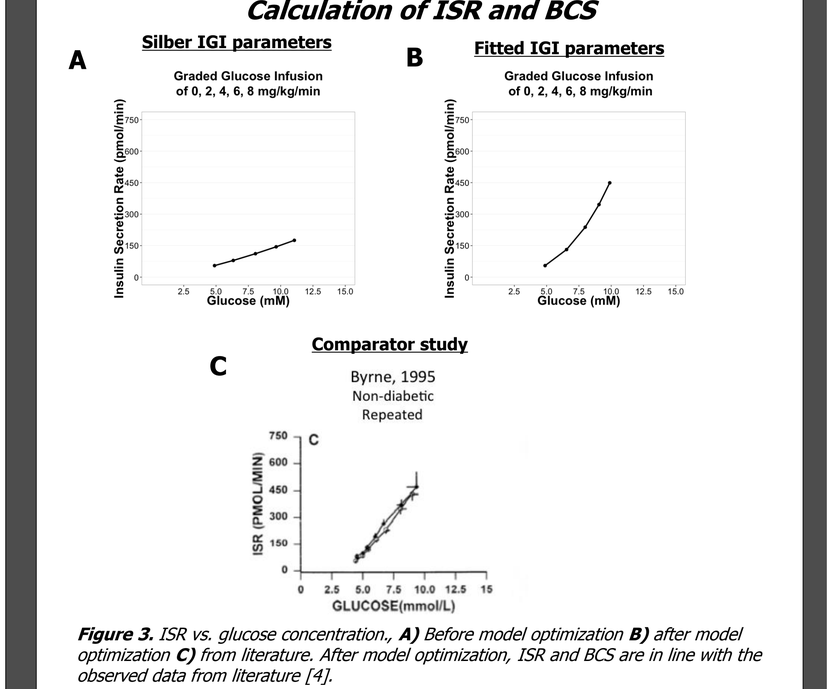

Figure 3. *ISR vs. glucose concentration., **A)** Before model optimization **B)** after model optimization **C)** from literature. After model optimization, ISR and BCS are in line with the observed data from literature [4].*

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 GDIS and ISR from animal to human.**

[1] Silber HE, Jauslin PM, Frey N, Gieschke R, Simonsson USH, Karlsson MO. An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocations. J Clin Pharmacol 2007;47:1159–71.
[2] Craig Fancourt, Wei Gao, Rolien Bosch, Chandni Valiathan, Ryan Vargo, P.A. Kothare, Teun Post , Application of the Integrated Glucose-Insulin Model to the Graded Glucose Infusion and Glucose Clamp Studies, ACOP 2014.
[3] Alskär et al. Using allometric scaling on an integrated glucose insulin model for humans to investigate anti-diabetics drug effects in rats, PAGE 21 (2012) Abstr 2540 [www.page-meeting.org/?abstract=2540]
[4] Byrne et al. (1995). Insulin secretion and clearance during low-dose graded glucose infusion. *American Journal of Physiology-Endocrinology and Metabolism*, 31(1), E21.
[5] Hanna E. Silber, Nicolas Frey, Mats Karlsson. An integrated Glucose-Insulin Model to Describe Oral Glucose Tolerance Test Data in Healthy Volunteers. J Clin Pharmacol 2010;50:246-256