Translational Modeling of Regular Human Insulin Pharmacokinetics and Glucose Dynamics in Minipig and Dog

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Objectives

- To develop a translational PKPD model that characterized the dynamic interaction of glucose and insulin following administration of recombinant human insulin (RHI) in minipigs and dogs with the ability to translate PK and PD in animals to humans
- The model aimed to quantify the difference in PK and PD parameters between
  - Species: minipigs, dogs, and humans
  - Disease state: diabetic and nondiabetic

Methods

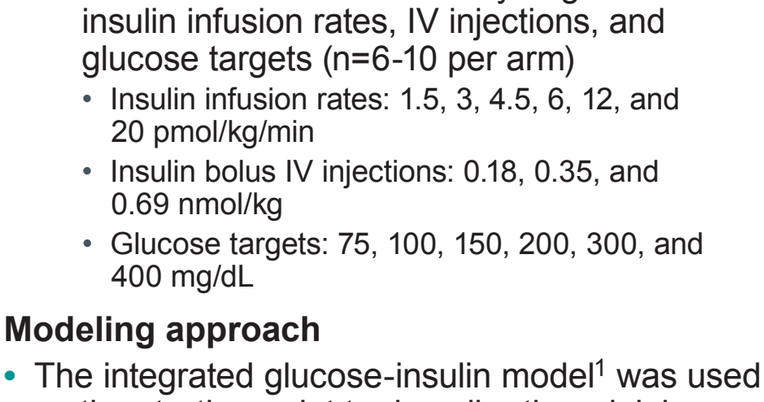
Animal data

- Minipig
  - Time-course insulin and glucose data were available from 5 different studies in both diabetic and nondiabetic minipigs administered a single bolus IV injection of RHI at multiple dose levels (n=6-12 per group)
    - Diabetic minipigs: 0.17, 0.35, 0.69, 0.9, and 1.4 nmol/kg
    - Nondiabetic minipigs: 0.17, 0.35, and 0.69 nmol/kg
- Dog
  - Time-course insulin and glucose data were generated in 4 glucose IV clamp studies in somatostatin-infused healthy dogs at various insulin infusion rates, IV injections, and glucose targets (n=6-10 per arm)
    - Insulin infusion rates: 1.5, 3, 4.5, 6, 12, and 20 pmol/kg/min
    - Insulin bolus IV injections: 0.18, 0.35, and 0.69 nmol/kg
    - Glucose targets: 75, 100, 150, 200, 300, and 400 mg/dL

Modeling approach

- The integrated glucose-insulin model[1] was used as the starting point to describe the minipig PKPD data
- Model parameters were allometrically scaled, estimated for a typical human body weight of 70 kg, to allow for translation to other species
- The parameters V_G, V_P, V_G, and K_{IE} were taken from literature[1], allometrically scaled from literature, and fixed
- The final minipig model was allometrically scaled[2] to the dog using individual body weights and baseline insulin and glucose to predict the data observed in the dog, followed by re-estimation of parameters

The integrated glucose-insulin model



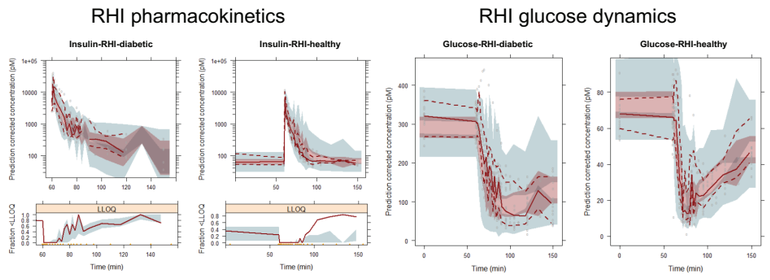
Allometrically scaled and fixed parameters: V_G, V_P, V_G, and K_{IE}

References

1. Silber HE, et al. An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocations. *J Clin Pharmacol.* 2007;47:1159-1171.
2. Alskär et al. Using allometric scaling on an integrated glucose insulin model for humans to investigate anti-diabetics drug effects in rats. Presented at the 21st meeting of the Population Approach Group in Europe. June 5-8, 2012, Venice, Italy. Abstract 2540.
3. Yki-Järvinen H, Young AA, Lamkin C, Foley JE. Kinetics of glucose disposal in whole body and across the forearm in man. *J Clin Invest.* 1987;79(6):1713-1719.
4. Hansen IL, Cryer PE, Rizza RA. Comparison of insulin-mediated and glucose-mediated glucose disposal in patients with insulin-dependent diabetes mellitus and in nondiabetic subjects. *Diabetes.* 1985;34(8):751-755.
5. Becker RH, Frick AD, Burger F, Scholtz H, Potgieter JH. A comparison of the steady-state pharmacokinetics and pharmacodynamics of a novel rapid-acting insulin analog, insulin glulisine, and regular human insulin in healthy volunteers using the euglycemic clamp technique. *Exp Clin Endocrinol Diabetes.* 2005;113(5):292-297.

Results

Visual predictive check – final minipig model



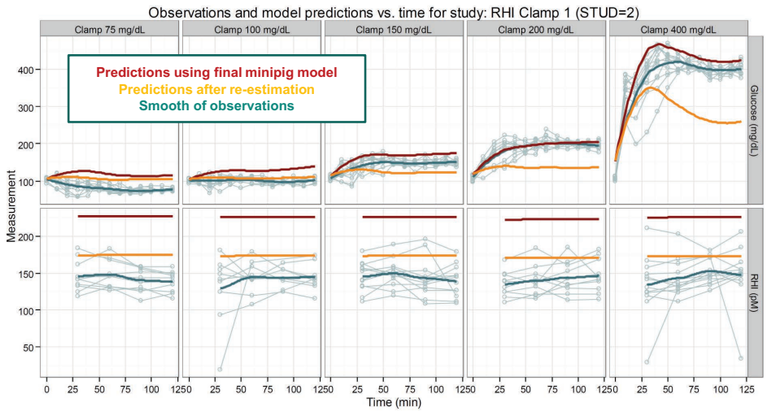
Red lines: 10th, 50th, and 90th percentiles of observations.
Gray and red shades: 10th, 50th, and 90th percentiles of predictions.

Final minipig parameters

Parameter (unit)	Description	Typical Value	RSE	IIV (CV)	RSE
CLI_RHI (L/min)	CL of RHI	0.783	36%	55%	59%
QI_RHI (L/min)	Q of RHI	0.227	39%	92%	96%
V1I_RHI (L)	V1 of RHI	4.02	28%	59%	33%
V2I_RHI (L)	V2 of RHI	1.13	52%	79%	68%
D_V2I_RHI	Proportional increase in V2_RHI in diabetic: V2=V2I_RHI·(1+D_V2I_RHI)	3.18	66%	ne	
ISS_H (pM)	Insulin baseline	55.9	18%	30%	26%
GSS_H (mg/dL)	Glucose baseline in healthy	72.9	1.9%	11%	17%
GSS_D (mg/dL)	Glucose baseline in diabetic	289	2.3%	9.7%	19%
CLG (L/min)	Insulin-independent glucose CL	0.038	27%	101%	21%
CLGI_RHI_H (L/min/pM)	RHI-dependent glucose CL in healthy	0.00392	63%	67%	47%
CLGI_RHI_D (L/min/pM)	RHI-dependent glucose CL in diabetic	0.000808	39%	67%	47%
QG (L/min)	Q of glucose	0.442*			
V1G (L)	V1 of glucose	9.33*			
V2G (L)	V2 of glucose	8.56*			
KGE (min^{-1})	Effect delay rate constant (ke0) for glucose on EGP	0.0292	16%	68%	18%
KIE (min^{-1})	Effect delay rate constant (ke0) for insulin on EGP	0.0213*			
GPRG_RHI_H	Shape factor for glucose feedback on EGP for healthy receiving RHI	-1.07	20%	ne	
GPRG_RHI_D	Shape factor for glucose feedback on EGP for diabetic receiving RHI	-1.4	57%	ne	

*Parameter fix to prior estimate.
IIV=inter-individual variability; CV=coefficient of variation; L=liter; h=hour; D=diabetic; H=healthy; RSE=relative standard errors; ne=not estimated. RSE is related to the standard deviation for the IIV terms and for the residual errors.

Final model predictions for RHI in the dog



Final dog parameters

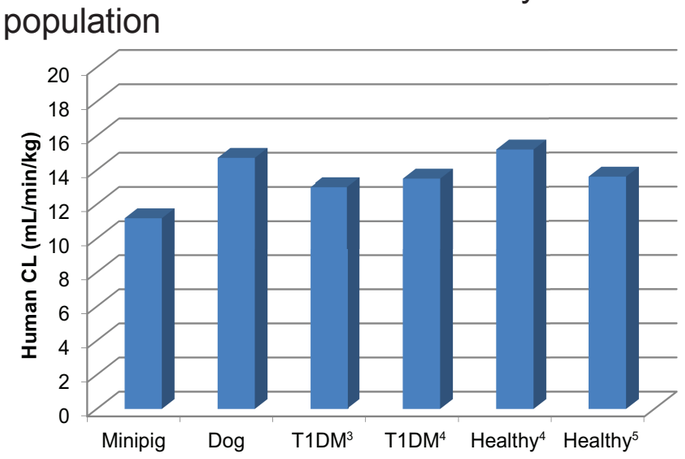
Parameter (unit)	Description	Typical Value	RSE	IIV (CV)	RSE
CLI_RHI (L/min)	CL of RHI	1.03	7.3%	55%*	
QI_RHI (L/min)	Q of RHI	0.123	30%	92%*	
V1I_RHI (L)	V1 of RHI	5.30	16%	59%*	
V2I_RHI (L)	V2 of RHI	1.08	35%	79%*	
ISS (pM)	Insulin baseline	43.4	7.1%	66%	6.8%
CLG (L/min)	Insulin-independent glucose CL	0.139	9.9%	274%	8.0%
CLG_RHI (L/min/pM)	RHI-dependent glucose CL	0.00128	4.7%	102%	47%
QG (L/min)	Q of glucose	0.442*		ne	
V1G (L)	V1 of glucose	9.33*		ne	
V2G (L)	V2 of glucose	8.56*		ne	
KGE (min^{-1})	Effect delay rate constant (ke0) for glucose on EGP	0.0738	6.2%	241%	8.2%
KIE (min^{-1})	Effect delay rate constant (ke0) for insulin on EGP	0.0213*		58%*	
GPRG_RHI	Shape factor for glucose feedback on EGP receiving RHI	-7.09	4.7%	ne	

*Parameter fix to prior estimate.
IIV=inter-individual variability; CV=coefficient of variation; L=liter; h=hour; D=diabetic; H=healthy; RSE=relative standard errors; ne=not estimated. RSE is related to the standard deviation for the IIV terms and for the residual errors.

Human Predictions

Prediction of human PK for RHI from minipig and dog

- Predicted human clearance for RHI based on minipig and dog in comparison to reports on human CL from literature in healthy and T1DM population



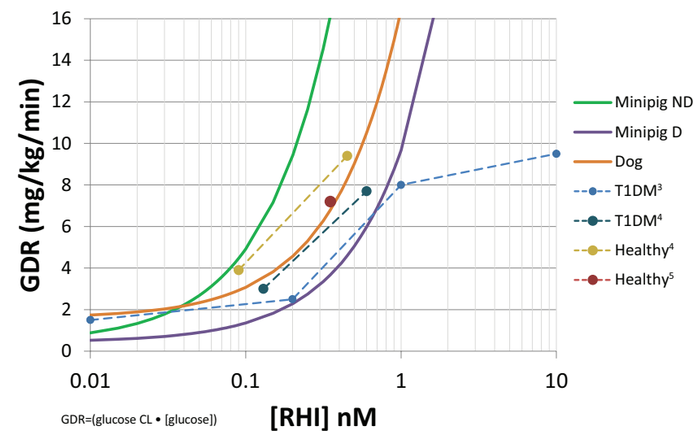
Human Predictions (cont'd)

Prediction of human PK for RHI from minipig and dog

- Human RHI clearance was predicted to be 30% higher based on dog rather than on minipig data
- Predicted human RHI was in a similar range to human clearance
  - Reports on human insulin clearance are ~15 mL/min/kg (at therapeutic concentrations) and can range from 5 to 30 mL/min/kg
- No evidence of saturable insulin-dependent CL was present in animals
  - Literature reports saturable insulin CL in man at high exposures[4]
- The CL of RHI was independent of disease state; the Vss was slightly higher in the diabetic minipig

Prediction of human PD for RHI from minipig and dog

- Predicted human glucose disposal rate (GDR) for RHI based on minipig and dog in comparison to reports on human GDR from literature in healthy and T1DM population



Prediction of human PD: glucose disposal rate based on minipig and dog data

- The insulin-dependent glucose CL was
  - 5x faster in nondiabetic compared with diabetic minipigs
  - 3.7x slower in dogs compared with diabetic minipigs
- The effect of glucose on its own production (GPRG) was different between diabetic and nondiabetic minipigs and between species
- In comparison to clinical RHI data found in the literature, the dog model could predict PD for RHI in healthy human subjects, up to therapeutic concentrations. Similarly, the diabetic minipig could predict RHI PD in T1DM patients
  - Saturation in GDR (as observed in humans[3]) could not be identified in dog and minipig and warrants further model exploration

Conclusions

- An integrated PKPD model of glucose and insulin after administration of RHI was successfully developed from minipig data, applied to the dog clamp data, and extrapolated to humans
- In comparison to literature clinical RHI data, the dog model could predict PK and PD for RHI in healthy human subjects, up to therapeutic concentrations. Similarly, the diabetic minipig could predict RHI PD in T1DM patients, albeit with a 30% underprediction of RHI CL
- This model builds a foundational framework for the extrapolation of insulin kinetics and glucose dynamics across species that were applied to predict human PKPD for a novel insulin in comparison to RHI