A Disease Model for the Regulation of the Glucose-Insulin System

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Objectives

The aim of the project was to develop an integrated mechanistic model to describe the regulation of glucose and insulin following different kinds of provocations.

Methods

Drug-free data from 30 healthy volunteers and 42 patients were used. All patients (PAT) and 24 of the volunteers (HV and HV-INS) received a single intravenous dose of glucose. The glucose was enriched with [6,6-$^2H_2$]glucose, on average 10% of the total glucose dose. After 20 minutes the patients and 10 of the volunteers (HV-INS) received a 5-minute insulin infusion. The remaining 6 volunteers (CLAMP) received a single dose of [3-^{3}H]glucose at basal and elevated insulin levels. Glucose was kept constant. See abstract for doses. Blood samples were drawn pre-dose and until 240 minutes post-dose for the determination of plasma glucose, [6,6-$^2H_2$]glucose, [3-^{3}H]glucose and insulin concentrations. These concentration versus time data were modeled simultaneously using non-linear mixed effect modeling in NONMEM.

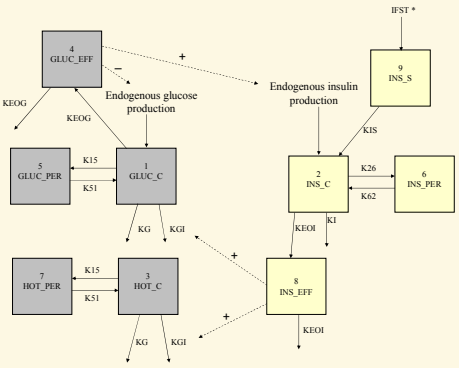

Figure1: Schematic presentation of the model.
GLUC = total glucose, Hot = labeled glucose, INS = insulin.
** The first insulin response is triggered by the glucose infusion*

Results

The glucose sub-model contained a two-compartment disposition model with endogenous production, insulin-independent (K_G) and insulin-dependent (K_{GI}) elimination. The insulin sub-model contained a two-compartment disposition model with endogenous production and release (K_{IS}) and linear elimination (K_I). The labeled (hot) glucose sub-model contained a two-compartment disposition model with parameter values same as for the glucose sub-model. Feed-back loops were incorporated for the regulation of glucose on its own production, on insulin production and for insulin effect on glucose elimination. These were mediated through effect compartments for total glucose and insulin to account for time delay that was seen in the system. The model is presented schematically in Figure 1.

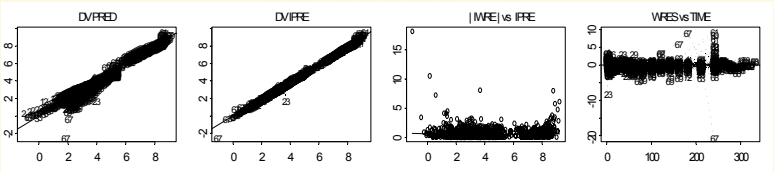

Figure 2: Goodness of fit plots for the final model. The left panel shows the population predictions versus the observed (log-transformed) data, the second panel shows the individual predictions versus observed data, the third panel shows the absolute value of the individual weighted residuals versus individual predictions and the last panel shows the weighted residuals versus time.

Parameter estimates for the final model are presented in table 1. Parameters with similar estimates for healthy volunteers and patients were merged whereas other parameters were estimated separately for the two sub-populations. Parameters that were estimated separately for healthy volunteers and patients are: the insulin-independent (K_G) and insulin-dependent (K_{GI}) elimination of glucose, the nonlinear influence of glucose on glucose production (GPRG) and the first insulin response (IFST).

Final model	Parameter	Volunteers (SE%)	Patients (SE%)
Glucose	VG (L)	9.75 (4.3%)	
	KG (/min)	0.00678 (18%)	0.00278 (13%)
	KGI (/min/conc)	0.000904 (13%)	0.00028 (8.5%)
	KEOG (/min)	0.0527 (6.6%)	
	K15 (/min)	0.0365 (11%)	
	K51 (/min)	0.0486 (6%)	
	GPRG (-)	-3.01 (-11%)	-0.367 (-16%)
Insulin	KI (/min)	0.00678 (6.5%)	
	IFST	674 (16%)	29.8 (8.7%)
	K26 (/min)	0.141 (4.4%)	
	K62 (/min)	0.000799 (7.4%)	
	KEOI (/min)	0.019 (10%)	
	IPRG (-)	4.59 (0.5%)	
	VI (L)	6.17 (6.6%)	
	KIS (/min)	0.536 (19%)	
Residual error (SD for additive on log-transformed data)	Tot glucose	0.0449 (4.1%)	
	Insulin	0.254 (6%)	
	Hot glucose	0.0768 (15%)	
	Early error	3.01 (15%)	

Table1: Parameter estimates for the final model

Figure 2 shows the basic goodness of fit plots for the final model. Figure 3 shows some representative individuals from the different trial designs (HV, HV-INS, PAT, CLAMP).

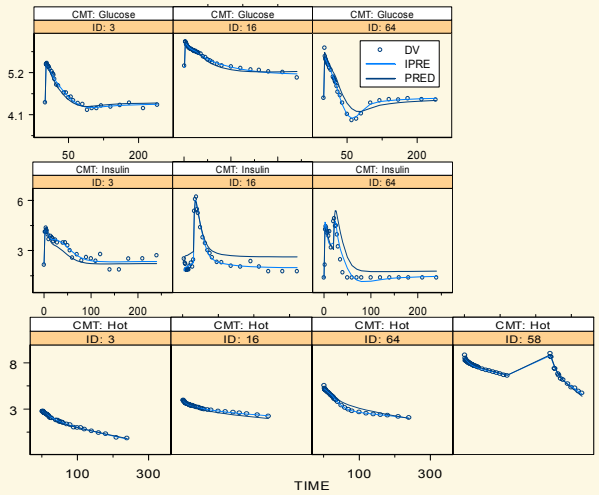

Figure3: Concentration-time plots of representative individuals receiving different dosing schemes. The upper panel shows total glucose, the middle panel shows insulin and the lower panel shows labeled glucose. DV=observed data, IPRE= individual predictions and PRED=population predictions. ID=3 (HV), ID=16 (PAT), ID=64 (HV-INS) and ID=58 (CLAMP).

Conclusion

The model presented here allows the simultaneous prediction of insulin, glucose and labeled glucose levels without drug-effect in volunteers and patients which can be of use in the development of antidiabetic drugs. The differences that has been observed between healthy volunteers and patients are the expected, based on the physiological changes in diabetic patients.