Impact of genotype assumption in a semi-mechanistic PK model of metformin

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Aims

To develop a semi-mechanistic model of metformin PK and investigate the impact of different ways of handling missing genetic variants in transporters on metformin pharmacokinetics.

Trans-porters

Metformin needs transporters to cross cell membranes, as it is protonated at normal pH in the body. Among these transporters are organic cation transporters (OCT) and multidrug and toxin extrusion transporters (MATE). Reduced function alleles for *OCT1* are called *O1R*.

ATM

The ataxia telangiectasia mutated (*ATM*) gene has been associated with metformin treatment success and was also genotyped.

Data

Data from three studies were available; one single and two steady-state studies. Plasma concentration and urine samples were collected in 87 healthy volunteers. Subjects were genotyped for SNPs previously associated with metformin PK (*MATE1* variants-rs2289669, rs2252281; *MATE2-K* variant-rs12943590; *OCT1* variants-rs622342, reduced function variants (rs12208357, rs34130495, rs72552763 and rs34059508, *O1R*); *OCT2* variant-rs316019; *ATM*-rs11212617) [1]. Information on two SNPs (rs12943590 and rs11212617) was missing in 49% of the individuals (84% of the individuals in the single-dose study).

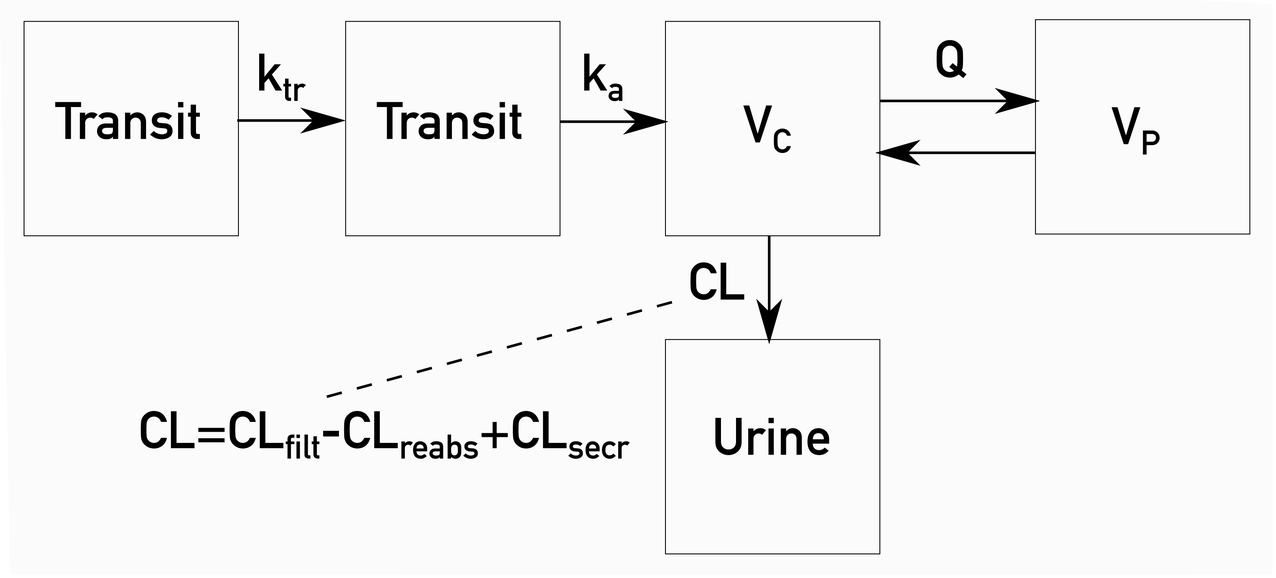

Figure 1. Structural model for metformin pharmacokinetics.

Table 1. Parameter estimates of the base model without covariates.

Parameter	Estimate	CV
CL_{secr} (L/h)	27.3	23.9%
V2 (L)	40	46.3%
Q/Q steady state (L/h)	17/3.68	50.3%
V3 (L)	77.9	40.5%
MTT (h)	0.164	113.1%†
k_a (/h)	0.323	10.4%
F	0.459	48.8%†,‡
V_{max} (L/h)	11	-
k_m*1000 (mg/L)	0.0909	-
Residual error (prop.)§	0.1077	10.8%

† Inter-occasion variability (IOV); ‡ On logit scale; § For late samples (24 h) * 5.05

Model

A 2-compartment model, including renal clearance with saturable reabsorption ($CL_{reabs}=V_{max}*C/(k_m+C)$), filtration that was proportional to GFR ($CL_{filt}=GFR*f_u$), and active secretion fitted the data well.

Results

No covariates influenced the absorption rate constant (k_a), but CL increased by 0.7% per kg. Estimated bioavailability (F) was 49% for subjects with wildtype of *O1R* and 43% for subjects with the SNP. *MATE1* variant rs2289669, *OCT1* variant rs622342 and AGE was found to affect CL, however not when excluding incomplete cases. These covariates mainly improve the fit of single dose-PK. Depending on the approach, different genotypes affected inter-compartmental clearance (Q): *OCT2* variant when missing was assumed to be wt (ii), *MATE2-K* variant when missing was assumed to be wt/v (iii), *ATM* variant when missing was assumed to be v/v (iv) or inferred by the model (v).

Proportions of genotypes after different assumptions

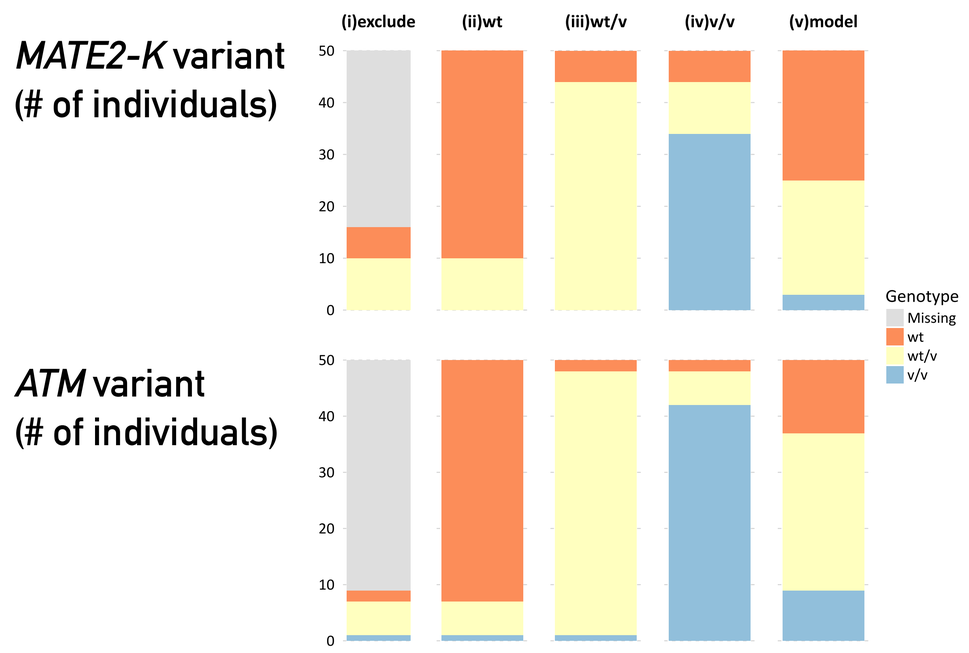

Figure 2. Proportions of genotypes dependent on assumption. Only data from the single-dose (n=50) study shown, as only one individual in the steady-state studies had missing genotype information.

Missing genotypes

Missing genotypes were handled by (i) excluding incomplete cases, (ii) assigning to wildtype (wt), (iii) heterozygote variant (wt/v), (iv) homozygote variant (v/v) or (v) model-based estimation of genotype.

Con-clusions

As expected, how the missing genotypes were handled influenced the covariate inclusion. However, excluding them according to approach (i) affected the inclusion of covariates as there was a correlation between missingness and study design. In this particular case, exclusion of incomplete cases removed data from the single dose study which is less interesting for treatment of a chronic disease and the results from excluding incomplete cases was the most robust method.

Modeling the missing genotypes with approach (v) [2] should be the best method, as this makes allows to respect the proportions of genotypes (which can be seen in Figure 2). However, this makes model runtimes much longer.

Model fit

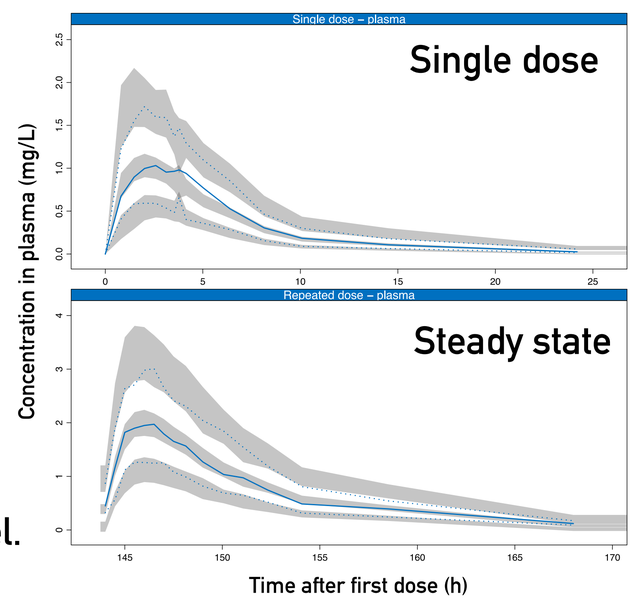

Figure 3. Visual predictive check of the base model.

Table 2. Included covariate relationships and effect sizes. Note that effects on F were measured on logit scale.

Parameter	Covariate	(i) exclude	(ii) wt	(iii) wt/v	(iv) v/v	(v) model
F	rs11212617					-1.17§
	O1R	2.31	4.67†	4.90	4.95	2.93†
CL	AGE		-0.010	-0.010	-0.011	-0.0095
	BW	0.010	0.0070	0.0072	0.0070	0.0087
	rs2289669		0.16‡	0.16	0.17	
	rs622342		-0.18‡	-0.18	-0.16	
	rs11212617					-0.20‡
Q	rs12943590			0.69‡		
	rs11212617				-0.38	0.17‡
	rs316019		0.54§	0.57§		

† Dominant; ‡ Recessive; § Additive

[1] Gong, Li et al. "Metformin Pathways: Pharmacokinetics and Pharmacodynamics." Pharmacogenetics and genomics 22.11 (2012): 820–827.
[2] Johansson, Åsa M., and Mats O. Karlsson. "Comparison of Methods for Handling Missing Covariate Data." The AAPS Journal 15.4 (2013): 1232–1241.

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