



The population pharmacokinetics of Compound X following single and multiple intravenous infusions, to healthy subjects and subjects following surgery.

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Background and Aim

The aim of this study was to characterise the pharmacokinetics (PK) of Compound X in healthy subjects and subjects receiving Compound X following surgery, with compound X administered as single or multiple intravenous infusions (i.v.).

Methods

A population PK (Pop PK) model was developed using NONMEM (ICON plc v7.2) to characterise the time course of Compound X serum concentrations and its between-subject variability (BSV) derived from i.v. data, obtained from 9 clinical studies (5 healthy volunteer and 2 surgery patient studies) and in total comprised of 370 subjects from which 5764 serum samples were taken. The doses tested ranged from 1 to 80 mg.

The stepwise covariate modelling (SCM) module in PsN was used to run the covariate analysis with an inclusion criteria of $p < 0.05$ and a backward exclusion criteria of $p < 0.01$ [1]. In total 13 continuous and 3 categorical demographic and physiological covariates were tested. All 16 were tested on clearance (CL) and 4 on the central volume of distribution (Vd). Additionally the LASSO method was also used and compared with the SCM [2].

Validations were performed on the base and final covariate models using goodness of fit, drop in objective function value (OFV) and visual prediction criteria (VPC).

Results

The PK of Compound X following i.v. administration was adequately described using a two compartment model with first order elimination, combined residual error model and a full omega block and was structurally consistent with previously published Pop PK models for oral formulations.

The addition of covariates caused a substantial reduction in the BSV in CL using with both the SCM and LASSO covariate analysis methods (Table1) compared with the base model. The eta shrinkage increase slightly but remained $< 15\%$ for all parameters.

The VPCs of the final base, SCM and LASSO models (Figure 1), indicate the observable reduction in variability is small but between the SCM and LASSO methods but both indicate an improvement over the base model.

Parameter	SCM method	LASSO method
Δ OFV	-130.32	-126.029
Δ in no. parameters	+7	+10
CL Covariates	GP, CRCL and WT	GP, SEX, CRCL, WT, SGPT, SGOT and AGE
Vd - Covariates	GP and WT	WT and SEX
Δ CL BSV	Reduced by 52.5 %	Reduced by 50.9 %
Δ Vd BSV	Increased by 18.6 %	Increased by 5.7 %
Δ V2 BSV	Increased by 5.6 %	Increased by 3.2 %
Δ Q BSV	Reduced by 8.1 %	Increased by 2.3 %

Table 1. Addition of covariates using the SCM and LASSO methods.

Comparing the change (Δ) from base model in; objective function (OFV), total number of parameters and the between subject variability (BSV) of the parameters. Covariates added ; GP – grouping variable (healthy volunteer with long infusion, healthy volunteer with short infusion, surgery type with long infusion); WT - weight, CRCL - creatinine clearance, SGPT – serum glutamate pyruvate transaminase, SGOT - serum glutamate oxaloacetate transaminase.

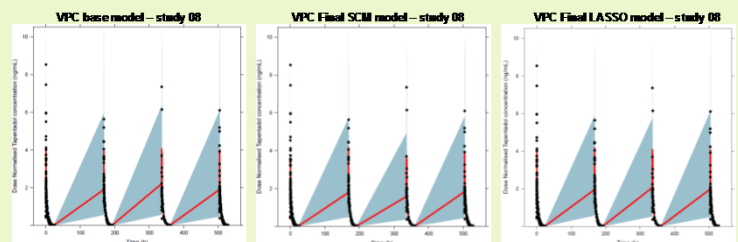


Figure1. VPCs of the final base, SCM and LASSO models.

Discussion & Conclusion

The Pop PK model developed using data from i.v. administered Compound X to healthy volunteers and subjects following surgery adequately described the i.v. PK of Compound X. The final LASSO and SCM models will be validated using an external data set and using bootstrap methods. The model with the best predictive performance will be used to simulate exposures for exposure-adverse event analysis.

References

1. Lindbom *et al.* (2005). PsN-Toolkit – a collection of computer intensive statistical methods for non-linear mixed effect modelling using NONMEM. *Comput Methods Programs Biomed.* 79:241-57
2. Ribbing *et al.* (2007). The lasso- a novel method for predictive covariate model building in nonlinear mixed effects models. *Pharmacokinet. Pharmacodyn.* 34: 485-517