Population Pharmacokinetics of Dabigatran in Bioequivalence Studies

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Objective

To characterize the population pharmacokinetics (PK) of dabigatran following oral administration of 150 mg dabigatran tablet and to quantify its sources of PK variability.

Methods

A total of 702 healthy volunteers who received repeated administration of dabigatran tablet in 14 replicated cross-over bioequivalence (BE) studies were included in this analysis. Only the PK data from the reference formulation were used for the population PK modeling. PK data were analysed using non-linear mixed effect modeling with NONMEM. The inter-subject and inter-occasion on PK parameters were assessed and the effect of selected covariates on dabigatran's PK was investigated. Model evaluation was performed using predictive checks and non-parametric bootstrap.

Results

A two compartment model with a time-dependent absorption process, linear distribution and linear elimination was developed to best describe the PK data. Residual variability (RV) was modelled using the both sides transformation. The time dependency was described as follows:

$$k_a(t) = k_{a,max} \frac{t^H}{t_{50}^H + t^H} \quad \text{Equation 1}$$

where $k_{a,max}$ is the maximum value of k_a, t_{50} is the time at which k_a assumes 50% of value of $k_{a,max}$, and H is a shape factor that modulates the onset of $k_{a,max}$.

Table1. Parameter estimates and non-parametric bootstrap analysis of the final model to describe dabigatran pharmacokinetics

Original dataset		Non-Parametric Bootstrap (N = 885 replicates out of 1000)	
Model Parameters	**Estimate (RSE%)**	**Mean (RSE%)**	**95% Confidence Interval**
F	1 Fixed	1 Fixed	1 Fixed
CL (L/h)	109 (1.5)	108 (1.6)	(105; 112)
V_c (L)	70.9 (7.4)	70.2 (13.1)	(52.9; 88.9)
Q (L/h)	99.5 (2.3)	98.9 (2.6)	(94.5; 104)
V_p (L)	716 (1.8)	714 (1.9)	(689; 743)
k_a (h^{-1})	0.297 (1.3)	0.296 (1.5)	(0.288; 0.305)
T_{50} (h)	0.880 (1.7)	0.882 (2.3)	(0.840; 0.921)
H	5.1 (2.5)	5.1 (1.5)	(4.76; 5.45)
Interindividual variability (CV %)			
ω_{CL}	23.3 (6.9)	23.1 (7.8)	(21.2; 24.7)
ω_{Vc}	95.3 (11.6)	96.6 (17.4)	(76.8; 110)
ω_{T50}	20.9 (12.4)	20.9 (11.8)	(18.3; 23.2)
ω_{RV}	37.1 (7.0)	37.3 (7.3)	(34.4; 39.8)
Interoccasion variability (CV %)			
π_{F1}	59.3 (5.9)	59.1 (5.7)	(55.9; 62.5)
π_{T50}	24.0 (6.8)	24.0 (6.2)	(22.5; 25.5)
Residual variability (CV %)			
σ	12.0 (1.5)	12.0 (1.6)	(11.7; 12.4)

Clearance (CL), apparent volume of distribution (V) and t_{50} were estimated to be 109 L/h, 787 L and 0.880 hours, respectively. Inter-individual variability (expressed as % of coefficient of variation) was estimated in CL (23.3%), V (95.3%), t_{50} (20.9%) and RV (37.1%). Inter-occasion variability in the fraction of drug absorbed and t_{50} were quantified to be 59.3% and 24.0%, respectively. The data did not support the inclusion of inter-study variability on PK parameters.

Among the covariates evaluated, age, sex, body weight, height, body mass index, race, ethnicity and region were found not to have a significant impact on drug exposure in terms of AUC (less than 20%) and were not included in the final model.

Figure 1. Diagnostic plots of the final model to characterize dabigatran pharmacokinetics

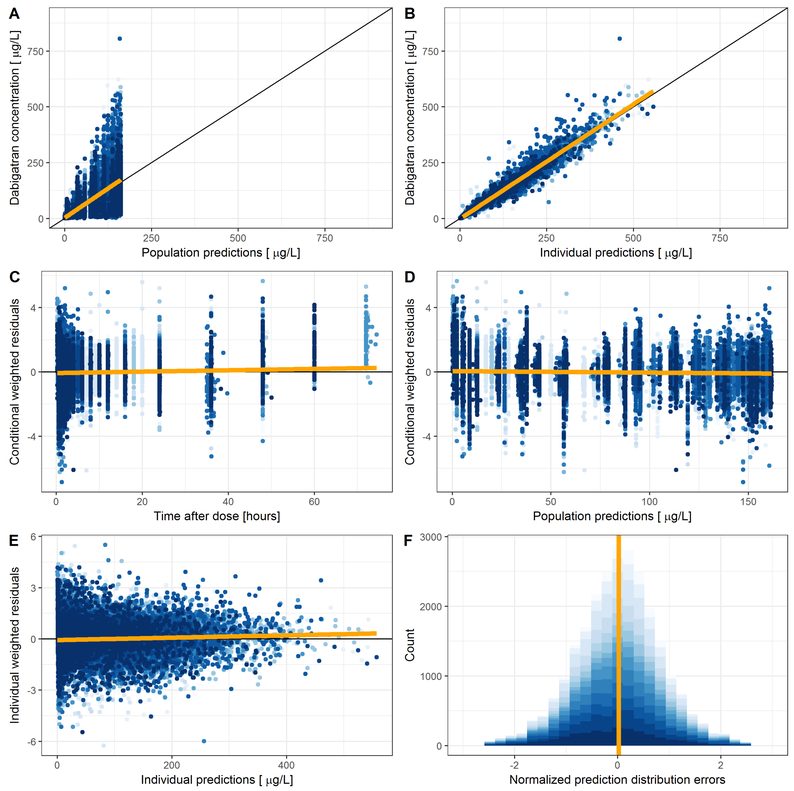
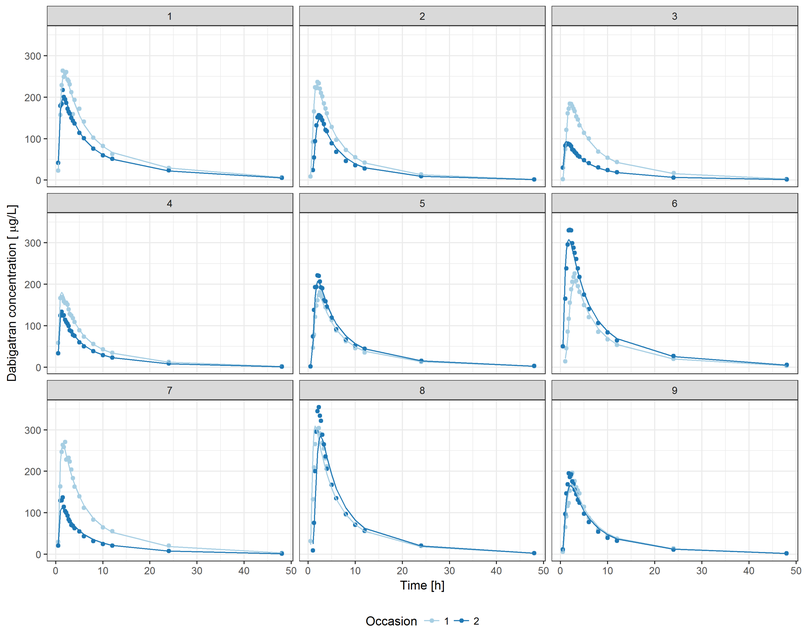
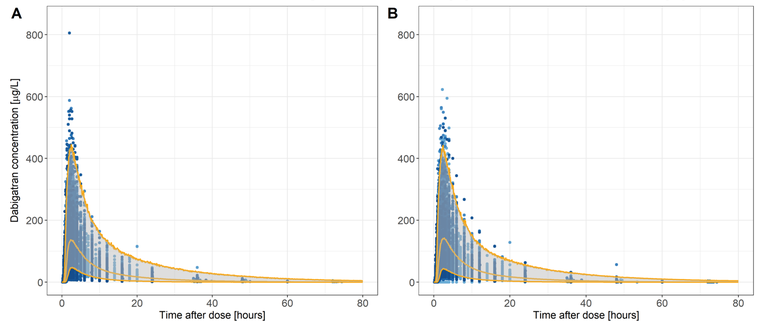


Figure 2. Representative time course of dabigatran total plasma concentration in 9 random subjects stratified by occasion



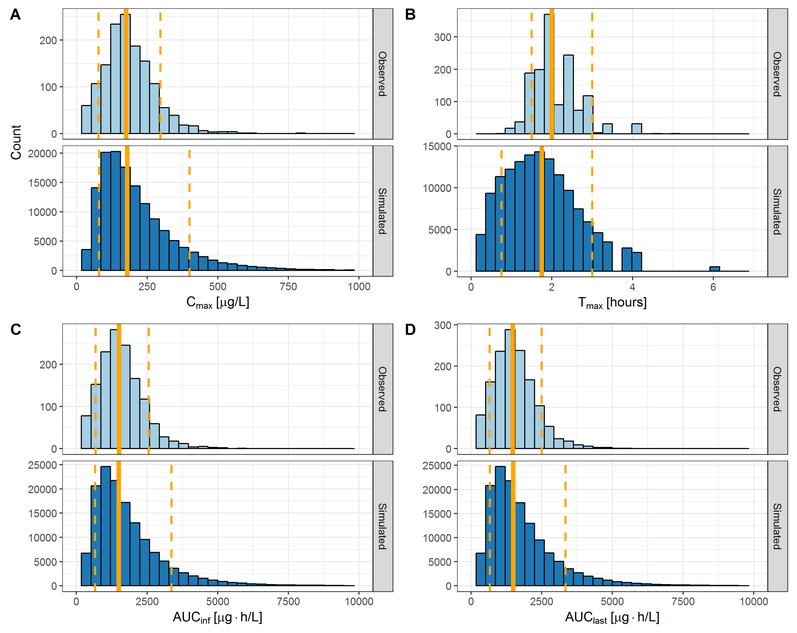
Non-parametric bootstrap and visual predictive check confirmed that the model was appropriate to describe the time course of dabigatran plasma concentrations.

Figure 3. Visual predictive check for total dabigatran plasma concentration stratified by first occasion (A) and second occasion (B)



The time dependency in the absorption phase may be due to dabigatran's pH-dependent solubility. The final model well characterized the population and individual PK of dabigatran, and it can be used to perform model-based optimization of the PK sampling times for future BE studies.

Figure 4. Comparison of observed and simulated dabigatran's pharmacokinetics exposure measurements



Conclusions

The incorporation of a mechanistic time-dependent absorption process in the final population PK model can adequately describe observed PK profiles of dabigatran. The final model can be used to guide future BE studies, such as model-based optimization of the PK sampling times to better characterize the absorption phase.

Disclaimer

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