Population Pharmacokinetics of a New Anticoagulant Drug in Clinical Development

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Introduction

The drug under investigation acts as a direct inhibitor of the proteases thrombin and factor Xa. This mode of action leads to a potent inhibition of the coagulation cascade, which might proof useful in various indications. The drug is administered as an intravenous solution due to its low oral bioavailability.
A population pharmacokinetic (PopPK) model for this drug was to be developed based on all available data from healthy subjects. The model development should include an initial screening for covariates that might influence the pharmacokinetics of the drug.

Data and Methods

Data from three phase I studies were available for analysis. The design characteristics of the studies as well as the plasma concentrations-time profiles are presented in Figure 1. The dataset for population pharmacokinetic modelling included data from 95 subjects who contributed 1842 plasma concentration measurements of the drug.
The demographic characteristics age, weight, height and body surface area (BSA) as well as creatinine clearance were to be tested as covariates on the pharmacokinetic parameters. As expected based on the inclusion criteria the distributions of these characteristics were narrow (Figure 2). Covariates were tested using a forward inclusion and backward elimination process. During the forward inclusion, the significance level was p=0.05 with 1 df (ΔOBJF value of 3.84) and during the backward elimination, p=0.001 with 1df (ΔOBJF value of 10.8). The analysis was performed using NONMEM (version 5, level 1.1), the FOCE INTERACTION estimation method was applied.

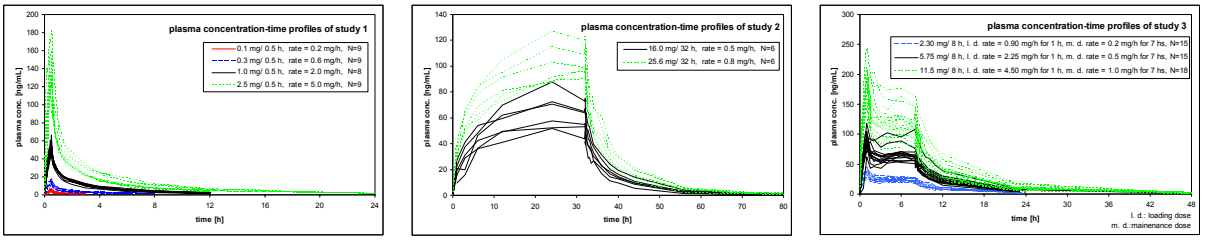

Figure 1: Design Characteristics and Plasma Concentration-Time Profiles

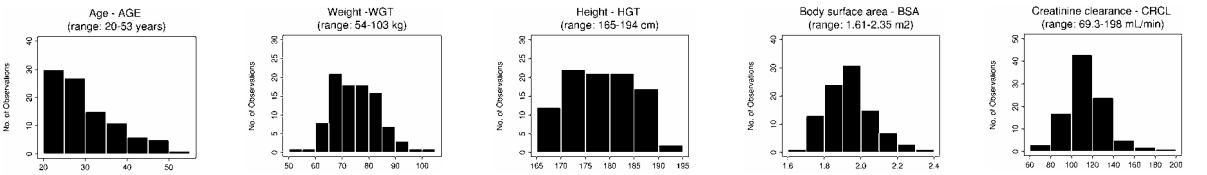

Figure 2: Covariate Distributions

Results

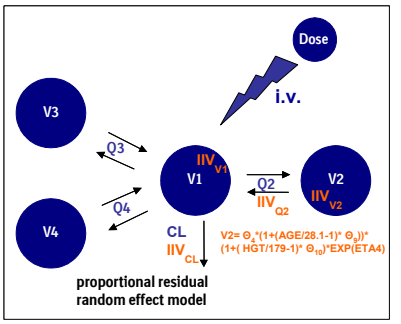

Figure 3: Pharmacokinetic Model

A three compartment model was found to be sufficient to describe each study separately. However, when the three studies were combined, a four compartment model was necessary to account for all apparent distribution phases.

Table 1: Typical Population Parameter Estimates

Parameter	Value	SE%
Fixed effects		
CL (L/h)	8.10	2.3
V1 (L)	10.0	4.4
V2 (L)	13.6	6.0
V3 (L)	12.8	8.9
V4 (L)	12.4	9.3
Q2 (L/h)	21.4	7.8
Q3 (L/h)	3.57	13.4
Q4 (L/h)	0.691	18.4
AGE_V2, Θ_9 (%)	0.505[&]	17.8
HGT_V2, Θ_{10} (%)	3.25[&]	19.1
random effects		
IIV_{CL} (CV%)	21.9	17.3*
IIV_{V1} (CV%)	28.2	19.0*
IIV_{V2} (CV %)	24.6	18.9*
IIV_{Q2} (CV %)	43.7	41.5*
Cov_V2/CL	0.046[§]	16.7
prop. Residual random effect	9.1	9.7*

*: SE% given on the variance scale
&: % change in volume of distribution of V2 per % change in age/height from the mean age/height of the population (decrease ⇒ decrease)
§: Covariance between IIV_{CL} and IIV_{V2}. The estimate translates in a regression coefficient of correlation of 0.853

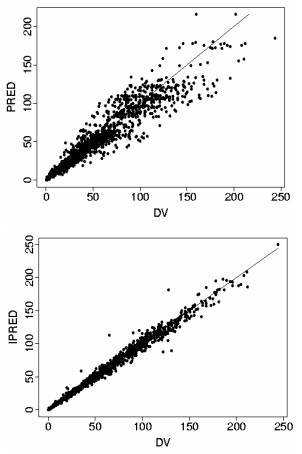

Figure 4: Goodness of Fit Plots

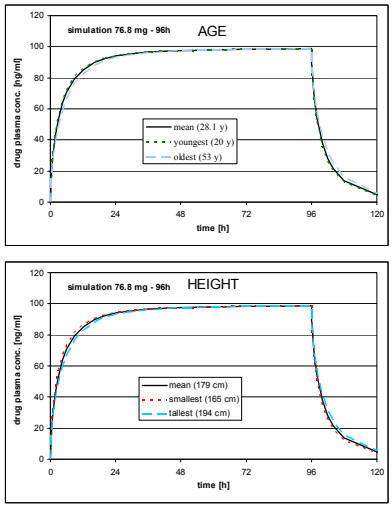

Figure 5: Influence of Covariates on PK Profiles

Conclusions

- A pharmacokinetic model based on all available phase I data is available to simulate and evaluate the influence of different dosing schedules and changes of the typical pharmacokinetic parameters (e.g. CL) on the pharmacokinetic profiles of the anticoagulant drug.
- Age and height were found to have a statistically significant influence on V2. However, the impact on the plasma concentration time profile is negligible (Figure 5).
- Steady-state plasma concentrations in healthy subjects are not influenced by age, weight, height, body surface area, or creatinine clearance. However, this finding has to be confirmed in the patients population that will probably exhibit much wider distributions of the covariates tested so far.