Population Pharmacokinetics of Plasma-Derived Factor IX

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INTRODUCTION

Haemophilia B patients are treated with infusions of factor IX and are dosed based on patient factors and the measured levels [1, 2]. Two different types of treatments exist; prophylactic and on-demand, both of which are expensive treatments. Prophylactic treatment has been shown to result in improved patient outcome with regards to bleeding events and is therefore preferred [3]. The doses have traditionally aimed to maintain a FIX level above 0.01 U/mL, the threshold between severe and moderate haemophilia B. By individualizing FIX doses, excess doses can be avoided thereby reducing the cost of treatment.

OBJECTIVES

I. Evaluate and further develop a previously described population pharmacokinetic (POPPK) model for FIX [2].

II. Use the developed POPPK model for establishment of the number and timing of samples needed to predict individual doses with acceptable accuracy and precision, for future use in pharmacokinetic (PK) tailored dosing, using a Bayesian approach.

DATA

The data used in this study was compiled from 5 studies [4-8] and patient characteristics are summarized in Table 1 below. Some patients received more than one FIX concentrate type and were featured in multiple studies.

The patients had moderate to severe haemophilia B and were treated with various FIX concentrates including 1: FIX Grifols, 2: AlphaNine, 3: Immunine, 4: Octanine, 5: Preconativ, 6: Nanotiv or 7: Mononine.

Table 1: Patient characteristics of the data used in this study. Unless otherwise specified, values are the mean values with standard deviations reported in parenthesis.

Stud	No. of Patients	Weight, kg	Age, years	No. of Samples	FIX Concentrates	Reference
1	25	63.6 (14.6)	23.1 (8.8)	7-14	2, 3, 4	[4]
2	25	69.7 (13.0)	25.8 (8.7)	7-11	1	[5]
3	5	61.0 (10.0)	41.5 (9.3)	15-17	5, 6, 7	[6]
4	6	64.7 (11.6)	42.8 (8.8)	17	6	[7]
5	8	66.6 (10.6)	37.64 (13.0)	10-15	3, 6	[8]

METHODS

The workflow of this study can be seen in Figure 1 below. NONMEM (v. 7.3), R (http://www.r-project.org), Xpose4 and PsN [9-11] were used for modelling, simulation, data visualization, data management and model diagnostics. The POPPK model was developed using non-linear mixed effects modelling, which employs maximum likelihood estimation methods to obtain parameter estimates corresponding to values which maximize the likelihood for the data to occur.

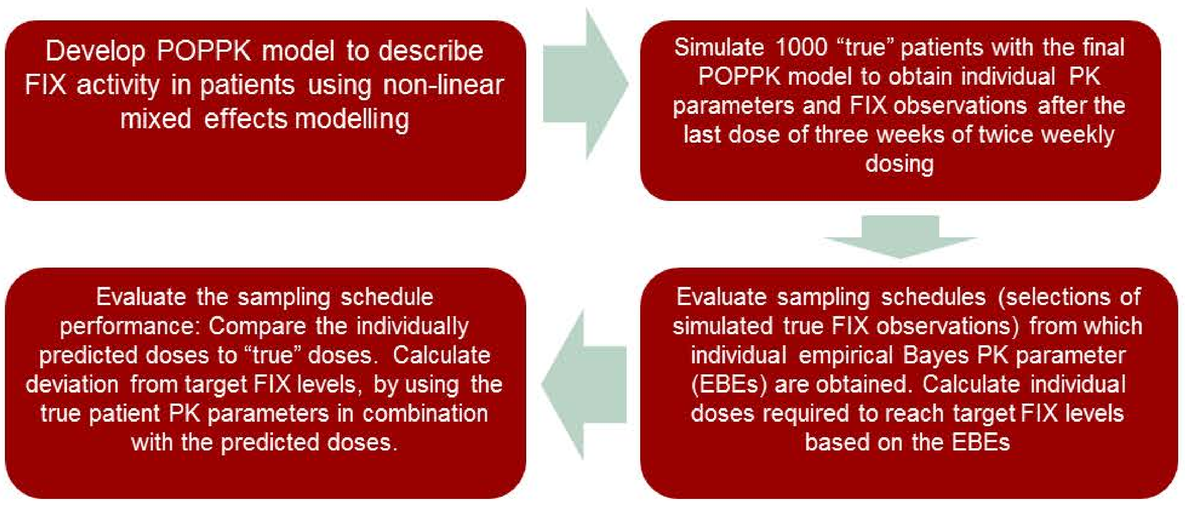

Figure 1: Study workflow. The end results were the error in predicted individual doses reaching the target FIX activity at trough and the error in reaching the target FIX activity.

The clinically relevant covariates body weight (BW) and FIX concentrate were added to the model with Equations 1 and 2. BW was added allometrically to parameter estimates and the allometric exponent θ_j was fixed to 0.75 and 1, for clearance and volume terms, respectively. θ_i refers to the typical parameter value for a patient with median BW or a patient recieving the reference FIX concentrate. θ_k refers to the effect of concantrate type on clearance in percentage. Model performance was evaluated with basic goodness of fit plots and visual predictive checks (VPCs) in addition to evaluations of estimated parameter precision.

$$Typical\ parameter\ value = \theta_i * \left(\frac{BW}{Median\ BW}\right)^{\theta_j} \qquad \text{Equation 1}$$

$$Typical\ parameter\ value = \theta_i * (1 + \theta_k) \qquad \text{Equation 2}$$

An analytical solution to the series of differential equations was used to calculate the required dose to achieve a FIX activity level of 0.01U/mL at 96 hours post-dose/at trough based on the EBEs. The relative error in dose and FIX activity was calculated with Equation 3.

$$Relative\ Error = \frac{Predicted\ - True}{True} * 100\% \qquad \text{Equation 3}$$

RESULTS

The final model (Figure 2) was a 3-compartment model including BW and FIX concentrate as covariates. Concentrate 7 was found to have a 22% lower activity clearance and concentrates 1, 3 and 4 had activity clearance estimates that were 24% higher than the reference concentrates (2, 5 and 6).

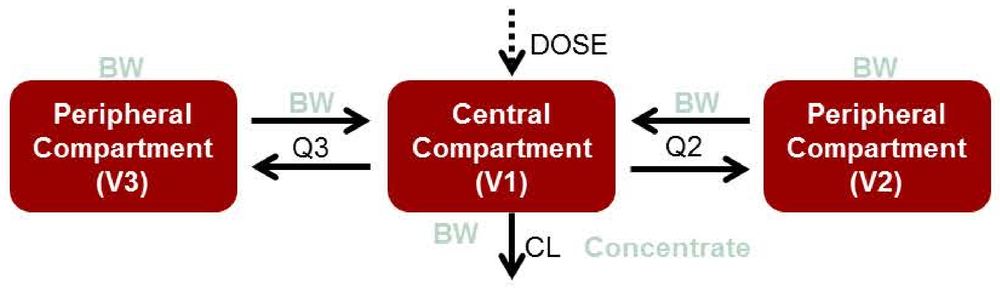

Figure 2: Final POPPK model for FIX activity. Variables in grey are covariates incorporated in the model. CL clearance; Q2 and Q3 inter-compartmental clearances; V1 central volume of distribution,;V2 and V3 peripheral volumes of distribution.

The typical parameter estimates for the model were in agreement with previously published results [3]. A VPC can be seen below (Figure 3).

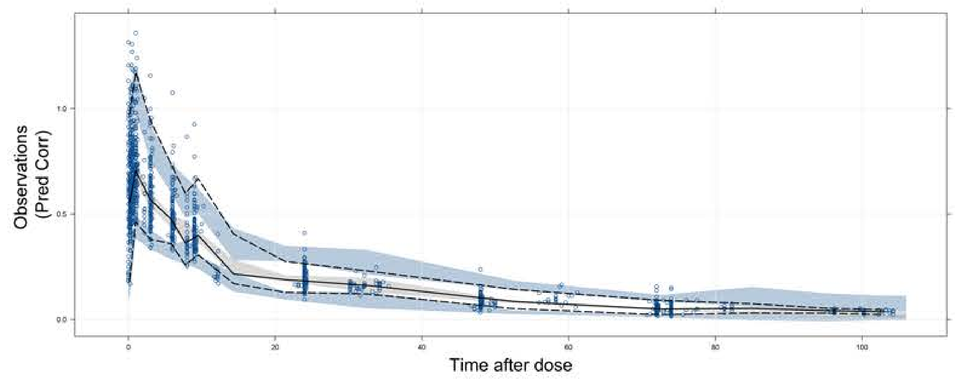

Figure 3: Prediction corrected VPC of the final model. The lines represent the 5th, 50th and 95th percentiles of the data and the shaded areas are the model prediction intervals around the percentiles. Model performance can be deemed to be good if the percentiles of the data fall within the shaded regions.

The relative error of the individually predicted doses and FIX activities at 96h after the last administered dose are shown in Figure 4 for different sampling schemes.

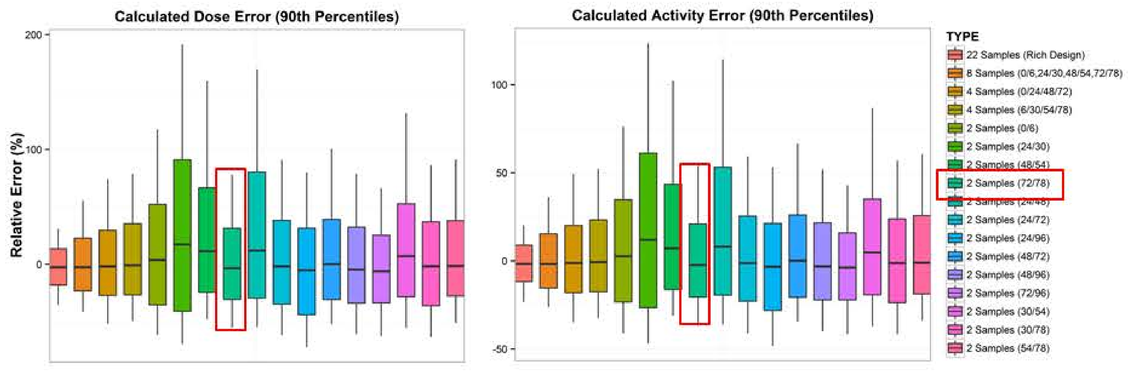

Figure 4: Relative error of model predicted doses and FIX activity for different sampling schedules. Boxes represents the inter-quartile range and vertical lines the 90th percentiles.

The percentage of individuals receiving adequate doses based on the dose predictions is shown in Table 2 to the right. The numbers are based on a sampling schedule where samples are drawn at 72 and 78 hours after the last dose and on an activity goal of 0.015 U/mL. This sampling schedule was considered to result in a dose and activity imprecision that was acceptable and most precise of the evaluated schedules.

Table 2: The percentage of patients obtaining an adequate FIX activity level based on calculated doses.

Activity (U/mL)	% Patients
> 1 at 0.5h	20.4
> 2 at 0.5h	4.4
0.01 < Activity < 1 at 96h	87.6
< 0.01 at 96h	12.4

CONCLUSION AND DISCUSSION

FIX activity in moderate to severe haemophilia patients can be described with a three compartment model. The model performs well as evaluated by goodness-of-fit plots and VPCs. Two samples during the infusion period are sufficient to obtain adequate individual PK parameter estimates to be used for individualizing doses. The proposed routine for PK tailored dosing is able to predict doses that result in a FIX activity target level of > 0.01 U/mL where 87.6% of patients receive an adequate dose for the desired activity level.

ACKNOWLEDGEMENTS

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