Development of a population pharmacokinetic model of coagulation factor VIII in Korean hemophilia A patients and its clinical application

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Directed by Professor Kyung Soo Park

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This certifies that the Doctoral Dissertation of

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Development of a population pharmacokinetic model of coagulation factor VIII in Korean hemophilia A patients and its clinical application

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Objectives: The prophylactic and episodic treatment is essential for the better quality of life and health status in patients with hemophilia. However, since pharmacokinetic (PK) variabilities of coagulation factor VIII are known to be substantial, dose individualization is strongly recommended for external preparations. In this study, we aimed to develop a population PK model of coagulation factor VIII and investigate factors affecting PK variation.

Materials and Methods: In total, 24 Korean patients with hemophilia A were enrolled in this study. Patients developing high titer inhibitors (> 5 Bethesda Units) were excluded. With 2-5 samples per patient, population PK modeling was developed using NONMEM ver7.3, including covariate analysis. Statistical analysis and graphical inspection were done using R. 3.3.3.

Results: A two-compartment model with first-order elimination described our data well, with disposition parameters scaled using allometry. The von willebrand factor level and the age were the significant covariates for systemic clearance (CL) (both $P<0.01$). The typical values of estimated central volume of distribution, CL, and inter-compartmental clearance was 38.4 dL, 2.76 dL/hr, and 6.4 dL/hr, respectively. The elimination half-life was estimated to be 11.2 hr.

Conclusions: This was the first population PK model of coagulation factor VIII developed for the Korean population. Despite sparse sampling, the model successfully described the data, with good parameter precision. The model and covariate information obtained can be applied for improving dose regimens in Korean hemophilia patients

Keywords: hemophilia, pharmacokinetic model, coagulation factor viii, precision medicine, prophylactic therapy

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I. INTRODUCTION

Hemophilia is a X-linked inherited coagulation factor deficiency. The prevalence of hemophilia A is known to be 17.1 in 100,000 males and that of hemophilia B is 3.8 in 100,000 males[1]. In Korea, about 1890 cases of hemophilia A and 450 cases of hemophilia B were reported in the year of 2018, according to the annual report of Korean Hemophilia Foundation and 2018 annual global survey of the World Federation of Hemophilia[2].

Since the coagulation factor VIII (FVIII) replacement therapy was introduced, the survival rate of hemophilia patients has dramatically increased, which has led to a longer lifespan, approaching that of healthy population[3]. As a result, the quality of life of hemophilia patients is becoming the matter of interest[4]. The coagulation factor treatments for hemophilia comprise the prophylactic treatment to avoid breakthrough bleedings and enhance the quality of life and the episodic treatment to manage acute bleeding episodes[5,6]. However, because pharmacokinetic (PK) variability of

coagulation FVIII is known to be substantial[7], dose individualization for each patient has been increasingly recommended.

The traditional approach used for PK studies of coagulation FVIII was to obtain 10-11 blood samples over 2-3 dosing intervals[8]. However, the procedure is cumbersome and would be an enormous burden, especially for children.

These limitations with the traditional approach can be overcome using population PK approaches as illustrated previously[9], in which, based on sparse samples collected from individuals, typical values of PK parameters, their variabilities, and associated covariate effects are estimated. Recently, computational tools specialized for coagulation FVIII population PK have been developed and used to provide personalized care for Western patients, including WAPPS Hemo (Web-Accessible Population PK Service-Hemophilia), developed by McMaster University, and myPKFiT ™, developed by Takeda[10,11]. Using a therapeutic monitoring scheme, these tools provide an individual prediction for plasma FVIII concentrations using estimated individual PK parameters.

Recognizing the importance of population approaches in drug treatment described above, in this study, we aimed to develop a population PK model of coagulation FVIII and investigate factors affecting PK variation in the Korean population. In doing so, influences of potential covariates on PK such as age, body weight, and blood types, will be examined, as well as the influence of von Willebrand Factor (VWF) Antigen level, which has been recently reported to be meaningful[12]. In addition, potential ethnic differences in FVIII pharmacokinetics will be explored based on a previous report[13]. It is anticipated that the importance of population PK for personalized care will increase with novel hemophilia therapies available in the field[14].

II. MATERIALS AND METHODS

1. Patients and data collection

Korean hemophilia A patients aged 1 year and older were recruited in this study. Patients with an inhibitor level of more than 5 Bethesda Units were excluded. Finally, a total of 24 patients were enrolled, 20 from the Korea hemophilia foundation and 4 from the Hemato-Oncology Department of Yonsei University Severance Hospital. Individuals who had previous dosing records or the elapsed time since the last dose longer than five half-lives of FVIII were included in this study.

This study was approved by the institutional review board of Severance Hospital (IRB# 4-2015-1100) and carried out following the relevant regulatory requirements including the Declaration of Helsinki and the Korean Good Clinical Practice.

2. Factor VIII and von Willebrand Factor assay

For all types of preparation, FVIII activity was measured by a 1-stage clotting assay using a BCS XP Hemostasis System (Siemens, Munich, Germany) or an STA compact hemostasis system (Diagnostica Stago, Parsippany, NJ) at the department of laboratory medicine at Severance Hospital with the lower limit of quantification (LLOQ) being 1 IU/dL. Plasma levels of VWFpp and VWF:Ag were measured by enzyme-linked immunosorbent assay (Immucor GTI Diagnostics, Waukesha,WI). VWF:FVIIIB was measured by solid-phase binding assay, as described, using 1.25 U/mL recombinant FVIII (ADVATE; Takeda, Tokyo, Japan) and a horseradish peroxidase–conjugated polyclonal sheep anti-human FVIII antibody (Affinity Biologicals, Ancaster, ON, Canada) for detection.

3. Population PK modeling

A. Basic structural model

Subjects were administered with their regular dose of FVIII preparation for prophylactic treatment. Blood samples for concentration measurement were taken at prescheduled sampling time points: Predose, 0.5hr, 1hr, 2hrs, 3hrs, 12hrs, 24hrs, and 36hrs after IV dosing.

Using a mixed effect model framework, a model parameter was formulated as:

$$P_i = \theta \cdot \exp(\eta_i)$$

where P_i is the parameter value of individual i, θ is the typical parameter value, and η_i is a random interindividual difference following a Gaussian distribution with mean zero and variance ω^2. For residual variability, additive, proportional, and combined error models were evaluated, where the combined error model was formulated as:

$$Y_{ij} = PRED_{ij} \cdot \left(1 + \varepsilon_{pro_{ij}}\right) + \varepsilon_{add_{ij}}$$

where Y_{ij} and $PRED_{ij}$ are the observed and predicted concentrations for individual i at time point j, respectively. The $\varepsilon_{pro_{ij}}$and $\varepsilon_{add_{ij}}$ denote proportional and additive residual error that are normally distributed with mean zero. Here, the variance of $\varepsilon_{pro_{ij}}$ and $\varepsilon_{add_{ij}}$ were assumed to dffer between the 2 institutions.

The plasma concentrations of coagulation FVIII were fitted with a mammillary compartment PK model. Drug elimination was assumed to follow first-order kinetics and one or two-compartment disposition model was tested. Using allometry based on the body weight (WT), typical volume and clearance parameters were described by the following equation:

$$\theta = \lambda_1 * \left(\frac{WT}{median\ WT}\right)^{\lambda_2}$$

In this expression, λ_1 is the parameter value for a subject with the median WT within the study data set and λ_2 is the allometric exponent which was fixed at 1 and 0.75 for volume and clearance parameters, respectively. The typical value of clearance was allowed to vary among the types of FVIII preparation used in this study.

Baseline concentrations (BASE) of endogenous coagulation FVIII and its variabilities were incorporated in the model as a parameter to be estimated, instead of subtracting it from the observations.

B. Covariate model

Continuous variables such as age (AGE), blood VWF levels (VWF), AST (GOT) level, ALT (GPT) level, total bilirubin and eGFR (CKD-EPI) and categorical variables such as ABO blood types (ABO) and severity of hemophilia (SEV; defined as severe for FVIII level < 1 IU/dL, moderate for 1-5 IU/dL, and mild for 5-40 IU/dL) were tested for the covariate effect on the PK parameters of FVIII. Preliminary covariate explorations were done by linear regression of covariates on the estimates of individual parameters using R. A covariate search was conducted using a stepwise covariate model-building approach based on the likelihood ratio test, with selection criteria of $p < 0.05$ for forward addition and $p < 0.01$ for backward deletion. The relationships between covariate and model parameters were tested with both linear and exponential functions for continuous covariates and with linear function for categorical covariates.

C. Model selection and evaluation

Using the final PK model, the appropriateness of the model was comprehensively evaluated by considering the following indices: physiological plausibility, goodness-of-fit diagnostics, model stability and parameter precision, and visual predictive check (VPC). For VPC, 1,000 simulated datasets were created to compare the model predicted values to the observations.

D. Simulation

The final FVIII population PK model was used to simulate FVIII activity–time profiles in patients given conventional prophylactic doses with different dosing intervals; (i) single dose of 20-50 IU/kg, (ii) multiple dose of 20-50 IU/kg given twice a week at 0 and 3.5 days or thrice a week at 0, 2.33 and 4.66 days 17. For simulation, 1000 replicates of the dataset were generated, each being sampled by randomly selecting a set of 26 patients with replacement from the original dataset. Individual WT and VWF levels of the patients included in the population PK modeling were used in the simulation dataset, with IV bolus administration assumed. The median and 90% prediction intervals of the simulated FVIII activity–time profiles were calculated for different dosing regimens. For single-dose simulations, the duration in which FVIII activity stayed above 1 IU/dL was predicted. For multiple-dose simulations, the median trough level of FVIII and its 90% prediction intervals were calculated. Also, the percentage of patients with FVIII level above 1 IU dL at the end of the dosing interval was presented for each multiple dosing regimen.

E. Software

Data analysis and output evaluations were performed using R (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria) and NONMEM ver 7.3 (ICON Development Solutions, Ellicott City, MD, USA) was used in the PK model development. The first-order conditional estimation with interaction method was used to estimate typical PK parameters, interindividual variability, and residual variability throughout the model development process. Perl speaks NONMEM (PsN ver. 4.9.0) and XPOSE 4 (ver.4.0) in R were used to perform VPCs and covariate model building.

III. RESULTS

1. Subjects characteristics

A total of 24 patients with hemophilia A, comprising 21 severe, 2 moderate and 1 mild cases, were enrolled in the study. The subject's median age was 27 yrs (ranged from 9 to 75 yrs), and their median WT was 69.5 kg (ranged from 27.2 kg to 110 kg). The ABO distribution was 10, 6, and 8 subjects for type A, B and O, respectively, and the median value of VWF at pre-dose was 115.4 IU/dL (ranged from 71.7 to 229 IU/dL). The type of FVIII preparations used in this study were Advate® (Takeda, Tokyo, Japan), Greenmono® (Green cross pharma company, Seoul, South Korea), Xyntha® (Pfizer, NY, USA), and Kogenate® (Bayer healthcare, Leverkusen, Germany). None of the enrolled patients developed inhibitors of FVIII.

The summary of baseline characteristics of subjects is described in table 1.

Table1. Baseline characteristics of the study subjects

Demographic	Value*
Age (years)	27 (19.50-42.50)
WT (kg)	69.5 (58.50-75.25)
VWF (IU/dL)	115.4 (100.1-147.7)
AST (IU/L)	22 (17.75-26)
ALT (IU/L)	17 (14-23.25)
BUN (mg/dL)	12.5 (10.43-14.82)
Scr (Serum creatinine, mg/dL)	0.74 (0.66-0.85)
eGFR (CKD-EPI)** (mL/min/1.73m^2)	119.5 (111.1-132.1)
Total bilirubin (mg/dL)	0.59 (0.39-0.9)
ABO, n (%)	
A	10 (41.7%)
B	6 (25.0%)
O	8 (33.3%)
AB	0 (0.0%)
Severity of HA	
Mild	1 (4.2%)
Moderate	2 (8.3%)
Severe	21 (87.5%)
Preparations	
Advate[a]	12 (50%)
Greenmono[b]	6 (25%)
Xyntha[c]	4 (16.7%)
Kogenate[d]	2 (8.3%)

*Data are given as median (1st quartile – 3rd quartile) for continuous values, and number (percentage %) for discrete values.
Abbreviation: VWF, Von willebrand factor; HA, Hemophilia A
**GFR (CDK-EPI) was obtained from formula using serum creatinine:

GFR = $141 \cdot min\left(\frac{Scr}{0.9}\right)^{-0.411} \cdot \max\left(\frac{Scr}{0.9}\right)^{-1.209} \cdot 0.993^{Age}$

Min = indicates the minimum of $\frac{Scr}{0.9}$ or 1

Max= indicates the maximum of $\frac{Scr}{0.9}$ or 1

[a] Takeda, Tokyo, Japan
[b] Green cross pharma company, Seoul, South Korea
[c] Pfizer, NY, USA
[d] Bayer healthcare, Leverkusen, Germany

2. Population PK modeling

A total of 98 samples were taken for plasma concentration of coagulation FVIII (2 subjects with 2 sampling points each, 5 subjects with 3 points each, 10 subjects with 4 points each, and 7 subjects with 5 points each).

A two-compartment disposition model with first order elimination well described our data with good precision, the schematic diagram of which is shown in Figure 1. For handling BQL observations, M6 method was applied with the variance of $\varepsilon_{add_{ij}}$ fixed to the value of $(\frac{LLOQ}{2})^2$ [15,16], since M3 and M4 methods were not successful in minimization.

Figure 1. Schematic diagram of structural model. K12, K21 represent rate constants between central compartment (V1) and peripheral compartment (V2).

Covariate analysis

In the first step, VWF was added to systemic clearance (CL) as their relationship was the most significant, decreasing the NONMEM objective function value (OFV) by 11.5 ($p<0.001$). Then, in the second step with VWF added to CL, incorporating AGE into CL further decreased OFV by 8.5 ($p<0.005$). While ABO had a significant

relationship with CL (P<0.01) in the first step, it was not found to be singificant in this step and was not included in the model.
Both VWF and AGE showed negative relationship with the CL, and applied exponentially in the model.
No covariates were selected in respect of other paramters such as V2 and BASE. The SEV, AST, ALT and GFR was not significantly related to any parameters.

Final model parameter estimates

For individual with WT of 70kg, 27 years of age and VWF of 115.4 IU/dL, the CL for Advate and Xyntha was 2.76 dL/h. The CL of individual who used the FVIII preparation of Greenmono and Kogenate respectively showed approximately 58% larger and 18% smaller value of CL compared to Advate and Xyntha. The V1, V2 and inter-compartmental clearance (Q) for individuals with WT of 70kg were 38.4 dL, 5.7 dL, and 6.4 dL/h, respectively.

Given these results, typical values of CL, V1, V2, and Q, denoted as TVCL, TVV1, TVV2, and TVQ, are expressed in equations below:

(1) $\text{TVCL(dL/hr)} = 2.76 \times \left(\frac{BWT}{70}\right)^{0.75} \times e^{(-0.0052*(\text{VWF}-115.4) - 0.0135*(\text{AGE}-27))} \cdot (1 + TYPE)$

; TYPE = 0.58 for Greenmono, -0.18 for Kogenate preparation, and 1 for Advate and Xyntha.

(2) $\text{TVV1} = 38.4 \times \left(\frac{\boldsymbol{BWT}}{\boldsymbol{70}}\right)$

(3) $\text{TVV2} = 5.7 \times \left(\frac{\boldsymbol{BWT}}{\boldsymbol{70}}\right)$

(4) $\text{TVQ} = 6.3 \times \left(\frac{\boldsymbol{BWT}}{\boldsymbol{70}}\right)^{\boldsymbol{0.75}}$

The distribution and elimination half-life were approximately 0.53h and 11.2h, respectively.

The inter-individual variability (IIV) of central volume of distribution (V1) and CL was very small and insignificant, in terms of OFV, compared to peripheral volume of distribution (V2) (Coefficient of Variation (CV) of 141.4%), thus it was not considered in our model. As a result, the IIV only for V2 and BASE (CV of 92.1%) was included in our final model. The effects of covariates on TVCL are depicted in Figure 2.

The summary of result is shown in Table 2.

Table 2. Final model parameter estimates

Parameter*	Estimate (unit)	RSE (%)
Structural parameters		
V1	38.4 (dL)	5.4
V2	5.7 (dL)	35.8
CL	2.76 (dL/h)	6.1
Q	6.4 (dL/h)	13.8
BASE	1.48 (IU/dL)	30.7
CLAGE**	-0.0132	27.3
CLVWF**	-0.0052	12.4
TYPE0** (Advate, Xyntha)	0	
TYPE1** (Greenmono)	0.58	38.1
TYPE2** (Kogenate)	-0.18	62.9
Inter-individual variabilities		
ω^2_{V2}	141.4 (CV%)	17.3
ω^2_{BASE}	92.1 (CV%)	12.7
Residual error		
σ^2_{pro1}	15.8 (CV%)	21.5
σ^2_{pro2}	34.6 (CV%)	17.9

*All clearance and volume parameters were allometrically scaled to body weight of 70 kg, with an allometric exponent of 0.75 for clearance and 1 for volume parameters.
Abbreviation: RSE, relative standard error; BSV, between subject variabilities; CV, coefficient of variation.

* Symbols are: V1, Central volume of distribution;V2, Peripheral volume of distribution; CL, Clearance; Q, Inter-compartmental clearance; BASE, Baseline concentration of FVIII; σ^2_{pro1}, proportional error variance for data from study1; σ^2_{pro2}, proportional error variance for data from study2

** CLAGE, CLVWF, TYPE1, and TYPE2: covariate coefficients for clearance, which were defined as:

$$\text{TVCL} = 2.76 \times \left(\frac{BWT}{70}\right)^{0.75} \times e^{(-\text{CLVWF}*(\text{VWF}-115.4) - \text{CLAGE}*(\text{AGE}-27))} \cdot (1 + \text{TYPE})$$

Model evaluation

The goodness of fit assessment and diagnostic VPC results are presented in figure 3 and 4, respectively. Goodness of fit plots demonstrate that the model predicted concentrations and the observations are in good agreement (figure 3a). Also, the population predictions and individual predictions were evenly distributed across the line of identity, indicating a good model fit (figure 3b). In addition, the conditional weighted residuals were symmetrically distributed around the line of zero without an obvious trend, indicating no evidence of model misspecification (figure 3c). Overall, the goodness-of-fit assessment showed no clear systematic bias in the structural and residual error models. VPCs with 95% prediction intervals using the final population PK model are shown in figure 3. VPC plots showed that most of the observed concentrations were overlaid within 95% of the predictive interval of simulated data, suggestive of the adequate predictive performance of the final model. From this result we can conclude that our model performs well in predicting the FVIII concentrations.

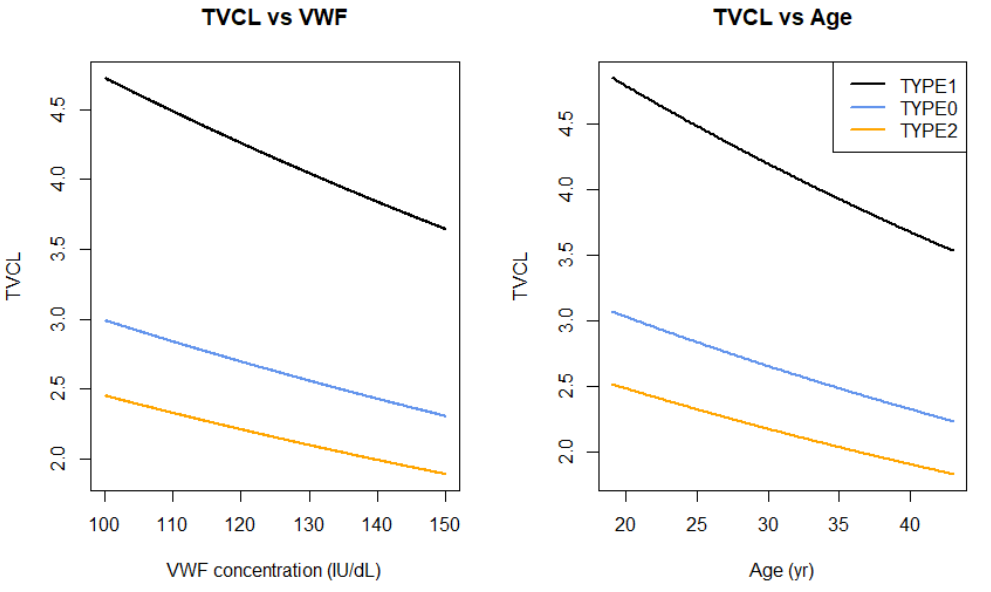
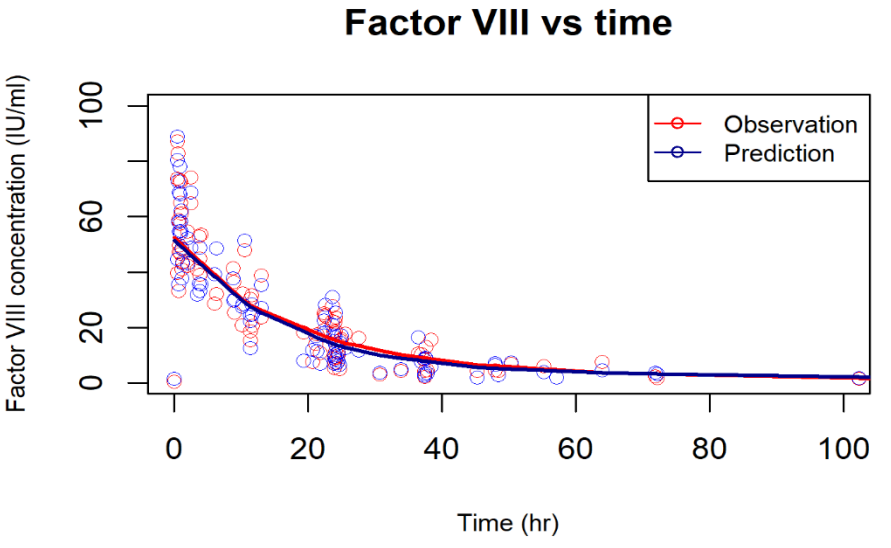
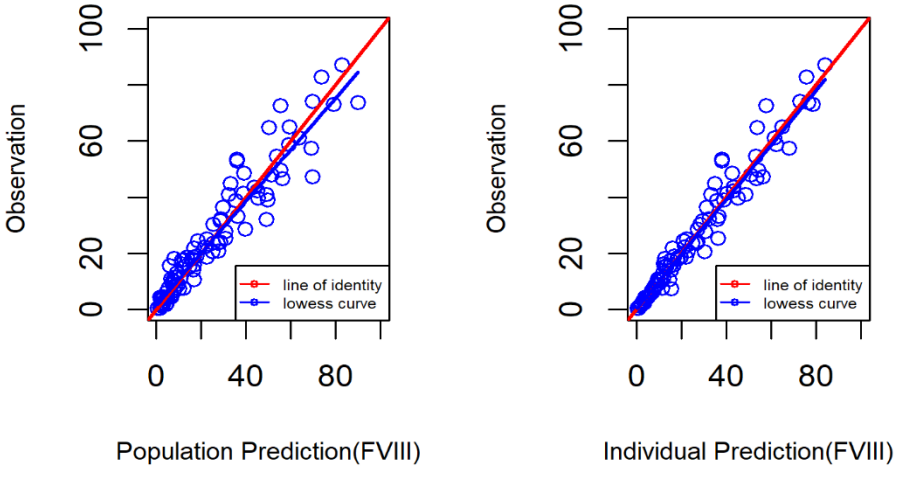


Figure 2. Covariate effects on TVCL. The predicted TVCL in relation to covariates: (Left) TVCL vs VWF and TYPE, (right) TVCL vs age and TYPE. TYPE, type of preparation (TYPE0: Advate and Xyntha, TYPE1: Greenmono, TYPE2: Kogenate); TVCL, typical value of clearance; VWF, von Willebrand factor.

(A)



(B)



(C)

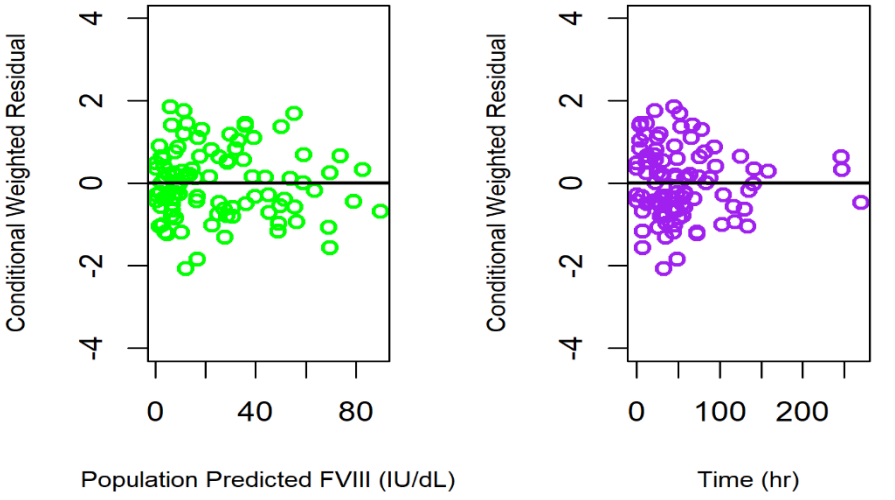


Figure 3. Goodness of fit plots of the population PK model of coagulation FVIII. (A) predicted concentrations and observation vs time, (B) observation vs population prediction (left) and vs individual prediction (right), (C) conditional weighted residual vs population prediction (left) and vs time (right). FVIII, coagulation factor VIII.

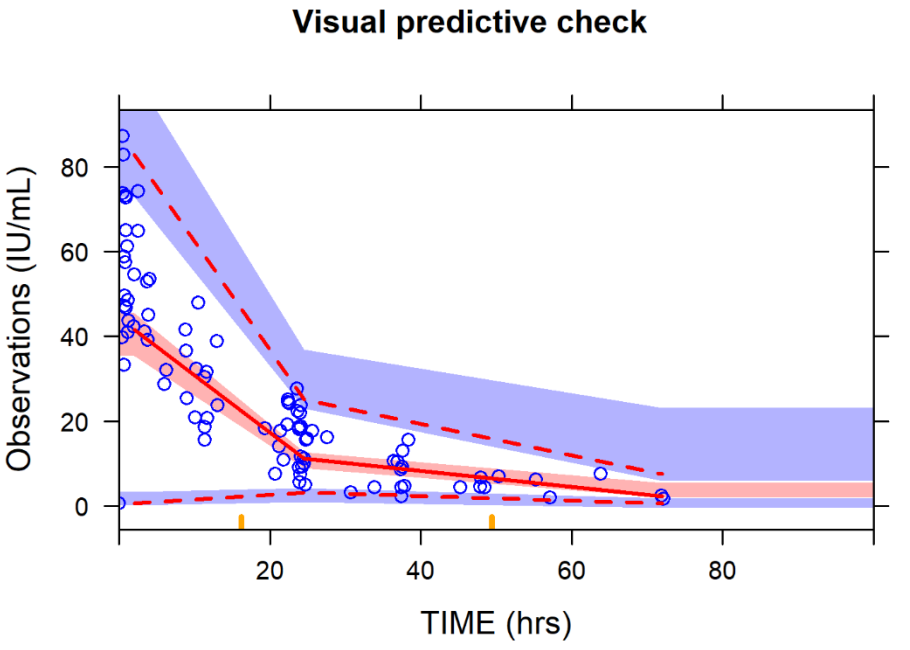


Figure 4. Visual predictive checks of the Pop-Pk model of coagulation factor. The 3 lines in the figures represent observed concentration values (upper dashed line: 95 percentile, middle solid line: 50 percentile and lower dashed line: 5 percentile). All lines are well within their corresponding predictive bands of 95% confidence interval acquired after 1,000 simulation.

Individual PK profiles

From the individual parameters acquired from the final model, their estimated half life was compared with the value predicted from Wapps-Hemo application. Most of the results were similar, but some were quite different. These results are summarized in Table 3.

3. Simulation

For simulation analysis, individuals with baseline FVIII level < 1 IU/dL (severe hemophilia) were selected from the 1000 replicated datasets with 26 patients for each dosing regimen. In single dose scenario, 8593, 8696, 8765, 8533 patients were selected for 20, 30, 40, 50 IU/Kg dose regimen, respectively. In multiple dose secenario, 8746 and 8655 patients were selected respectively for 20 IU/kg twice weekly and thrice weekly regimen and 8694 and 8768 patients were selected for 50 IU/kg twice weekly mad thrice weekly regimen, respectively. The simulated FVIII level vs time curves are depicted in Figure 5-6.

The median (90% prediction interval) and 25th percentile duration for which FVIII activity was maintained above 1 IU dL with 20–50 IU/kg dose scenarios are shown in Table 4.

Table 5 shows the median (90% prediction intervals) and 25th percentile of the FVIII activity level, and the percentage of patients projected to maintain FVIII activity level above 1 IU/dL at the end of each dosing interval. For single dose, the median duration of FVIII level maintained above 1 IU/dL following doses of 20, 30, 40 and 50 IU/kg were about 3.5, 3.8, 4.1 and 4.2 days, respectively. For multiple-dosing scenario, the trough FVIII level and the percentage of patients who maintained FVIII activity levels above 1 IU/dL at the end of the dosing interval were predicted. For twice weekly dosing (days 0 and 3.5) with 50 IU/kg, 65.1% of patients were predicted to maintain a FVIII activity level above 1 IU/dL at day 7. For three-times-weekly dosing (days 0, 2.33, and 4.66) with 50 IU/kg, 94.1% of patients were predicted to maintain a FVIII activity level above 1 IU dL at day 7.

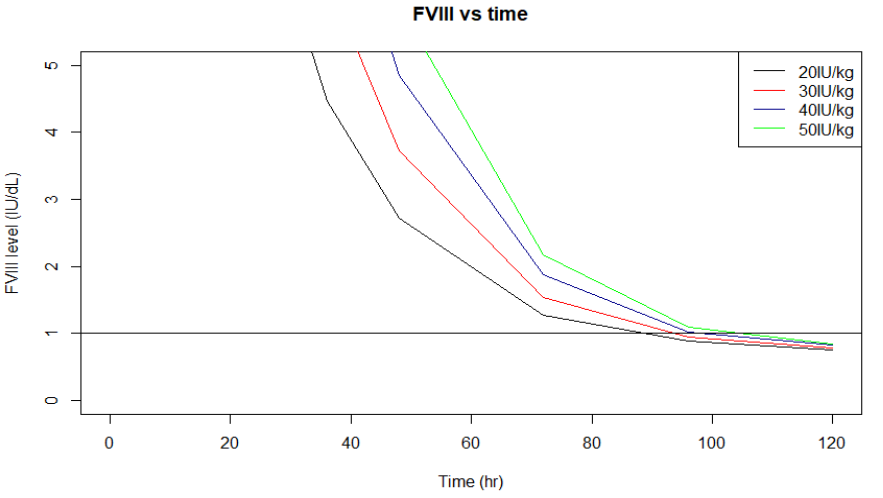


Figure 5. FVIII concentration vs time curve. Simulated median FVIII level in patients with severe hemophilia A after dosing with 20 IU/kg (black), 30 IU/kg (red), 40 IU/kg (blue), and 50 IU/kg (green).

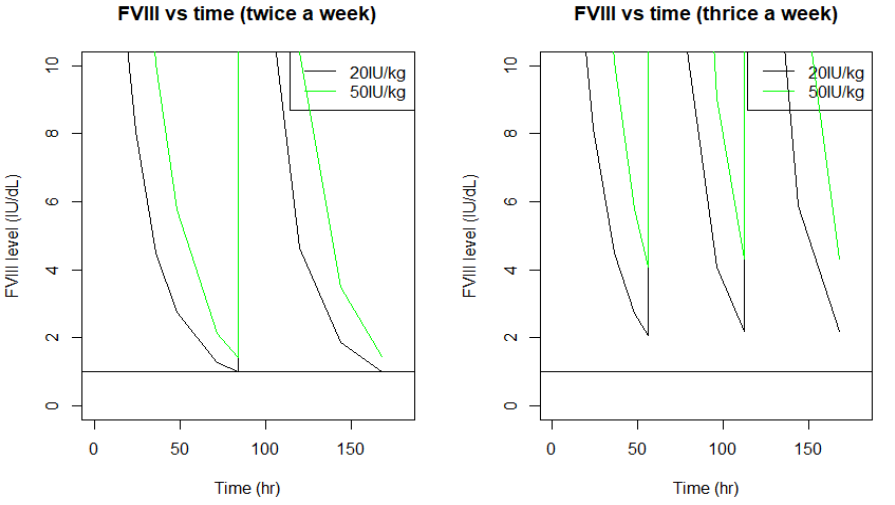


Figure 6. FVIII concentration vs time curve. Simulated median FVIII level in patients with severe hemophilia A after dosing with 20 IU/kg (black) and 50 IU/kg (green) for twice a week (left) and thrice a week (right).

Table 3. Summary of individual half - life (Final model vs Wapps-Hemo*)

Patient number	HL (conservative)	HL (balanced)	HL (optimistic)	HL* (conservative)	HL* (balanced)	HL* (optimistic)
1	13.2	13.8	14.4	14.25	17.25	20.5
2	14.1	14.7	15.3	16	18.75	22
3	9.3	9.9	10.5	9.5	11	12.75
4	9.0	9.5	9.9	10.25	11.75	13.25
5	7.0	7.6	8.2	8	9	10.25
6	13.7	13.8	13.9	10.5	12.5	14.5
7	13.9	14.8	15.8	11	13	15.5
8	17.9	18.1	18.3	14	16.75	20.25
9	10.9	11.3	11.8	7	9	11.25
10	7.1	7.9	8.7	11.75	13.25	15.25
11	13.4	14.4	15.4	10.25	13.25	17.25
12	8.8	9.1	9.5	8.75	10.5	12.5
13	15.0	15.8	16.7	18	21.5	25.75
14	8.8	9.3	9.7	8.25	10.25	12.5
15	13.7	14.4	15.0	16.25	19.25	22.75
16	16.9	17.7	18.5	12	16	21.5
17	12.0	12.2	12.4	8.5	10.25	12
18	14.1	15.1	16.2	13.5	15.75	18.5
19	9.5	10.1	10.7	10	13.5	18.25
20	7.9	8.3	8.8	17.25	23	30.5
21	14.3	15.3	16.3	12.5	14.25	16.25
22	15.0	15.9	16.8	13.5	15.25	17.5
23	12.2	12.9	13.6	10	13.25	17.25
24	11.0	11.4	11.7	11	13.25	15.75

HL, Half-Life; Conservative: lower bound of 95% interval. Balanced: mean value. Optimistic: upper bound of 95% interval.
HL*: Results from Wapps-Hemo application.

Table 4. Summary of simulation (duration of FVIII level that were maintained above 1 IU / dL, following a single dose of 20,30,40, 50 IU / kg)

Single IV dose	Median (hours)	25th percentile (hours)	90% PI (hours)
20	84.5	62	50.1-120
30	91.4	66.7	54-120
40	97.7	70.9	58.2-120
50	101.9	74.9	60.8-120

Table 5. Summary of the simulated trough level of FVIII activity following multiple doses of 20 or 50 IU / kg IV administration

Regimen	PK sampling (day)	Median trough (day)	Percentage of patients maintaining above 1IU/dL of FVIII level
20 IU/kg on day 0 and 3.5	3.5	1.0 (0.47-2.25)	50.5
20 IU/kg on day 0 and 3.5	7	1.0 (0.47-2.45)	51.1
50 IU/kg on day 0 and 3.5	3.5	1.43 (0.55-4.73)	65
50 IU/kg on day 0 and 3.5	7	1.44 (0.55-5.15)	65.1
20 IU/kg on day 0, 2.3, 4.6	2.3	2.06 (0.8-4.36)	82.3
20 IU/kg on day 0, 2.3, 4.6	4.6	2.18 (0.8-5.12)	82.7
20 IU/kg on day 0, 2.3, 4.6	7	2.18 (0.8-5.39)	82.7
50 IU/kg on day 0, 2.3, 4.6	2.3	4.09 (1.19-10)	94
50 IU/kg on day 0, 2.3, 4.6	4.6	4.31 (1.20-12)	94.1
50 IU/kg on day 0, 2.3, 4.6	7	4.32 (1.2-12.46)	94.1

PI, prediction interval; PK, pharmacokinetic. The lower limit of quantification (LLOQ) for the chromogenic assay is 1 IU/dL. Simulated activity may be below the LLOQ.

4. Application development

The web-based simulation application, K-POP-PK, was developed using Rshiny package (Figure 7). With patient information, dosing record, and few data of consequent plasma concentrations, timely predicted individual concentration curve for FVIII can be obtained. (https://wylee.shinyapps.io/hemoA/)

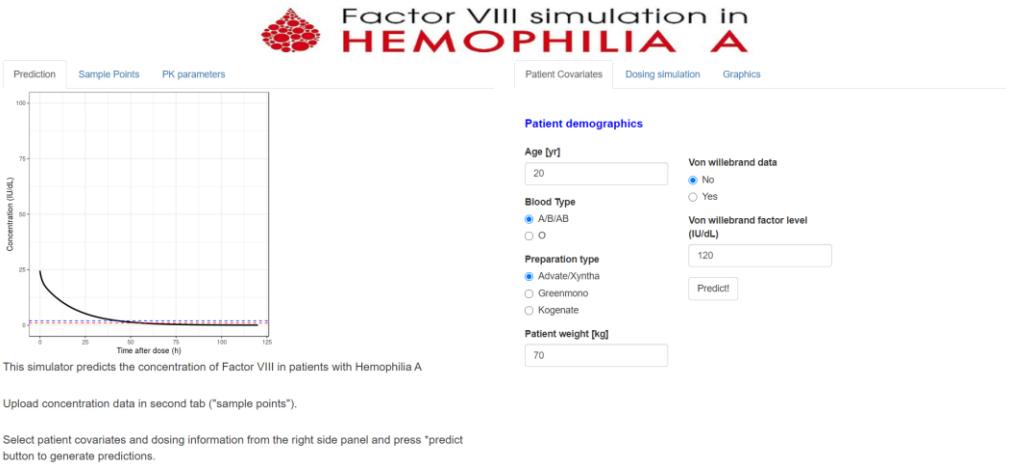


Figure 7. K-POP-PK application. A web-based application for simulating plasma FVIII level in patients with hemophilia A. The horizontal dotted lines in blue and red indicate 3 IU/dL and 1 IU/dL concentration level.

IV. DISCUSSIONS

While there have been several population PK studies of recombinant coagulation FVIII, this is the first one in Korean population. In this study, the PK of FVIII was best described by a two-compartment model with a small TVV2 as in previous studies[9,17,18] but our results showed a few different outcomes.

First, while the estimate of V1 was similar (38.4 dL vs 35.2 dL), V2 was estimated to be about 2 fold larger in our study (5.7 dL vs 2.65 dL) compared to the previous studies[18,19.] IIV of V2 was included in the model instead of IIV of V1 which was insignificant and trivial in our case. The V2, peripheral volume, which could be the rapid clearance of exogenous FVIII by the reticulo-endothelial system (RES) instead of a true peripheral distribution compartment, showed significant variation between individuals showing 141.4% of coefficient of variation (CV). So because of the different profiles for IIV the estimates of V1 and V2 can not be directly compared to the results from previous studies. It could partially be explained by the various types of preparation used in this study. Also, it might be due to the small sample size used for the analysis.

Second, the estimated Q for the typical patient with 70kg WT in this study was 6.4 dL/h, which was approximately 2.5 to 3.75 fold larger, compared to the former studies on Advate and other FVIII preparations[9,18], in which the values were 1.71 dL/h and 2.63 dL/h, respectivly. The reasons for this faster disposition process involved between central and peripheral compartments are not obvious. One reason might be the types of preparation used in this study. Another reason could be the ethnic difference, which is known to be one of the major sources of PK variability in protein drug [20,21].

Third, the estimated CL in this study was 2.76 dL/h which was slightly larger than the previous studies[9,18], where the value was 2.35 dL/h for Advate population PK study and 2.29 dL/h for population PK study with multiple FVIII product. The elimination T½ of factor VIII was comparable to other studies; 11.2 hrs in this study, 12.2 hrs for study of Advate, and 12~14 hrs for study with multiple FVIII products[9,18].

ABO could also affect the clearance. It was previously found that the elimination T½ of FVIII was shorter in hemophilia patients with blood type O than in those with other blood types[22,23]. So the nature of our data that included higher proportion of individuals with blood type O (33.3%) compared to other study (26.5%)[18] could be one reason. In addition, the ethnicity could be one of the reason for these differences that should be considered[13,20,21].

Eventhough the estimated CV of V2 was large, no covariates were found. Although it showed some relationship with the types of preparations of FVIII, when tested statistically in the preliminary process of finding potential covariates using R, it was not considered in our model for the small sample size of Kogenate user (two individuals). The IIV of BASE was also large, for our data included mild and moderate cases of hemophilia A.

Since PK variabilities of FVIII among individuals are high, further studies regarding the genetic determinant of VWF clearance and FVIII binding may also be needed.

Although there is a study in which AGE was excluded in the model[19], it was found to be a significant covariate to CL in our case ($P<0.005$), even after WT was applied allometrically. WT was positively related to the CL, while AGE was negatively related, yielding a yearly CL decrease of approximately 1.2% after 27 years old. This relationship of age to CL was in accordance with previous studies, but its covariate effect was approximately 42% to 60% smaller comparing to our study[9,18,19].

The VWF stabilize the FVIII in plasma by forming complex. As a result, lower VWF is related to higher clearance of the FVIII. In our model, VWF showed strongly significant relationship to CL which decreases exponentially by $e^{-0.0052\cdot(VWF-115.4)}$.. These results agree with previous studies[13,14].

For ABO, it was tested as a categorical covariate with 2 levels, type O and other types, for our result showed no difference between subtype A and B, just as the result from a previous study[13]. Consequnetly, the type O group showed 48.4% larger clearance of FVIII compared to other blood types. The mean value of VWF in type O and other

types was 101.3 and 142.5 IU/dL, respectively, showing significant difference between the groups ($p < 0.01$, two sample t test). This result agrees with a previous study which concludes individuals with blood type O have lower level of VWF due to their higher clearance of VWF[22]. From these results and considering the correlation between VWF and ABO (correlation coefficient of -0.46; $p < 0.05$), we expect ABO can be used in the model instead of VWF for wider and easier use in clinical practice. This could be considered especially in the clinical settings where VWF analysis results are not easily obtainable.

Population PK will be more and more useful in the era of novel treatment in hemophilia[24]. Products with elongated half-life such as Eloctate and Adynovate for hemophilia A and Alprolix and Idelvion for hemophilia B have been developed[25]. These products provide benefit to patients by reducing the frequency of infusions during prophylaxis and by improving adherence to the treatment. With these medications, more patients can maintain their quality of life conveniently and save medical costs at the same time. But these enhanced half life (EHL) products can show the larger inter-individidual variability in PK parameters and their covariates can be different from the standard half-life products[26]. In hemophilia B with the more frequent single nucleotide variants, the variability in PK can be more remarkable[27] and there can be an issue of cross reactive material, the blood protein concentration may not being able to reflect the protein activity directly[12,27]. Moreover, if the infusion of EHL drug preparations is not frequent enough, it can not sufficiently prevent breakthrough bleeding episodes in patients who are physically active due to their coagulation factor level remaining below 3% for a long time, thus potentially increasing the risk of bleeding events[27,28]. More smart use of newer products can be made by using population PK.

V. CONCLUSION

This study has a limitation; due to a small number of patients used in the analysis, the results obtained need to validated with more patients. Nevertheless, this was the first study describing population PK of FVIII in the Korean population, based on sparse samples obtained from a prospectively designed trial. It is expected that the results of this study can be used to extending FVIII PK analyses to other sources of variation, including ethnic and potentially genetic differences.

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ABSTRACT (IN KOREAN)

한국인 A형 혈우병 환자를 대상으로 혈액 응고인자 8의 약동학적 모델 개발과 임상적용

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이 우 열

목적: 본 연구는 한국인 A형 혈우병 환자의 개인별 맞춤 치료를 통해 환자의 기대수명과 삶의 질 개선에 기여 하고자 혈액응고 인자 8의 한국형 약동학적 모델을 수립하여 예방적 약물 치료에 적용 시키는데 있다.

재료와 방법: 세브란스 병원 소아 혈액 종양과와 한국 혈우병 재단의 A형 혈우병 환자에서 혈액 응고인자 8 투여 후 시간에 따른 혈장내 농도 데이터를 이용하여 분석 하였다. 투약기록이 있거나 4-5 반감기가 지난 환자들을 대상으로 하였고 응고인자 8에 대한 항체가 5 Bethesda unit 이상을 보이는 환자들은 분석 대상에서 제외 하였다. 총 24명 환자의 농도 데이터를

사용하여 혼합효과 모델을 수립하였다. 모든 모델 탐색 과정은 NONMEM 7.3을 이용하여 수행되었으며 시각적 탐색은 R. 3.5.2를 이용하여 수행되었다.

결과: 2구획 분포 및 1차제거 모형으로 혈액 응고인자 8의 농도가 잘 예측이 되었다. 상대 성장 이론을 분포용적과 청소율에 적용하였다. Von Willebrand 인자의 농도와 나이가 공변량으로 채택되어 청소율에 적용 되었다. 중앙구획 분포용적과 청소율은 각각 38.4 dL, 2.76 dL/h 로 산출 되었다. 소실 반감기는 11.2 시간으로 산출 되었다. 해외의 모델과 비교시에 분포용적과 청소율이 한국인에서 더 크게 산출이 되었으며 일부 환자들 개인의 반감기 예측 값에서 상당한 차이를 보였다.

결론: 본 연구를 통하여 한국인에서 혈중 혈액응고 인자 8의 투여 후 시간에 따른 농도를 예측할 수 있었다. 본 모델에 향후 더 많은 환자들의 데이터를 추가하여 발전 시켜 환자의 개인 별 맞춤 치료에 유용한 도구로 이용될 수 있을 것이다.

핵심되는 말: 혈우병, 약동학 모델, 혈액응고인자, 정밀의료, 예방적치료