

A population pharmacokinetic model for perioperative dosing of factor VIII in hemophilia A patients

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ABSTRACT

The role of pharmacokinetic-guided dosing of factor concentrates in hemophilia is currently a subject of debate and focuses on long-term prophylactic treatment. Few data are available on its impact in the perioperative period. In this study, a population pharmacokinetic model for currently registered factor VIII concentrates was developed for severe and moderate adult and pediatric hemophilia A patients (FVIII levels <0.05 IUmL⁻¹) undergoing elective, minor or major surgery. Retrospective data were collected on FVIII treatment, including timing and dosing, time point of FVIII sampling and all FVIII plasma concentrations achieved (trough, peak and steady state), brand of concentrate, as well as patients' and surgical characteristics. Population pharmacokinetic modeling was performed using non-linear mixed-effects modeling. Population pharmacokinetic parameters were estimated in 75 adults undergoing 140 surgeries (median age: 48 years; median weight: 80 kg) and 44 children undergoing 58 surgeries (median age: 4.3 years; median weight: 18.5 kg). Pharmacokinetic profiles were best described by a two-compartment model. Typical values for clearance, inter-compartment clearance, central and peripheral volume were 0.15 L/h/68 kg, 0.16 L/h/68 kg, 2.81 L/68 kg and 1.90 L/68 kg. Interpatient variability in clearance and central volume was 37% and 27%. Clearance decreased with increasing age ($P<0.01$) and increased in cases with blood group O (26%; $P<0.01$). In addition, a minor decrease in clearance was observed when a major surgical procedure was performed (7%; $P<0.01$). The developed population model describes the perioperative pharmacokinetics of various FVIII concentrates, allowing individualization of perioperative FVIII therapy for severe and moderate hemophilia A patients by Bayesian adaptive dosing.

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Introduction

Hemophilia A is an X-linked hereditary bleeding disorder characterized by a deficiency of coagulation factor VIII (FVIII). Current management of hemophilia patients consists of replacement therapy with plasma derived or recombinant factor concentrates in case of acute bleeding (“on demand”) or to prevent spontaneous or perioperative bleeding (“prophylaxis”). The aim of long-term prophylactic treatment is to prevent severe joint damage and subsequent long-term invalidity by raising FVIII trough plasma concentrations to at least 0.01 IUml⁻¹.^{1,2} To acquire adequate hemostasis in the surgical setting, normalization of coagulation factor levels is advocated for 7-14 days after surgery in most perioperative protocols.³

Treatment with factor concentrates is costly. In the Netherlands, total annual costs of replacement therapy are estimated at more than 130 million euro and include costs for prophylactic and “on demand” treatment.^{4,7} In the Canadian Hemophilia Registry, perioperative consumption amounts to 1%-3% of the total annual amount administered.⁸

As we have reported earlier, coagulation factor plasma concentrations as recommended by National and International Guidelines are often exceeded in the perioperative setting to avoid lower plasma concentrations and a possibly higher bleeding risk, with additional costs.^{9,10} In a retrospective analysis of hemophilia A patients undergoing surgery, 45% of FVIII plasma concentrations were below the target range during the first 24 hours after surgery and 75% of the plasma concentration were above the target range after six days of hospitalization. In addition, a reduction of 44% in factor concentrates could have been reached if plasma concentrations had been maintained within target levels in the perioperative setting.⁹

In the prophylactic setting, Carlsson *et al.* have shown that FVIII consumption can be significantly reduced by application of pharmacokinetic (PK) modeling to individualize dosing regimens.¹¹⁻¹⁴ In the perioperative setting, Longo *et al.* have reported excessive FVIII consumption and clearance in 50% of surgical hemophilia patients due to unidentified factors.¹⁵ This suggests mechanisms of increased clearance due to hemostatic challenges during surgery. Although an initial preoperative factor concentrate bolus dose may be individualized by individual PK parameters obtained after an individual PK profile based on a prophylactic population PK model, this may not be applicable as soon as a surgical procedure is initiated. A perioperative population PK model, however, would make PK-guided iterative adaptive Bayesian dosing with a potential concomitant decrease of factor concentrate consumption possible. During this procedure individual PK parameters are iteratively up-dated by combining PK information (e.g. dose, concentration, time) from the indi-

vidual patient with *a priori* PK information (e.g. average clearance, variability) from the population. But this information is not currently available and has, therefore, never been performed.

In order to construct a perioperative population PK model of this kind, to facilitate Bayesian adaptive dosing in severe and moderate hemophilia A, we collected detailed retrospective FVIII infusion data in patients who had undergone surgery under replacement therapy with various similar FVIII concentrates from five hemophilia treatment centers.

Methods

Patients' characteristics and data collection

Severe and moderate hemophilia A patients of all ages with FVIII plasma concentration less than 0.05 IUml⁻¹ who had undergone elective, minor or major surgical procedures between 2000 and 2013 from five Academic Hemophilia Treatment Centers in the Netherlands were included.⁹ Patients received replacement therapy consisting of various recombinant factor concentrates (Kogenate FS: Bayer, Berkely, Ca, USA; Helixate FS: CSL Behring, Marburg, Germany; Advate and Recombinate: Baxter Bioscience, Thousand Oaks, CA, USA; Refacto AF: Pfizer, New York, NY USA) or plasma derived factor concentrates (Aafact: Blood Transfusion council of the Netherlands Red Cross; Hemofil M: Baxter Bioscience, Thousand Oaks, CA, USA) to achieve target FVIII plasma concentrations as set by the National Hemophilia Consensus. This guideline recommends peak and trough FVIII plasma concentrations on consecutive postoperative days (Table 1): 0-24 hours 0.80-1.00 IUml⁻¹; 24-120 hours 0.50-0.80 IUml⁻¹ and more than 120 hours 0.30-0.50 IUml⁻¹.³ The following retrospective data were collected: FVIII dosages, detailed timing of administration and timing of FVIII blood sampling, mode of infusion (continuous or bolus infusion), all achieved FVIII plasma concentrations (both trough, peak and steady state plasma concentrations), patients' and surgical characteristics, and concomitant medication with a possible effect on hemostasis (i.e. tranexamic acid, heparin, desmopressin and non-steroidal anti-inflammatory drugs). Patients' characteristics included: body weight, length, lean body mass,^{16,17} body mass index (BMI),¹⁸ blood group, von Willebrand Factor (VWF) antigen and VWF activity (historically measured), liver and renal function, clinical bleeding phenotype, history of FVIII inhibiting antibodies, intensity of prophylactic dosing regimen, brand of concentrate, and treatment center. Surgical characteristics included type and severity of surgical procedure categorized into minor, major and high risk according to Koshy *et al.*¹⁹ In all centers, FVIII plasma concentrations were measured by one-stage clotting assays. The study was not subject to the conditions of the Medical Research Involving Human Subjects Act, as patient data were analyzed anonymously. The study was approved by all local Medical Ethics Committees; one center required prior patient informed consent.

Table 1. Prevalence of under- and overdosing in the perioperative period.*

Time (hours)	0-24		24-120		>120	
Consensus	0.80-1.00 IUml ⁻¹		0.50-0.80 IUml ⁻¹		0.30-0.50 IUml ⁻¹	
% above	33%	(>1.00 IUml ⁻¹)	59%	(>0.80 IUml ⁻¹)	75%	(>0.50 IUml ⁻¹)
% below	45%	(<0.80 IUml ⁻¹)	7%	(<0.50 IUml ⁻¹)	9%	(<0.30 IUml ⁻¹)

*According to the National Hemophilia Consensus.

Pharmacokinetic modeling

Population PK is defined as the study of sources of variability in drug concentrations after dosing that occurs both in individual patients and between patients.²⁰ In the present population analy-

sis, all plasma concentration time points were analyzed simultaneously using non-linear mixed-effects modeling software (NONMEM v.7.2.0; Globomax LLC, Ellicott City, Maryland, USA).²¹ All PK-related abbreviations and terminology are described in *Online*

Table 2. Characteristics of the study population.

Patients' characteristics	Total cohort		Adults		Children	
	N.	(%)	N.	(%)	N.	(%)
N. of patients	119		75		44	
Age (years)	40	[0.2-78]	48	[19-78]	4	[0.2-17.3]
Weight (kg)	75	[5-111]	80	[45-111]	19	[5-85]
Severe hemophilia (FVIII levels <0.01 IUml ⁻¹)	83	(69.7)	49	(65.3)	34	(77.3)
On prophylaxis	84	(70.6)	51	(68.0)	33	(75.0)
Blood group O*	51	(50.5)	34	(50.0)	17	(51.5)
Historical VWF levels (mmol)						
Antigen	1.1	[0.3-2.5]	1.2	[0.3-2.5]	0.9	[0.5-2.3]
Activity	1.1	[0.2-2.7]	1.4	[0.2-2.7]	0.9	[0.4-1.7]
Surgical characteristics						
Total n. of surgical procedures	198		140		58	
N. of patients undergoing:						
1 procedure	75	(63.0)	43	(57.3)	32	(72.7)
2 procedures	26	(21.8)	15	(20.0)	11	(25.0)
3 procedures	9	(7.6)	9	(12.0)	0	(0.0)
>4 procedures	9	(7.6)	8	(10.7)	1	(2.3)
Major surgical procedure	97	(49.0)	86	(61.4)	11	(19.0)
Type of surgical procedure						
General	6	(3.0)	6	(4.3)	0	0
Colo-rectal	5	(2.5)	4	(2.9)	1	(1.7)
Vascular	1	(0.5)	1	(0.7)	0	0
Cardio-thoracic	1	(0.5)	1	(0.7)	0	0
Orthopedic	94	(47.5)	91	(65.0)	3	(5.2)
Urology	12	(6.1)	4	(2.9)	8	(13.8)
Maxillofacial	2	(1.0)	2	(1.4)	0	0
Ear-nose-throat	11	(5.6)	6	(4.3)	5	(8.6)
Eye	3	(1.5)	3	(2.1)	0	0
(Re)placement of central intravenous catheters	32	(16.2)	1	(0.7)	31	(53.4)
Miscellaneous	31	(15.7)	21	(15.0)	10	(17.2)
Replacement therapy with factor concentrate, hospitalization and blood loss						
Mode of infusion						
Continuous	115	(58.1)	88	(62.9)	27	(46.6)
Bolus	83	(41.9)	52	(37.1)	31	(53.4)
Product type						
Recombinant	152	(76.8)	99	(70.7)	53	(91.4)
Plasma derived	46	(23.2)	41	(29.3)	5	(8.6)
Duration of hospitalization (days)	9	[1-50]	9	[1-50]	7	[1-16]
Complications during the perioperative period						
N. of patients with a complication						
Bleeding	48	(24.2)	45	(32.1)	3	(5.2)
Re-operation	6	(3.0)	6	(4.3)	0	0
Hemoglobin drop >20 gL ⁻¹ and/or erythrocyte transfusion	38	(19.2)	36	(25.7)	2	(3.4)
Bleeding with prolonged hospitalization	5	(2.5)	4	(2.9)	1	(1.7)
Thrombosis	0	0	0	0	0	0
FVIII data						
FVIII measurements (trough, peak and SS)	1389		1124		265	
Prior to surgery	158	(11.4)	114	(10.1)	44	(16.6)
Day 1 (0 - 24 hours)	323	(23.2)	246	(21.9)	76	(28.7)
Day 2 - 5 (24 - 120 hours)	473	(34.0)	363	(32.3)	110	(41.5)
Day > 6 (>120 hours)	436	(31.4)	401	(35.7)	35	(13.2)

N.: number; %: percentages; kg: kilogram; FVIII: coagulation factor VIII; IUml⁻¹: international units per milliliter; BU: Bethesda Units; VWF: von Willebrand factor; mmol^l: millimolar per liter; gL⁻¹: gram per liter; SS: steady state; *blood group known for 101 patients.

Supplementary Table S1. More specifically, first-order conditional estimation (FOCE) method with interaction was applied, allowing interaction between structural and residual variance components. The statistical package R v.2.14.2 (The R Foundation for Statistical Computing) and Xpose version 4²² were used for data set check-out, exploration and model diagnostics. Pirana software was used as an interface between NONMEM, R and Xpose.²³

Model diagnostics included the evaluation of the goodness of fit plots, the objective function value (OFV), the precision of the parameter estimates and the shrinkage of estimated random parameters. The OFV is a measurement of goodness of fit of the model and is proportional to minus two times the logarithm of the likelihood (-2log likelihood) of the data. Competing hierarchical models were compared by calculating the difference between their OFV. This ratio is assumed to be χ^2 distributed. Therefore, if models differ by one parameter, a decrease in OFV of 3.84 corresponds to $P=0.05$ (1 degree of freedom) and OFV decreases of 6.63 and 10.8 correspond to $P=0.01$ and 0.001, respectively.

Structural model development

FVIII plasma concentrations were described by a two-compartment PK model. Estimated (fixed) parameters were clearance (CL), volume of distribution of the central compartment (V1), inter-compartment clearance (Q), and volume of distribution of the peripheral compartment (V2). The structural model also accounted for the individual endogenous baseline FVIII plasma concentration. PK parameters were allometrically scaled to account for the wide range of body weights of both adult and pediatric patients. An allometric power model was used with power exponents fixed at 0.75 for clearances and 1.0 for volumes of distribution,²⁴ as described in the following equations:

$$CL_i = \theta_{CL} \times (BW_i/68)^{0.75}$$

$$V1_i = \theta_{V1} \times (BW_i/68)$$

In this expression, CL_i and $V1_i$ are the typical clearance and central volume of distribution for an individual i with body weight BW_i while θ_{CL} and θ_{V1} are the respective parameter values for a subject with a body weight of 68 kilogram.

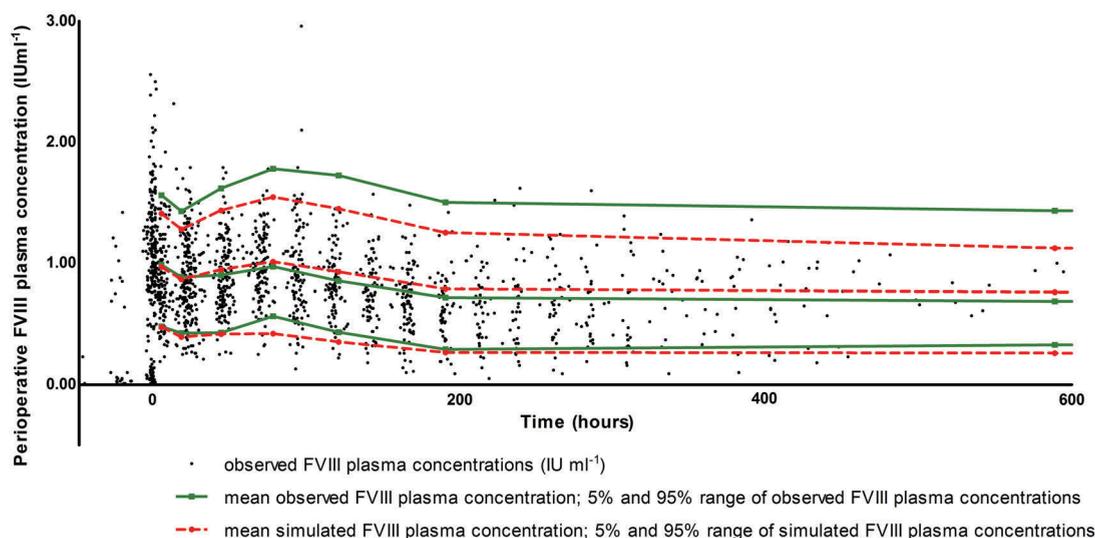


Figure 1. Perioperative FVIII plasma concentrations and visual predictive check for observed FVIII plasma concentrations. Perioperative FVIII plasma concentrations consist of trough, peak and steady state concentrations for both modes of therapy (continuous infusion and bolus infusion therapy). Visual predictive check for the observed FVIII plasma concentrations, given the final model. Observed FVIII plasma concentrations and mean, 5th percentile and 95th percentile observed and simulated FVIII plasma concentrations.

Table 3. Model-building steps resulting in significant decreases in objective function value (OFV).

Model		NOP	OFV
Structural model*			
1	One compartment with IIV on V1 and CL	7	-2604.5
2	Two compartments with IIV on V1 and CL	9	-2799.3
3	Inclusion of individual endogenous baseline FVIII plasma concentrations	9	-2816.1
Covariates on CL (added to model 3)			
4	Age	10	-2851.8
5	Age, blood group	11	-2862.3
6	Age, blood group, bleeding complication	12	-2886.7
7	Age, blood group, bleeding complication, severity of surgical procedure	13	-2895.2
Covariates on V1 (added to model 7)			
8	Age	14	-2911.8
Error model (added to model 8)			
9	Center (two categories)	16	-2930.6

*Allometric scaling based on body weight was applied with an allometric exponent of 0.75 for the clearance parameters and 1 for the volume terms; under prediction of FVIII plasma concentrations of a B-domain deleted product was implemented. NOP: number of estimated parameters; OFV: objective function value; IIV: inter-individual variability; V1: volume of the central compartment; CL: clearance.

The random parameters inter-individual variability (IIV) and inter-occasion variability (IOV) of the PK parameters were estimated using an exponential function according to:

$$CL_i = \theta CL \times e^{(\eta_i + \kappa_i)}$$

where η_i and κ_i represent the IIV and IOV, respectively, and are assumed to be symmetrically distributed with a mean of 0 and an estimated variance of ω^2 and π^2 . IIV and IOV were included in the model if shrinkage was less than 20%.²⁵ The structural model also accounted for under prediction of plasma concentrations of a B-domain deleted product (Refacto[®]) due to known discrepancies and influence of one-stage laboratory assays on plasma concentrations,^{26,27} as described:

$$C_{pred, bdp} = C_{pred} \times (1 - \theta_{bdp})$$

Where $C_{pred, bdp}$ and C_{pred} are the predicted concentrations of the B-domain deleted product ($_{bdp}$) and other products, respectively, and θ is the fractional decrease in concentration. Residual variability in FVIII concentration was described using a combined error model.

Covariate search

After obtaining the structural model individual empirical Bayesian estimates were obtained for all PK parameters. Correlations between these parameters and patients' and surgical

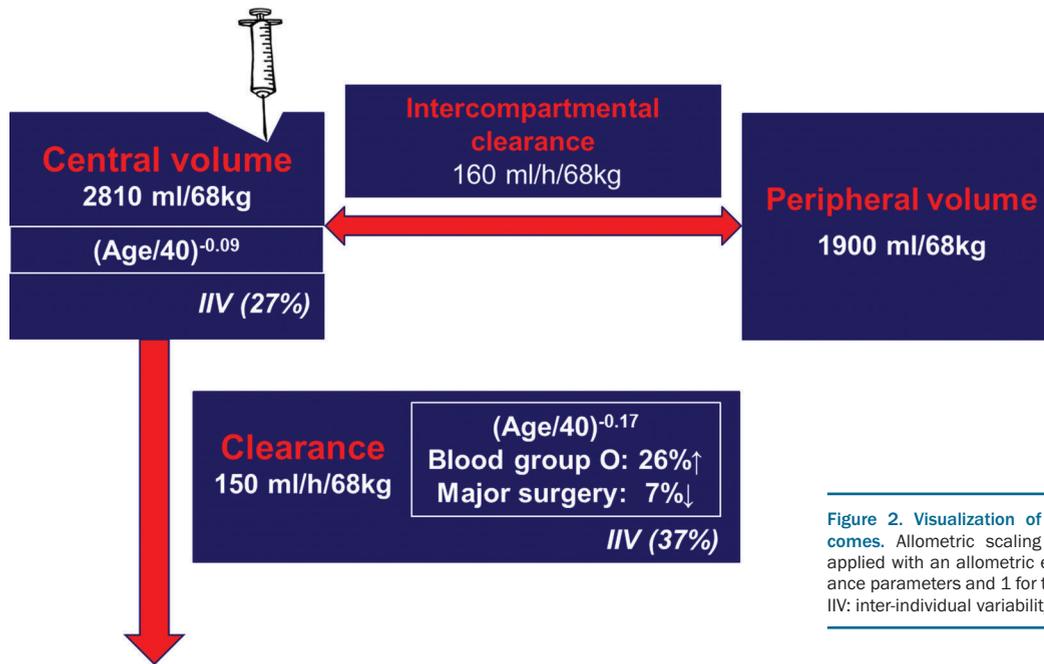


Figure 2. Visualization of NONMEM analysis and outcomes. Allometric scaling based on body weight was applied with an allometric exponent of 0.75 for the clearance parameters and 1 for the volume terms; age in years; IIV: inter-individual variability.

Table 4. Parameter estimates for the final model and bootstrap analysis.

Parameter	Structural model		Final model		Bootstrap analysis final model	
	Mean	(%RSE)	Mean	(%RSE)	Mean	(%RSE)
Structural model						
1 - Clearance (CL; mL/h/68 kg)	190	(5)	150	(8)	160	(5)
2 - Volume of central compartment (V1; mL/68 kg)	3030	(3)	2810	(4)	2810	(3)
3 - Inter-compartmental clearance (Q; mL/h/68 kg)	170	(17)	160	(20)	170	(15)
4 - Volume of peripheral compartment (V2; mL/68 kg)	1930	(12)	1900	(11)	1890	(8)
B-domain deleted product	0.32	(11)	0.34	(13)	0.33	(10)
Covariate parameters						
5 - CL - Age (change with increasing age)			-0.17	(22)	-0.16	(13)
6 - CL - Blood group O (% difference)			26	(7)	27	(22)
7 - CL - Major surgical procedure (% difference)			-7	(6)	-7	(34)
8 - V1 - Age (change with increasing age)			-0.09	(28)	-0.09	(18)
Inter-individual variability						
Clearance (% CV)	45	(13)	37	(14)	36	(10)
Volume of central compartment (% CV)	29	(13)	27	(14)	26	(11)
Residual variability						
<i>Additive residual error (SD; IUml⁻¹)</i>						
Center 1,2,3			0.15	(12)	0.14	(9)
Center 4,5			0.05	(28)	0.05	(20)
<i>Proportional residual error (% CV)</i>						
Center 1,2,3			0.18	(15)	0.18	(9)
Center 4,5			0.23	(9)	0.23	(7)

RSE: relative standard error; CL: clearance V1: volume of central compartment; Q: inter-compartmental clearance; V2: volume of peripheral compartment; CV: coefficient of variation; SD: standard deviation.

characteristics, and the use of concomitant medication were explored graphically. All covariates were tested in a univariate analysis. The most clinically relevant and statistically significant covariate was retained in the model: a stepwise forward approach was used to determine clinical and statistically significant covariates with $P < 0.05$. Backward elimination was performed to confirm that all included covariates in the final model were statistically significant with $P < 0.01$. As the occurrence of a bleeding complication could not be related to actual FVIII plasma concentrations,⁹ occurrence of a bleeding complication was not included in the final model. Moreover, only a limited difference in clearance was observed between patients with and without a bleeding complication (7%). Also, time dependent changes in clearance were tested during the perioperative period.

Final model and model evaluation

The stability and performance of the final model was checked using an internal validation procedure *via* the bootstrap resampling technique in which 1000 bootstrap datasets were generated by random sampling with replacement.²⁸ Visual predictive check plots obtained after Monte Carlo simulations of the study population were used to evaluate if the final model adequately described observed data.²⁹

Results

Patients and treatment in the perioperative setting

Our cohort consisted of 119 hemophilia A patients

Table 5. Model equations describing the perioperative population PK model.

CL	$CL \text{ (mL/h)} = 150 \times ((\text{body weight} / 68)^{0.75}) \times ((\text{age} / 40)^{-0.17}) \times (1.26^{\text{blood group}}) \times (0.93^{\text{severity of surgical procedure}})$
V1	$V1 \text{ (mL)} = 2810 \times (\text{body weight} / 68) \times ((\text{age} / 40)^{-0.09})$
Q	$Q \text{ (mL/h)} = 160 \times ((\text{body weight} / 68)^{0.75})$
V2	$V2 \text{ (mL)} = 1900 \times (\text{body weight} / 68)$

Body weight (kilograms); Age (years); blood group equals one in case of blood group O and zero in case of blood group non O; severity of surgical procedure equals one in case of a major surgical procedure and zero in case of a minor surgical procedure.

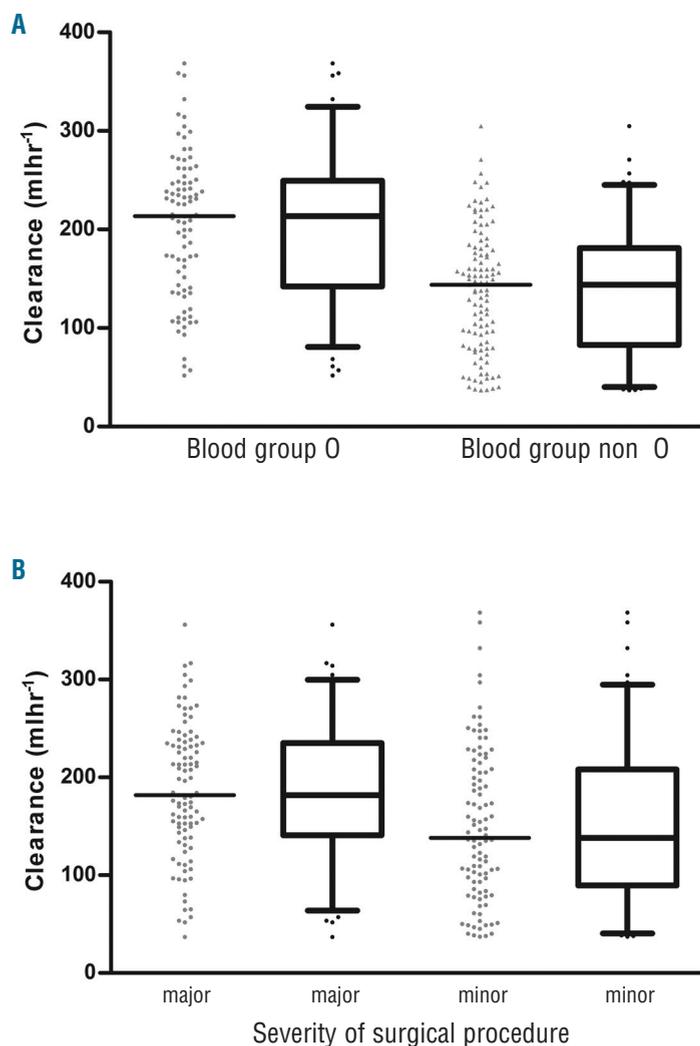


Figure 3. Graphical visualization of variability of the clearance and covariates. Visualization of variability of the clearance. (A) As a function of blood group O versus blood group non O. (B) As a function of severity of surgical procedure.

undergoing a total of 198 surgical procedures, as described previously.⁹ Patients were treated for up to two weeks after surgery according to the National Hemophilia Consensus (Table 1).³ Treatment consisted of a pre-operative bolus infusion of approximately 50 IU kg⁻¹ followed by a treatment scheme with either bolus infusions or continuous infusion therapy based on a clearance rate of 3–4 mL kg⁻¹ hour⁻¹. General characteristics of these included patients are shown in Table 2. Seventy-five patients underwent only one surgical procedure. Half of all patients had blood group O (51%). In 3% of all surgical procedures a severe bleeding complication occurred, defined as necessity of a red blood cell transfusion (RBCT) and/or necessity of a second surgical intervention, which could not be related to FVIII plasma concentrations. In total, 1389 FVIII measurements were obtained, equally distributed on consecutive days in the perioperative setting (Figure 1). Approximately 7 samples *per* patient were taken in the perioperative period. In summary, 45% of FVIII plasma concentrations were below the target range in the first 24 hours and 75% were above the target range after six days of hospitalization (Table 1).

Pharmacokinetic modeling

Structural model development: time profiles of FVIII plasma concentrations were best described by a two-compartment model with allometric scaling for body weight (Figure 2). By allometric scaling, all estimated PK parameters were normalized for a body weight of 68 kg. Model building steps that resulted in significant decrease of the OFV, and consequently a better fit of the model, are shown in Table 3. In the structural model, typical values for CL and V1 were 190 mL/hour/68 kg and 3030 mL/68 kg (Table 4). It was possible to estimate IIV for CL and V1, whereas estimates for IIV of Q and V2 were imprecise and accompanied by a large shrinkage of more than 40%.²⁵ Although this may suggest that there was no inter-patient variability in Q and V2, this is due to the fact that the available data were not sufficiently informative. The IIV for CL and V1 were respectively 45% and 29%, underlining the importance of tailoring therapy to the individual. Estimation of IOV on CL and V1 resulted in high shrinkage values for both parameters (34% and 46%, respectively); consequently IOV was not included in the model. Inclusion of individual endogenous baseline FVIII plasma concentrations and inclusion of a structural underprediction of plasma concentrations using a B-domain deleted product improved the model. A proportional underprediction of 0.34 (34%) in FVIII plasma concentration was estimated for this product. The residual error was described using a combined error model.

Covariate search: in the univariate analysis, significant covariates of clearance were age ($P < 0.001$), blood group ($P < 0.01$), severity of surgical procedure ($P < 0.01$), lean body mass ($P < 0.01$), use of tranexamic acid and heparin ($P < 0.05$), historically measured VWF antigen and activity levels ($P < 0.05$). Treatment center and type of product were not significant covariates. After the step forward analysis, only age, blood group, and severity of surgical procedure were significantly associated with clearance. After the inclusion of age in the model, VWF antigen and activity levels were no longer statistically significant. Age was also associated with V1 (Table 3). Different models were used to test possible time dependent changes in clearance during the perioperative period; however, no

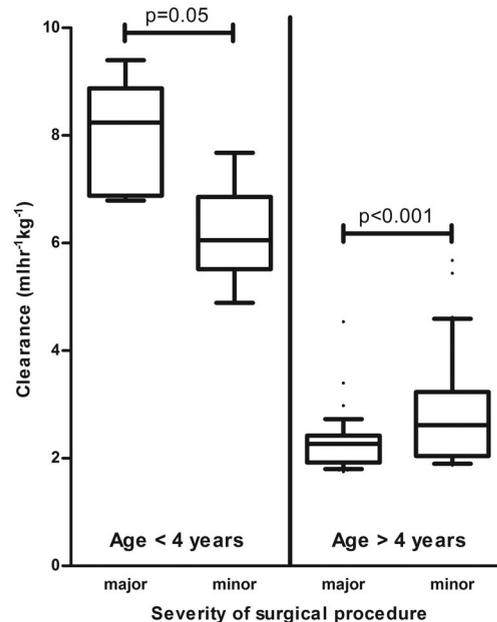


Figure 4. Clearance of FVIII in major and minor surgical procedures after stratification for age. Post hoc estimates of FVIII clearance, normalized for total body weight, and stratified for age (<4 years or >4 years) were categorized according to severity of surgical procedure. *A Spearman's correlation test was performed to test for clearance differences between major and minor surgical procedures. The median age of children included in the study was used as cut-off value for analysis. This was supported by results of Figure 5A.

differences were observed. Differences in residual error were detected for the different centers.

In the final model, IIV of CL decreased from 45% towards 37% after inclusion of these covariates. IIV of V1 decreased from 29% to 27%. The PK parameter estimates of the final model are presented in Table 4. Typical PK parameter estimates were described with the equations presented in Table 5.

According to the equation, clearance was 214, 169, 150 and 142 mL/h/68 kg for a typical patient (with blood group non-O undergoing a minor surgical procedure) with an age of 5, 20, 40 and 55 years, respectively. In case of a major surgical procedure, a small decrease in CL was observed of 7% (Table 4). Interestingly, individual *post hoc* clearances were higher in patients with a major surgical procedure (Figure 3B). This was, however, explained by collinearity between covariates; older patients underwent more major surgical procedures (Figure 4). Clearance increased by 26% in patients with blood group O. CL and elimination half-life are depicted as functions of age and body weight in Figure 5.

The adequacy of the derived final model is shown in Figure 6. Population and individually predicted concentrations for all patients were plotted against the measured concentrations in Figure 6. A good agreement was observed between FVIII concentrations predicted by the model and those assessed by laboratory measurements. Overall, standardized weighted residuals revealed a random distribution around zero, within a range of -2 to +2, indicative of an unbiased estimation (Figure 6C).

Model evaluation: a good agreement was found between parameter estimates of the final model and parameter estimates of the bootstrap analysis (Table 4). A visual predic-

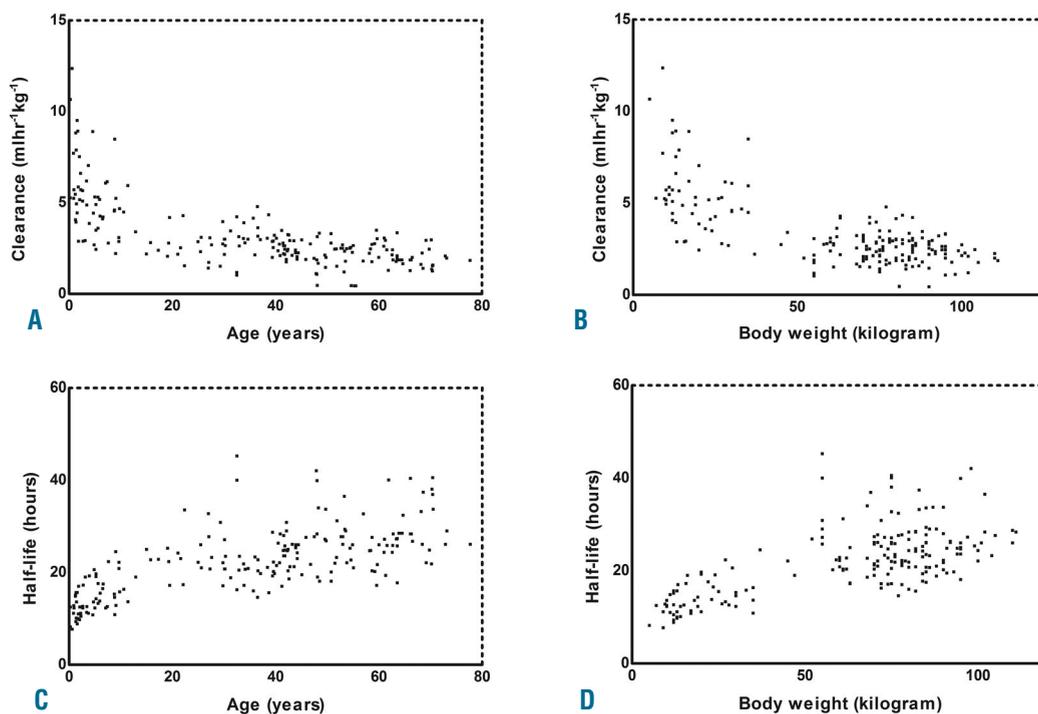


Figure 5. Clearance and elimination half-life as functions of age and body weight. (A) Clearance of FVIII, normalized for total body weight, as a function of age. (B) Clearance of FVIII as a function of body weight. (C) The elimination half-life of FVIII as a function of age. (D) The elimination half-life of FVIII as a function of body weight. Eta shrinkage was 10% and 20%, respectively, for the estimates of inter-individual variability of clearance and volume of the central compartment.

tive check was conducted by 1000 simulations based on the final model (Figure 1). It confirmed adequateness of the model, as 7% of the measured concentrations were calculated above the 95th percentile of the simulated concentrations and 9% of the measured concentrations were found to be below the 5th percentile of the simulated concentrations.

Discussion

In this study, a population PK model was constructed describing the perioperative PK of several FVIII concentrates in current use. The majority of these factor VIII concentrates were FVIII recombinant products (77% of surgical procedures), of which 14% were a B-domain deleted FVIII concentrate, as well as plasma-derived FVIII concentrates (23% of surgical procedures). In the population PK model, a difference in results due to the B-domain deleted FVIII concentrate (Refacto AF[®]) was accounted for. No other differences were observed between products. As this difference is incorporated into the population PK model, this perioperative FVIII population PK model can be used for all described FVIII concentrates. The developed model will facilitate Bayesian adaptive dosing, allowing individualization of FVIII dosing during the entire perioperative period. So far, only a few studies have reported application of PK-guided dosing during the perioperative period. Unfortunately, in all these studies, only the FVIII loading dose was based on an individual PK-profile obtained several days before surgery.³⁰⁻³⁵ Iterative perioperative FVIII dosing-adjustments after first loading dose

could not be performed as there was no population PK model. The perioperative population PK model presented here will now make Bayesian adaptive dosing in this setting possible. Moreover, it will consider all important patients' characteristics associated with clearance in the surgical setting.

The model presented here consists of a two-compartment model with allometric scaling of the PK parameters according to body weight. Both increasing age and increased severity of surgical procedure were overall significantly associated with a lower FVIII clearance, although individual clearance rates showed that patients with a major surgical procedure did demonstrate higher clearance rates. This contradiction may be due to the fact that included covariates in the PK model were confounders, e.g. older patients with a decreased CL of FVIII concentrate underwent major surgical procedures more often than younger patients. Also, increased consumption of concentrates due to blood loss and activation of coagulation are other possible modifying factors. In addition, blood group O was associated with higher FVIII clearance, which will be discussed in the following sections. Although it should be underlined that this population PK model represents an important development, it is important to realize that it does not account for pharmacodynamic outcome measures, as the occurrence of a bleeding complication could not be related to actual FVIII plasma concentrations due to scarcity of FVIII plasma concentrations during an acute bleeding event.

As in most resource rich countries, current perioperative replacement therapy in hemophilia A in the Netherlands consists of a FVIII loading dose followed by either contin-

uous FVIII infusion or treatment with FVIII bolus infusions while targeting predefined peak and trough FVIII plasma concentrations, as stated in the National Hemophilia Consensus.³ The retrospective study performed to collect data for this PK model has been described earlier.⁹ Results show the challenges of current perioperative dosing of FVIII replacement therapy in daily clinical practice when targeting prescribed FVIII plasma concentrations, as significant underdosing and overdosing were demonstrated. Moreover, it underlines the necessity of alternative more individualized dosing strategies in the perioperative setting; this is possible when PK-guided dosing based on a population PK model is applied.

PK-guided dosing based on population PK models has mainly been studied in the long-term prophylactic setting. However, in order to apply Bayesian adaptive dosing, it is necessary to utilize a population PK model appropriate for the individual patient and the specific setting concerned. In analyses preceding the construction of this perioperative population PK model, it was confirmed that the mean estimated PK parameters for prophylactic dosing, as reported by Björkman *et al.*,¹² did not reliably predict observed perioperative FVIII plasma concentrations. Using the prophylactic model, calculations showed an underprediction of perioperative FVIII concentrations of less than 1.00 IUml⁻¹ as well as an overprediction of FVIII concentrations of more than 1.00 IUml⁻¹. In other words, actual FVIII plasma concentrations were respectively higher and lower than those predicted by a prophylactic population PK model (*data not shown*). Therefore, it was concluded that prophylactic population PK models can not be applied in the perioperative setting. Use of the prophylactic model in this setting would generate a bias of predicted perioperative FVIII plasma concentrations.

In the prophylactic setting, a similarly constructed population PK model has already been applied.¹² CL, V1 and Q were actually in accordance when a comparison was made between perioperative and prophylactic PK population model (CL: 150 vs. 222 mL/h/68 kg; V1: 2810 vs. 3520 mL/68 kg; and Q: 160 vs. 256 mL/h/68 kg, respectively). However, in the present perioperative model, a value of 1880 mL/68 kg was found for V2 in contrast to a value of 240 mL/68 kg found in the prophylactic situation, suggesting a rapid redistribution of FVIII concentrate following intravenous administration.¹² Due to increased V2, calculated distribution half-life and elimination half-life are significantly larger (as half-life is a derivative of the distribution volume) in the perioperative setting in comparison with the prophylactic state (4 hours and 25 hours vs. 0.6 hours and 12 hours, respectively). These calculated half-lives are in accordance with previously described half-life observed immediately after surgery and half-life observed at steady state of 10 surgical patients described with a surgical model (9.6 and 17.8 hours, respectively) in comparison to 10 surgical patients described with an estimated half-life of 10.1 hours described with a non-surgical model.¹⁵ Unfortunately, the rapid redistribution was not quantifiable, due to minimal data of laboratory assessment after infusion. Previously, it has been suggested that V2 may reflect the FVIII distribution into extravascular spaces or within an intravascular compartment, more specifically as a reflection of adhesion to the vessel wall, or that it may reflect the process of a rapid initial elimination.^{36,37} We hypothesized that an extra intravascular component resulting in a large V2 may be the result of

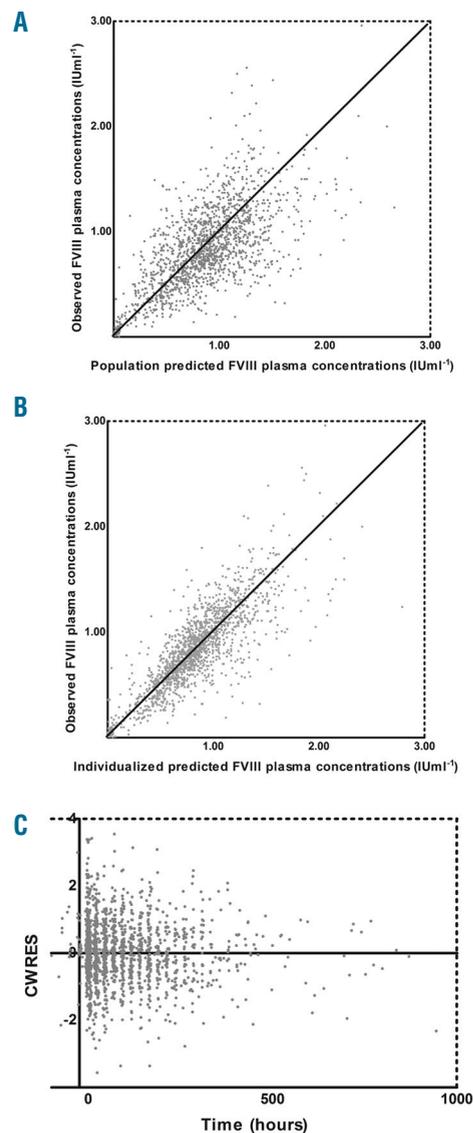


Figure 6. Observed and model-predicted FVIII plasma concentrations. NON-MEM model diagnostic plots, observed and model predicted FVIII plasma concentrations plotted against each other. (A) Population predicted FVIII plasma concentrations. (B) Individually predicted FVIII plasma concentrations. (C) Conditionally weighted residuals versus time.

the high affinity and stoichiometry of FVIII to VWF,³⁸ combined with the significant increase of VWF after surgery due to inflicted endothelial damage and its role in the acute phase reaction.³⁹ In addition, Deitcher *et al.* have shown that volume of distribution increases after desmopressin administration, which, of course, results in an overall increase in VWF levels.⁴⁰

Moreover, we believe that VWF may play a crucial role in the perioperative setting with regard to FVIII PK parameters, as previous studies have demonstrated a clear association between VWF plasma concentrations and FVIII half-life.^{41,42} This is not surprising, as VWF protects FVIII against proteolytic degradation by expression of ABH antigens on N-linked glycans and the uptake of the copper-binding protein ceruloplasmin.^{43,44} In addition, it has been shown that, in healthy individuals undergoing orthopedic surgery, VWF

decreases significantly intraoperatively and rises immediately after surgery.³⁹ Therefore, we suspected a time-dependent FVIII clearance in the presented PK model, with an increased clearance during the surgical procedure itself and a decrease in clearance directly after surgery. However, no time-dependent clearance could be established. Unfortunately, it was not possible to investigate the role of VWF plasma concentrations in our analyses in more detail, as VWF measurements are currently not routine practice in the perioperative setting and only historically measured VWF plasma concentrations were available in half of the study population. However, a 26% higher clearance rate was observed in blood group O patients in the perioperative setting, underlining the potential importance of measurement of VWF plasma concentrations in the perioperative setting if PK-guided dosing is implemented. This is supported by earlier reports that blood group O patients have around 25% lower VWF levels in comparison to patients with blood group non-O.⁴³ Strikingly, this effect of blood group on clearance was not significant in the prophylactic population PK model as shown by Björkman *et al.*¹² However, we are not informed if VWF levels were available for those analyses. In contrast, higher VWF levels may also help explain the unexpected overall lower clearance found in patients undergoing major surgical procedures. The ongoing prospective randomized controlled "OPTI-CLOT" trial (RCT) (described in more detail elsewhere)⁴⁵ will provide, among other things, an insight into the pathophysiology of VWF in hemophilia patients during the perioperative setting, and the relationship between VWF levels and estimates of FVIII PK parameters. These data will further validate the perioperative PK population model presented here, refining its applicability, and further defining the influence of possible modifying factors of PK parameters. Moreover, extending this population PK model, in combination with extended half-life (EHL) products in the near future could be of great value. However, first of all, studies are needed to document in detail associations between clearance of current FVIII products and EHL products within individuals.

Clinically, in the perioperative setting, adaptive Bayesian dosing can be used to optimize and individualize dosing in order to obtain desired target FVIII plasma concentrations with increased certainty. Bayesian analysis combines individual PK data with information from an available population PK model. Such a population PK

model is constructed from PK data of many individuals, and not only embodies defined patients' characteristics known to influence clearance and other PK parameters, but also as yet unidentified patients' characteristics which cannot be quantified. Individual patient information that is entered into the model must include dose and time point of factor concentrate administration, as well as the FVIII plasma concentrations achieved. Incorporation of the patient's body weight, blood group, age and severity of surgical procedure will improve estimation of the individual clearance of factor concentrate. In clinical practice, individual clearance and other PK parameter estimates can be made by a clinical pharmacologist experienced in this methodology and iteratively updated, leading to calculated dose adjustments. We are currently planning to develop a PK tool to implement this perioperative population PK model in daily clinical practice. The first dose of FVIII concentrate, still in steady state, will be based on individual PK parameters deducted from an individual PK profile constructed according to the prophylactic population PK model. As we were not able to demonstrate time-dependent changes in PK parameters during the perioperative setting, the perioperative population PK model described here can be applied to the complete perioperative period with varying target FVIII plasma concentrations, as described by National Guidelines.

In conclusion, we have constructed a perioperative population PK model facilitating iterative dose-adjustments by Bayesian analysis. We believe this model will prove its value as it will lead to optimization of current dosing strategies by reducing underdosing and overdosing, and, therefore, both a decrease of bleeding risk and an expected overall reduction of factor concentrate consumption with a subsequent reduction in costs.

Acknowledgments

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References

1. Fijnvandraat K, Cnossen MH, Leebeek FW, Peters M. Diagnosis and management of haemophilia. *BMJ*. 2012;344:e2707.
2. Collins PW, Blanchette VS, Fischer K, et al. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. *J Thromb Haemost*. 2009;7(3):413-420.
3. Leebeek FWG, Mauser-Bunschoten EP, Editors. [Richtlijn Diagnostiek en behandeling van hemofilie en aanverwante hemostasestoornissen]. Van Zuiden Communications BV. 2009;1-197.
4. Johnson KA, Zhou ZY. Costs of care in hemophilia and possible implications of health care reform. *Hematology Am Soc Hematol Educ Program*. 2011;2011:413-418.
5. Schramm W, Berger K. Economics of prophylactic treatment. *Haemophilia*. 2003;9 Suppl 1:111-115; discussion 116.
6. Feldman BM, Aledort L, Bullinger M, et al. The economics of haemophilia prophylaxis: governmental and insurer perspectives. Proceedings of the Second International Prophylaxis Study Group (IPSG) symposium. *Haemophilia*. 2007;13(6):745-749.
7. Nederlandse Zorgautoriteit. [Onderzoek naar de toegankelijkheid en betaalbaarheid van geneesmiddelen in de medisch specialistische zorg]. Available from: https://www.nza.nl/publicaties/1048188/Onderzoeksrapport_Toegankelijkheid_en_betaalbaarheid_van_geneesmiddelen_in_de_medisch_specialistische_zorg, 29-06-2015:1-110.
8. Traore AN, Chan AK, Webert KE, et al. First analysis of 10-year trends in national factor concentrates usage in haemophilia: data from CHARMS, the Canadian Hemophilia Assessment and Resource Management System. *Haemophilia*. 2014;20(4):e251-259.
9. Hazendonk HC, Lock J, Mathot RA, et al. Perioperative treatment of hemophilia A patients: blood group O patients are at risk of bleeding complications. *J Thromb Haemost*. 2016;14(3):468-478.

10. Hazendonk HCAM, Lock J, Fijnvandraat K, et al. A retrospective observational multicenter study on peri-operative Factor IX consumption in Hemophilia B ("OPTI-CLOT" studies). *J Thromb Haemost.* 2013;11:Suppl 2.
11. Carlsson M, Berntorp E, Björkman S, Lethagen S, Ljung R. Improved cost-effectiveness by pharmacokinetic dosing of factor VIII in prophylactic treatment of haemophilia A. *Haemophilia.* 1997;3(2):96-101.
12. Bjorkman S, Folkesson A, Jonsson S. Pharmacokinetics and dose requirements of factor VIII over the age range 3-74 years: a population analysis based on 50 patients with long-term prophylactic treatment for haemophilia A. *Eur J Clin Pharmacol.* 2009;65(10):989-998.
13. Bjorkman S, Oh M, Spotts G, et al. Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight. *Blood.* 2012;119(2):612-618.
14. Collins PW, Fischer K, Morfini M, Blanchette VS, Bjorkman S; International Prophylaxis Study Group Pharmacokinetics Expert Working G. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. *Haemophilia.* 2011;17(1):2-10.
15. Longo G, Messori A, Morfini M, et al. Evaluation of factor VIII pharmacokinetics in hemophilia-A subjects undergoing surgery and description of a nomogram for dosing calculations. *Am J Hematol.* 1989;30(3):140-149.
16. Boer P. Estimated lean body mass as an index for normalization of body fluid volumes in humans. *Am J Physiol.* 1984;247(4 Pt2):F632-636.
17. Peters AM, Snelling HL, Glass DM, Bird NJ. Estimation of lean body mass in children. *Br J Anaesth.* 2011;106(5):719-723.
18. Garrow JS, Webster J. Quetelet's index (W/H²) as a measure of fatness. *Int J Obes.* 1985;9(2):147-153.
19. Koshy M, Weiner SJ, Miller ST, et al. Surgery and anesthesia in sickle cell disease. Cooperative Study of Sickle Cell Diseases. *Blood.* 1995;86(10):3676-3684.
20. U.S. Department of Health and Human Services FaDA. Guidance for Industry. Population Pharmacokinetics.
21. Boeckmann AJ, Sheiner LB, Beal SL. NONMEM Users Guide. NONMEM Project Group. 2011;University of California at San Francisco (ICON Development Solutions Ellicott City, Maryland):1-165.
22. Jonsson EN, Karlsson MO. Xpose--an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed.* 1999;58(1):51-64.
23. Keizer RJ, van Bentem M, Beijnen JH, Schellens JH, Huitema AD. Pirana and PCluster: a modeling environment and cluster infrastructure for NONMEM. *Comput Methods Programs Biomed.* 2011;101(1):72-79.
24. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol.* 2008;48:303-332.
25. Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. *AAPS J.* 2009;11(3):558-569.
26. Hubbard AR, Weller LJ, Bevan SA. A survey of one-stage and chromogenic potencies in therapeutic factor VIII concentrates. *Br J Haematol.* 2002;117(1):247-248.
27. Hubbard AR, Sands D, Sandberg E, Seitz R, Barrowcliffe TW. A multi-centre collaborative study on the potency estimation of ReFacto. *Thromb Haemost.* 2003;90(6):1088-1093.
28. Ette EI. Stability and performance of a population pharmacokinetic model. *J Clin Pharmacol.* 1997;37(6):486-495.
29. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J.* 2011;13(2):143-151.
30. Batorova A, Martinowitz U. Continuous infusion of coagulation factors. *Haemophilia.* 2002;8(3):170-177.
31. Bidlingmaier C, Deml MM, Kumik K. Continuous infusion of factor concentrates in children with haemophilia A in comparison with bolus injections. *Haemophilia.* 2006;12(3):212-217.
32. Dingli D, Gastineau DA, Gilchrist GS, Nichols WL, Wilke JL. Continuous factor VIII infusion therapy in patients with haemophilia A undergoing surgical procedures with plasma-derived or recombinant factor VIII concentrates. *Haemophilia.* 2002;8(5):629-634.
33. Mulcahy R, Walsh M, Scully MF. Retrospective audit of a continuous infusion protocol for haemophilia A at a single haemophilia treatment centre. *Haemophilia.* 2005;11(3):208-215.
34. Srivastava A. Choice of factor concentrates for haemophilia: a developing world perspective. *Haemophilia.* 2001;7(1):117-122.
35. Stieltjes N, Altisent C, Auerswald G, et al. Continuous infusion of B-domain deleted recombinant factor VIII (ReFacto) in patients with haemophilia A undergoing surgery: clinical experience. *Haemophilia.* 2004;10(5):452-458.
36. Bjorkman S, Carlsson M, Berntorp E, Stenberg P. Pharmacokinetics of factor VIII in humans. Obtaining clinically relevant data from comparative studies. *Clin Pharmacokinet.* 1992;22(5):385-395.
37. Noe DA. A mathematical model of coagulation factor VIII kinetics. *Haemostasis.* 1996;26(6):289-303.
38. Vlot AJ, Koppelman SJ, van den Berg MH, Bouma BN, Sixma JJ. The affinity and stoichiometry of binding of human factor VIII to von Willebrand factor. *Blood.* 1995;85(11):3150-3157.
39. Kahlon A, Grabell J, Tuttle A, et al. Quantification of perioperative changes in von Willebrand factor and factor VIII during elective orthopaedic surgery in normal individuals. *Haemophilia.* 2013;19(5):758-764.
40. Deitcher SR, Tuller J, Johnson JA. Intranasal DDAVP induced increases in plasma von Willebrand factor alter the pharmacokinetics of high-purity factor VIII concentrates in severe haemophilia A patients. *Haemophilia.* 1999;5(2):88-95.
41. Vlot AJ, Mauser-Bunschoten EP, Zarkova AG, et al. The half-life of infused factor VIII is shorter in hemophilic patients with blood group O than in those with blood group A. *Thromb Haemost.* 2000;83(1):65-69.
42. Fijnvandraat K, Peters M, ten Cate JW. Inter-individual variation in half-life of infused recombinant factor VIII is related to pre-infusion von Willebrand factor antigen levels. *Br J Haematol.* 1995;91(2):474-476.
43. Klarmann D, Eggert C, Geisen C, et al. Association of ABO(H) and I blood group system development with von Willebrand factor and Factor VIII plasma levels in children and adolescents. *Transfusion.* 2010;50(7):1571-1580.
44. Lenting PJ, van Mourik JA, Mertens K. The life cycle of coagulation factor VIII in view of its structure and function. *Blood.* 1998;92(11):3983-3996.
45. Hazendonk HC, van Moort I, Fijnvandraat K, et al. The "OPTI-CLOT" trial. A randomised controlled trial on perioperative Pharmacokinetic-guided dosing of CLOTting factor concentrate in haemophilia A. *Thromb Haemost.* 2015;114(3):639-644.