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PHARMACOKINETIC-GUIDED DOSING OF CLOTTING FACTOR CONCENTRATES IN BLEEDING DISORDERS:

Towards individualization of treatment

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TOWARDS INDIVIDUALIZATION OF TREATMENT

Farmacokinetisch gestuurd doseren van stollingsfactoren in stollingsstoornissen
Op weg naar geïndividualiseerde behandeling

Proefschrift

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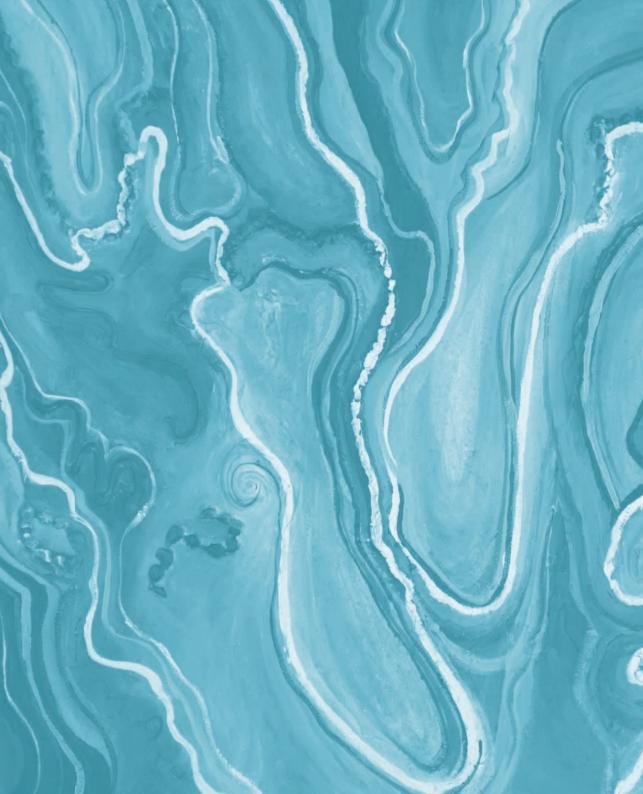prof.dr. T. van Gelder
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Discendo Discimus
"Al lerende leren wij"

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Chapter 1

General introduction and outline of the thesis

Pharmacokinetic-guided dosing of clotting factor concentrates in bleeding disorders: Towards individualization of treatment

HEMOSTASIS AND THROMBOSIS: A DELICATE BALANCE

When functioning adequately, hemostasis and thrombosis are in perfect balance. This balance is achieved by the various hemostatic and antithrombotic factors which safeguard individuals from bleeding and thrombosis. In various bleeding disorders, this balance is disrupted resulting in a bleeding tendency due to the presence of abnormal or the deficiency of coagulation factors. If clinically relevant, this can cause significant morbidity and even mortality when adequate treatment is not available or administered.
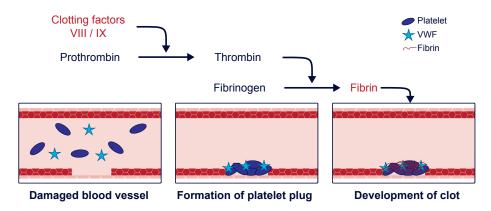
BLEEDING DISORDERS: A SHORT OVERVIEW

The most prevalent bleeding disorder is von Willebrand disease (VWD). VWD affects approximately 1% of the general population, although only 0.01% has clinical relevant bleedings.[1] VWD patients have either a quantitative and/or qualitative defect of von Willebrand factor (VWF) which leads to impairment of primary hemostasis.[2] VWD is classified as either type 1 (quantitative disorder), type 2 (qualitative disorder) or type 3 (quantitative disorder). Type 2 VWD is further categorized according to laboratory test results into type 2A, 2B, 2M and 2N. VWF is essential for the formation of the platelet plug as it activates platelets and leads to platelet adhesion and aggregation.[3]

During this process of primary hemostasis, secondary hemostasis is activated resulting in formation of thrombin. To enhance thrombin formation and to consequently stabilize the hemostatic clot by fibrin formation, factor VIII (FVIII) and factor IX (FIX) are indispensable (Figure 1). Therefore, in the bleeding disorders hemophilia A, caused by a deficiency or abnormal function of FVIII and hemophilia B caused by a deficiency or abnormal function of FIX, secondary hemostasis is incapacitated.

Hemophilia A and B are X-linked inherited bleeding disorders, mainly characterized by bleeding in joints and muscles. Hemophilia has a much lower prevalence than VWD. Global prevalence of hemophilia A is estimated at 1 in 5.000 male births and of hemophilia B at 1 in 30.000 male births.[4] Hemophilia patients are classified according to baseline FVIII or FIX plasma levels into severe (<0.01 IUmL^{-1}), moderate severe (0.01-0.05 IUmL^{-1}) or mild (>0.05 IUmL^{-1}) hemophilia.[5] Severe and some moderate severe hemo-

Figure 1. Steps towards the hemostatic clot

Clotting factors VIII / IX

Prothrombin → Thrombin

Fibrinogen → Fibrin

Platelet
VWF
Fibrin

Damaged blood vessel **Formation of platelet plug** **Development of clot**

philia patients, suffer from spontaneous bleeding into joints or muscles resulting in joint damage, hemophilia arthropathy and long-term disability.

The availability of replacement therapy with factor concentrates both prophylactically and "on demand", has greatly improved the lives of patients with a bleeding disorder. Thus leading to decreased morbidity and mortality and a great improvement of quality of life in these patient populations.[6] However although treatment has been successful, it is also costly. Therefore, it is continuously important to evaluate health care outcomes in these diseases and to evaluate if treatment can be improved.

CURRENT TREATMENT

In VWD, the majority of patients are only treated with replacement therapy with VWF (/ FVIII) concentrates or desmopressin (DDAVP) for acute bleeding or to prevent bleeding in case of trauma and/or dental or surgical procedures.[3] Only type 3 VWD patients, which account for less than 5% of all cases, may require prophylactic treatment with factor concentrate when bleeding occurs frequently. Most type 1 and some type 2 VWD patients are treated with DDAVP if a good response is established by an individual DDAVP test. DDAVP is a vasopressin analogue which increases endogenous release of VWF and FVIII from the endothelium. When patients do not respond to DDAVP or have contraindi-

cations for its use, treatment with factor concentrate is indicated. Factor concentrates for VWD patients often consist of combined VWF/FVIII concentrates derived from human plasma. The ratio of VWF activity versus FVIII may differ between concentrates.[7, 8] Dosing is usually based on both residual VWF and FVIII levels.[3] Although VWD is considered a milder bleeding disorder than hemophilia in most patients, treatment can be more challenging due to variation in VWD disease types and VWF gene mutations[2, 9], the varying residual endothelial VWF production, as well as VWF secretion and clearance and the different ratios of VWF and FVIII in available factor concentrates.

To prevent spontaneous bleeding events in severely affected hemophilia patients, replacement therapy with factor concentrates is administered prophylactically. Long-term prophylactic treatment, so called prophylaxis, in hemophilia is based on the observation that patients with baseline levels above 0.01 IUmL^{-1} have far fewer joint bleeds and less subsequent arthropathy.[10] This was confirmed in a randomized controlled trial in 65 boys younger than 30 months of age by Manco Johnson et al.[11], comparing prophylactic treatment consisting of infusions of 25 IUkg^{-1} every other day and "on demand" treatment in a dose of 40 IUkg^{-1} at the time of clinically recognized joint hemorrhage. Prophylactic treatment was associated with less cartilage damage in large joints on MRI imaging and an overall decrease of bleeding events, including joint hemorrhage. Moreover, several studies have proven that an initiation of prophylaxis at an early age is beneficial for joint status and may also prevent development of neutralizing antibodies against the deficient coagulation factor.[12-16] Prophylaxis consists of regular weekly infusions of factor concentrates usually two to three times per week in severe and moderate hemophilia A and two times per week for patients with severe or moderate hemophilia B. When initiating or monitoring prophylaxis, indication for treatment, clinical bleeding phenotype, and patient's daily activities are taken into account.[17] Dosage protocols vary from 15-40 IUkg^{-1} two to three times per week in both hemophilia A and B.[5, 15, 18-20]

"On-demand" treatment in hemophilia consists of replacement therapy after a bleed or to prevent bleeding in case of trauma, dental procedures or in the perioperative setting. Dosage recommendations in these settings (e.g. amount and duration; and predefined target ranges), are dependent on the severity of bleeding and type of surgical procedure respectively.[21, 22] For example, a bolus infusion of 50 IUkg^{-1} followed by twice a day 25 IUkg^{-1} in case of a life-threatening bleeding event in a hemophilia A patient aiming for a peak level of 1.00 IUmL^{-1} and subsequent trough levels of 0.50 IUmL^{-1}.

In general in hemophilia, dosing of replacement therapy is based primarily on the residual FVIII or FIX plasma concentration and body weight in kilograms (kg) while aiming for predefined target levels taking the average in vivo recovery (IVR) per factor concentrate into account. Often the treating physician is also influenced by clinical phenotype, and severity of (risk of) bleeding and crude estimates of factor concentrate clearance. Guidelines for FVIII dosing have always been based on an in vivo recovery (IVR) of 2.0 as postulated by Ingram et al. in 1981. This encompasses an increase of 2.0 $IUdL^{-1}$ per one $IUkg^{-1}$ infused FVIII factor concentrate.[23] An IVR of 2.0 is assumed to be equivalent to a plasma volume of 0.5 $dLkg^{-1}$.[23] For FIX dosing, an IVR of 1.0 is used. Amount of factor concentrate to achieve a certain FVIII or FIX plasma concentration is then calculated using the formula: body weight (kg) x desired FVIII increase ($IUdL^{-1}$)/2 in case of hemophilia A and body weight (kg) x desired FIX increase ($IUdL^{-1}$)/1 in case of hemophilia B. Accordingly, a target level level of 100 $IUdL^{-1}$ in a severe hemophilia A patient weighing 80 kg is approximately achieved by a dose of 4000 IU (80 x 100 / 2). However, this calculation does not take the interindividual differences in pharmacokinetic (PK) parameters of factor concentrates in individual patients into account. Therefore, we aimed to evaluate if adaptation of current dosing strategies may further individualize treatment and optimize quality of care.
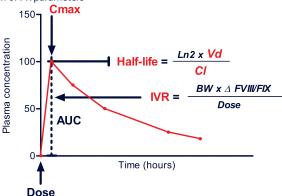
Several examples underline this statement. In the first publication by Ingram et al. it was already stated that IVR of the factor concentrate could not be applied in over- and underweighted patients.[23] More recently it was also demonstrated that children have a lower IVR, a relatively larger volume of distribution and higher clearance when compared to adults.[24] In general, a larger volume of distribution will lead to a longer half-life. However, contrastingly, children have a shorter half-life, due to a higher clearance when compared to adults.[24] Henrard et al. showed that a lower IVR was observed in 23 underweighted patients, namely a median IVR of 1.6 instead of 2.0.[25] In addition, this same group reported higher IVR values with a median IVR of 2.7 in 35 obese hemophilia A patients with a body mass index (BMI) > 29.6 kgm^{-2}), which will result in structural overdosing if these individuals are dosed according to the 2.0 IVR assumption.[25] All data support the generally accepted fact that plasma volume does not increase linearly with body weight, as documented in 1977 by Feldschuh et al.[26] and therefore body weight alone cannot possibly predict adequate dose in all individuals.

PHARMACOKINETIC PRINCIPLES IN TREATMENT OF BLEEDING DISORDERS

Pharmacokinetics (PK) describes drug absorption, distribution, metabolism and excretion of an externally administered drug. Application of PK principles in dosing of medication was first introduced by Buchanan in 1847. In this study, plasma concentrations were used to establish volume of distribution of aether as used in general anaesthesia.[27] PK of a drug may exhibit a large interindividual as well as an intra-individual variation. As replacement therapy in bleeding disorders is currently dosed primarily based on body weight, further individualization may be possible by application of PK principles. Knowledge of individual PK parameters (clearance, volume of distribution and elimination half-life) makes it possible to establish dosing intervals for a specific factor concentrate in a specific individual, in case of prophylaxis aiming for minimal trough levels. When considering the use of an average half-life of a factor concentrate, it is important to realize that half-life is determined by both volume of distribution and clearance (Figure 2). The latter are both variable between- and within patients. Furthermore, these PK parameters may vary depending on circumstances when the process of hemostasis is altered, prophylactic treatment versus "on demand" treatment in case of bleeding and to prevent bleeding in the perioperative period.

In the Bayesian procedure ("Bayesian forecasting"), PK data from a specific population is used to estimate the clearance and volume of distribution of a drug in a specific individual in which a limited blood sampling of the specific drug has taken place. This information is subsequently used to calculate the most appropriate dose for the individual patient (Figure 3). More importantly, within these population models covariates are implemented which are able to explain and quantify both inter-individual and intra-individual variability. In 2009 and 2013, Björkman et al. developed a population PK model for FVIII and FIX concentrate for treatment in the prophylactic setting.[28, 29] However, implementation of the Bayesian approach has not yet been achieved on a broader scale. This seems due to lack of knowledge of PK, and the complexity of necessary pharmaco-statistical analyses. Current developments described in this thesis, suggest that individualization of therapy by application of Bayesian analysis is promising and may be within reach.

Figure 2. Description of PK parameters

Description of PK parameters using non-compartimental principles. Administration of a bolus infusion of factor concentrate results in a peak plasma concentration, defined as **Cmax**. **Half-life** is derived from clearance (Cl) and volume of distribution (Vd) and is defined as the time required for the concentration to decrease with 50%. **Clearance (Cl)** is the volume of plasma cleared of the drug per unit time and is calculated as dose divided by the area under the curve. **Volume of distribution (Vd)** is the apparent volume in which a drug is distributed. **In vivo recovery (IVR)** is calculated as body weight (BW) (kilograms) x observed increase FVIII/FIX divided by the dose (in IU). **Area under the curve (AUC)** is the integral of the concentration-time curve.

AIMS OF THIS THESIS

The aim of this thesis is to evaluate the current dosing strategies of factor concentrates in von Willebrand disease and hemophilia A and B patients; and to establish whether more individualized dosing based on PK guided dosing using Bayesian techniques is feasible.

OUTLINE OF THE THESIS

In **part I**, we evaluated current treatment strategies in perioperative patients with a bleeding disorder by specification of concentrate administration and subsequently achieved peak and trough levels. These peak and trough levels were compared to target levels as prescribed by National guidelines to identify patients with levels under and

Figure 3. Bayesian analysis; relationship between population and individual pharmacokinetic curves

In Bayesian analysis, pharmacokinetic parameters in an individual patient are estimated from a limited number of plasma concentrations (depicted by red dots), and population pharmacokinetic data (depicted by black lines). The individual curve can be estimated for the individual patient, which is indicated by the red line. This process is repeated every time new plasma concentrations are obtained in the patient. Each measurement leading to optimization of the predictive value of the model to describe necessary doses to achieve specific plasma concentrations.

above target range. Moreover, potential predictors of levels under target range and above target range, as well as variables associated with concentrate consumption were collected and evaluated. In **chapter 2**, this was performed in severe and moderate severe hemophilia A patients needing replacement therapy with FVIII concentrate aiming to identify the extent and predictors of underdosing and overdosing in the perioperative period. In **chapter 3**, FIX concentrate infusion and achieved FIX plasma levels during surgical procedures in severe and moderate severe hemophilia B patients from both the Netherlands and the United Kingdom (UK) were analyzed and related to target levels stated in National guidelines of both countries, in order to investigate perioperative management and to assess predictors of low and high FIX levels. In **chapter 4**, VWF/FVIII concentrate infusion and achieved FVIII and VWF levels were analyzed in VWD patients requiring a surgical procedure, in order to investigate current perioperative management of VWD patients in a resource rich country.

In **part II**, two perioperative population PK models are presented which were constructed based on data described in **part I**. In **chapter 5**, a perioperative population PK model for patients with severe and moderate severe hemophilia A was constructed with data on amount of FVIII concentrate and all subsequently achieved FVIII plasma levels. The aim of such a model is to allow individualization of perioperative FVIII therapy for severe and moderate hemophilia A patients by Bayesian adaptive dosing. In **chapter 6**, a perioperative population PK model was constructed for severe and moderate severe hemophilia B patients. This constructed model describes factor IX concentrations and interpatient variability in the perioperative period, during FIX replacement therapy, ultimately leading to more individualized therapy.

In **part III**, different approaches to validate and to prove the feasibility of PK-guided dosing of factor concentrates in patients with a bleeding disorder are presented. In **chapter 7**, the design of the first large randomized controlled trial comparing PK-guided dosing with standard treatment in the perioperative setting is described. The aim of this study is to investigate whether perioperative PK-guided dosing of FVIII concentrate in hemophilia A patients receiving FVIII replacement therapy using a Bayesian approach, leads to a significant reduction in perioperative clotting factor consumption and more optimal dosing with achievement of FVIII levels within target range as prescribed by

National guidelines. In **chapter 8**, alternative dosing strategies of factor concentrates in overweight and obese hemophilia A patients are analyzed with the aim to establish the relevance of PK in individualization of treatment in these patient populations. In **Chapter 9**, the feasibility of PK-guided dosing using an individual PK profile and a perioperative population PK model in a complex hemophilia A patient at risk for both bleeding and thrombosis during a renal transplantation is illustrated.
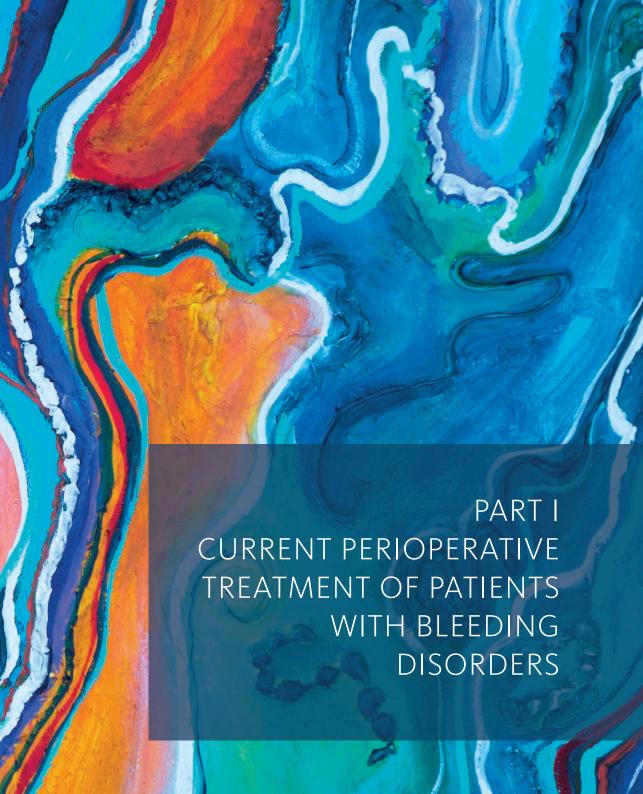
In **part IV**, the current benefits and limitations of PK-guided dosing are extensively discussed (**chapter 10**). In addition, a summary of the highlights of this thesis is provided (**chapter 11**).

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PART I
CURRENT PERIOPERATIVE
TREATMENT OF PATIENTS
WITH BLEEDING
DISORDERS

Chapter 2

Perioperative treatment of hemophilia A patients: Blood group O patients are at risk of bleeding complications

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SUMMARY

Background Perioperative administration of factor VIII (FVIII) concentrate in hemophilia A may result in both underdosing and overdosing, leading to respectively a risk of bleeding complications or unnecessary costs.

Objective This retrospective observational study aims to identify the extent and predictors of underdosing and overdosing in perioperative hemophilia A patients (FVIII levels <0.05 IUmL^{-1}).

Methods One hundred-nineteen patients undergoing 198 elective, minor or major surgical procedures were included (median age 40 years, median body weight 75 kilograms). Perioperative management was evaluated by quantification of perioperative infusion of FVIII concentrate and achieved FVIII levels. Predictors of underdosing and (excessive) overdosing were analyzed by logistic regression analysis. Excessive overdosing was defined as upper target level plus ≥0.20IUmL^{-1}.

Results Depending on postoperative day, 7-45% of achieved FVIII levels were under and 33-75% were above predefined target ranges as stated by National guidelines. A potential reduction of FVIII consumption of 44% would have been attained if FVIII levels had been maintained within target ranges. Blood group O and major surgery were predictive of underdosing (OR=6.3 95%CI[2.7-14.9];OR=3.3 95%CI[1.4-7.9]). Blood group O patients had more bleeding complications in comparison to patients with blood group non-O (OR=2.02 95%CI[1.00-4.09]). Patients with blood group non-O were at higher risk of overdosing (OR=1.5 95%CI[1.1-1.9]). Additionally, patients treated with bolus infusions were at higher risk of excessive overdosing (OR=1.8 95%CI[1.3-2.4]).

Conclusion Quality of care and cost-effectiveness can be improved by refining of dosing strategies based on individual patient characteristics such as blood group and mode of infusion.

INTRODUCTION

Hemophilia A is an X-linked inherited bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII). It is characterized by spontaneous bleeding or bleeding after minor trauma, typically in joints and muscles. In case of bleeding, patients are treated with intravenously administered factor replacement therapy. In severe (FVIII <0.01 IUmL^{-1}) and some moderate severe (FVIII between 0.01-0.05 IUmL^{-1}) cases, prophylactic treatment is administered to prevent spontaneous and frequent bleeding.[1, 2] In order to safeguard hemostasis in the perioperative setting, FVIII plasma levels are targeted according to guidelines for up to two weeks after surgery and consist of a FVIII bolus infusion of 50 IUkg^{-1}, followed by either continuous infusion or intermittent daily infusions based on a clearance rate of 3-4 ml kg^{-1} hour^{-1}, and under daily monitoring of FVIII plasma levels (Table 1).[3] Perioperative factor concentrate consumption is substantial and amounts to 15% of annual use in the hemophilia population.[4-6] To illustrate this, in the Netherlands over €100 million ($109 million) is spent annually on total factor concentrate for 1600 hemophilia patients per year, including €15 million ($16.4 million) alone for perioperative replacement therapy.[3, 4, 6] Fortunately, treatment is extremely effective as perioperative bleeding is rare, in those cases where replacement therapy is adequately available.[7, 8]

Table 1. Target FVIII levels in the perioperative period

Time		Target FVIII level (IUmL^{-1})
Day	Hours	
1	0- 24	0.80-1.00
2-5	24- 120	0.50-0.80
≥6	> 120	0.30-0.50

*   According to the National Hemophilia Consensus of the Netherlands[3]

IUmL^{-1} = International Units per milliliter

The standard perioperative dosing regimen, as described by the Consensus, consists of a FVIII bolus dose directly prior to surgery of 50 IUkg^{-1}, followed by either continuous infusion or intermittent daily bolus infusions. The rate of infusion (IU hour^{-1}) is obtained by multiplying the patient's bodyweight (kg) with clearance (3-4 mL kg^{-1} hour^{-1}) and target FVIII level (IUmL^{-1}). Subsequent FVIII clotting factor concentrate dosing will be based on daily monitoring of FVIII levels and adjusted according to doctor's opinion, based on a standard clearance of 3-4 mL kg^{-1} hour^{-1}.

Previous studies evaluating perioperative dosing of FVIII concentrate in hemophilia A suggest that improvement is warranted as overdosing is widely reported.[9-16] This is attributed to current dosing strategies based on body weight and crude estimations of clearance, without taking other individual patient characteristics into account. Additionally, the complexity of achieving targeted factor levels, and fear of bleeding play an important role in overdosing. Strikingly, in reported studies extent and timing of underdosing and overdosing have not been specified. Moreover, risk factors for underdosing and overdosing have hardly been explored and are urgently required to individualize dosing in the near future.

We aim to quantify the extent and timing of underdosing and overdosing in the perioperative setting and to identify its predictors in severe and moderate severe hemophilia A patients. We believe that both underdosing and overdosing can be reduced by alternative dosing strategies that take individual patient characteristics into account, leading to optimization of care and a greater efficacy of consumption of costly factor concentrate.

MATERIALS AND METHODS

Patients

This is a retrospective multicenter observational cohort study. Eligible patients were males with severe or moderate severe hemophilia A (FVIII levels <0.05 IUmL^{-1}) of all ages undergoing elective, minor or major surgery (Supplemental Table 1)[17] between 2000 and 2013 under FVIII concentrate replacement therapy with monitoring of FVIII plasma levels. First surgical procedure was performed on January 7th 2000 and last surgical procedure on February 19th 2013. Patients were recruited from five Academic Hemophilia Treatment Centers in the Netherlands (Erasmus University Medical Center Rotterdam (n=32); Academic Medical Center Amsterdam (n=32); University Medical Center Groningen (n=35); Radboud university medical center (n=12); and Leiden University Medical Center (n=8). Exclusion criteria included: the perioperative presence of FVIII neutralizing antibodies, patients with severe infections during the perioperative period and patients lacking accurate perioperative documentation. The study was not subject to the Medical Research Involving Human Subjects Act, as patient data were analyzed

anonymously. Moreover, the study was approved by all local Medical Ethics Committees; one center requiring prior patient informed consent.

Objectives

Objective of the study was to evaluate perioperative FVIII concentrate management in hemophilia A with regard to defined FVIII target ranges as stated by the National Hemophilia Consensus of the Netherlands and to identify potential predictors of underdosing and overdosing.

Methods

Data were collected on patient characteristics, type of surgical procedure, timing, dosing of FVIII administration and timing of blood sampling of FVIII plasma levels in $IUmL^{-1}$, during the hospitalization period. FVIII plasma levels were generally monitored daily and were measured by one-stage clotting assays in all participating centers. Perioperative blood loss and hemostasis were evaluated according to the definitions of the International Society of Thrombosis and Hemostasis[18] and quantified by severity of complications and/or necessity of second surgical intervention, hemoglobin decrease of ≥1.24 mmol/l and/or red blood cell transfusion (RBCTF) necessity, or bleeding prolonging hospitalization.

For our analysis we defined severe bleeding complications as bleeding requiring a second surgical intervention and/or the necessity of a RBCTF. Duration of hospitalization was defined by day of discharge minus day of surgical procedure and initiation of FVIII concentrate infusion. To increase data reliability, data were collected and checked by two individual researchers.

To acquire accurate insight into achieved FVIII plasma levels with regard to the target ranges stated in guidelines, only steady state FVIII plasma levels were included when replacement therapy was administered by continuous infusion and only FVIII trough plasma levels in case of administration by bolus infusion. Steady state FVIII plasma levels were defined as perioperative FVIII measurements sampled when FVIII concentrate substitution is equal to clearance and FVIII trough plasma levels as FVIII measurements prior to FVIII concentrate bolus infusion. FVIII peak levels after FVIII bolus infusion were not included in this analysis.

Statistical analysis

For comparison of FVIII concentrate consumption between groups the non-parametric Mann-Whitney U test was used. P for trend analysis using one-way ANOVA was performed to evaluate trends in FVIII consumption on consecutive days. Calculations were performed only on the first surgical procedure in each individual patient. Descriptive statistics are presented as median and interquartile range [IQR] for continuous variables and as number (No.) and percentages (%) for categorical variables. Comparison between proportions was done by means of Pearson Chi-Square test.

A hypothetical reduction of FVIII concentrate consumption, if National guidelines for perioperative target ranges had been maintained, was calculated by comparing the difference of achieved FVIII plasma level in each individual at different time points, to the prescribed lowest and highest target range level at that time point. First-order elimination curves were used to calculate the actual amount of FVIII concentrate underdosed or overdosed for the total population. The percentage of FVIII concentrate which could have been saved was calculated after subtraction of the amount of FVIII concentrate which was underdosed.

Prediction model for underdosing and overdosing

Underdosing was defined as all FVIII plasma levels under lowest predefined target range level and overdosing as all FVIII plasma levels above highest predefined target range level. Excessive overdosing was arbitrarily defined as the upper target range level with a deviation of ≥0.20 IUmL^{-1} to overcome the logistic delays caused by laboratory monitoring and adjustment of treatment. Potential predictors of underdosing in the first 24 hours after surgery, as well as overdosing and excessive overdosing were analyzed by a backward stepwise logistic regression analysis with elimination of variables with p>0.10. Potential predictors of underdosing or overdosing were defined before analysis on the basis of their potential effect on the pharmacokinetic parameters: clearance and/ or volume of distribution of infused FVIII concentrate. The following variables were collected: firstly, patient characteristics: age, body weight[19], blood group[20-22], historical values of von Willebrand Factor (VWF) antigen and VWF activity[23], history of FVIII neutralizing antibodies[8], type and brand of factor concentrate (recombinant or plasma-derived)[24] and mode of infusion (continuous or bolus infusion)[25]. Secondly, surgical characteristics: type and severity of surgical procedure categorized according to Koshy et al.[17]

Data management and statistical analysis were performed with IBM SPSS statistics for Windows, version 21.0 (IBM Corp, Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

Patient and surgical characteristics

Our study population consisted of 119 patients undergoing a total of 198 surgical procedures; 75 adults (140 surgical procedures; median age: 48 years; median body weight: 80 kg) and 44 children (58 surgical procedures; median age: 4 years; median body weight: 19 kg) (Table 2). The majority of patients were severe hemophilia A patients on prophylactic treatment (70%). Approximately, half of all patients were known with blood group O (51%). In adults median VWF:Ag level was 1.23 IUmL^{-1} and median VWF:Act level was 1.39 IUmL^{-1}. In children median VWF:Ag was 0.92 IUmL^{-1} and VWF:Act was 0.88 IUmL^{-1}. Forty-four patients underwent multiple surgical procedures; nine of these had more than four surgical procedures (Table 2). In adults, mainly major surgical procedures
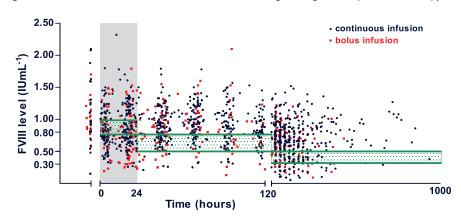
Figure 1. Achieved FVIII levels in adults and children receiving clotting factor replacement therapy

Achieved FVIII levels in hemophilia patients treated by continuous infusion (blue) and by bolus infusions (red). Predefined target levels as stated by the National Hemophilia Consensus are depicted as green boxes.[3]

Table 2. General characteristics

	Total cohort		Adults		Children	
	No. (%); or Median [IQR]					
Patient characteristics						
No. of patients	119		75		44	
Age (years)	40	[9-54]	48	[37-60]	4	[2-8]
Height (cm)	175	[162-182]	178	[173-182.0]	114	[89-136]
Body weight (kg)	75	[35-85]	80	[73-90]	19	[12-29]
Body mass index (kgm^{-2})	23	[17-26]	25	[23-28]	16	[14-18]
Severe hemophilia (FVIII levels <0.01 IUmL^{-1})	83	(70)	49	(65)	34	(77)
On prophylaxis	84	(71)	51	(68)	33	(75)
Blood group O*	51	(51)	34	(50)	17	(52)
Neutralizing antibody titer						
No	131	(66)	82	(59)	49	(85)
Historically	67	(34)	58	(41)	9	(15)
Maximum titer (BU)	0.3	[0.2-0.7]	0.3	[0.2-0.5]	0.2	[0.2-2.4]
Historical VWF levels (IUmL^{-1})						
Antigen$^{\#}$	1.1	[0.9-1.4]	1.2	[1.0-1.4]	0.9	[0.7-1.2]
Activity$^{\$}$	1.1	[0.9-1.6]	1.4	[1.1-1.7]	0.9	[0.7-1.2]
Chronic hepatitis C	57	(48)	55	(73)	2	(5)
Surgical characteristics						
No. of surgical procedures	198		140		58	
Total no. of patients undergoing:						
1	75	(63.0)	43	(57.3)	32	(72.7)
2	26	(21.8)	15	(20.0)	11	(25.0)
3	9	(7.6)	9	(12.0)	0	(0.0)
>4	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)	NA	NA
Colo-rectal	5	(2.5)	4	(2.9)	1	(1.7)
Vascular	1	(0.5)	1	(0.7)	NA	NA
Cardio-thoracic	1	(0.5)	1	(0.7)	NA	NA
Orthopedic	94	(47.5)	91	(65.0)	3	(5.2)

Table 2. General characteristics (continued)

	Total cohort		Adults		Children	
	No. (%); or Median [IQR]					
Urology	12	(6.1)	4	(2.9)	8	(13.8)
Maxillofacial	2	(1.0)	2	(1.4)	NA	NA
Ear-Nose-Throat	11	(5.6)	6	(4.3)	5	(8.6)
Eye	3	(1.5)	3	(2.1)	NA	NA
(Re)placement 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)	88	(63)	27	(47)
Bolus	83	(42)	52	(37)	31	(53)
Product type						
Plasma derived	46	(23)	41	(29)	5	(9)
Recombinant	152	(77)	99	(71)	53	(91)
Duration of hospitalization (days)	9	[5-12]	9.0	[5-14]	7	[6-10]
Complications during the perioperative period						
No. of patients suffering from a complication						
Bleeding	48	(24)	45	(32)	3	(5)
Re-operation	6	(3)	6	(4)	NA	NA
Hemoglobin drop >1,24 mmolL^{-1} and/or RBCTF	38	(19)	36	(26)	2	(3)
Bleeding with prolonged hospitalization	5	(3)	4	(3)	1	(2)
Thrombosis	NA	NA	NA	NA	NA	NA

No.=number (percentages); Median [IQR=Inter quartile range 25-75%]; cm=centimeter; kg=kilogram; kgm^{-2}=kilogram per square meter; FVIII=clotting factor VIII; IUmL^{-1}=international units per milliliter; BU=Bethesda Units; VWF=von Willebrand factor; mmolL^{-1}=millimolar per liter; NA=not applicable; RBCTF=red blood cell transfusion; *Blood group available in 101 patients (172 surgical procedures); #VWF antigen available in 67 patients (118 surgical procedures); $VWF activity available in 57 patients (98 surgical procedures)

(n=86; 61%) were performed, which were most often orthopedic procedures (n=91; 65%). Children mainly underwent minor surgical procedures (n=47; 81%), most frequently an insertion or removal of a central venous device (n=31; 53%) (Table 2). In 115 (58%) surgical procedures, FVIII replacement therapy was given by continuous infusion; these patients were mainly adults (n=88; 63%). In 83 (42%) surgical procedures, patients were treated by bolus infusion (Table 2). In 152 surgical procedures (77%) patients were treated with recombinant factor concentrates. Duration of hospitalization was similar in both adults and children treated by continuous infusion as compared to bolus infusion (adults nine [IQR: 6-15] versus eight [IQR: 4-13] days, *p*=0.09; children seven [IQR: 6-10] versus seven [IQR: 6-10] days, *p*=0.99).

Achievement of FVIII target range levels

Most perioperative FVIII plasma concentrations were outside the predefined target range in both adults and children. Achieved FVIII plasma concentrations in relationship to defined target ranges on consecutive days are depicted in Figure 1. In summary, on consecutive days deviations of FVIII levels with regard to predefined target range levels were increasingly significant (*p* for trend <0.01). The overall median deviation of FVIII plasma concentrations *below* the lowest required target range level varied from 0.17-0.11 $IUmL^{-1}$ for consecutive postoperative days and *above* the highest required target range level from 0.23-0.31 $IUmL^{-1}$ for consecutive postoperative days (Table 3). In the first 24 hours after surgery, 45% of measured FVIII levels were *below* lowest target range level with a median deviation *below* the lowest required target level of 0.17 $IUmL^{-1}$. After six days of postsurgical hospitalization, 75% of the FVIII levels were above highest target range level with a median deviation of 0.31 $IUmL^{-1}$. No evidence was found with regard to changes in dosing regimen over time during the overall study period as the proportion of underdosed and overdosed patients did not differ for surgical procedures performed before 2005 and after 2005 (Supplemental Table 2). In addition, specific treatment center was not associated with proportion of under- or overdosing (data not shown).

Predictors of underdosing and (excessive) overdosing

In our logistic regression model, blood group O and major surgery were predictive of underdosing (respectively OR=6.3 [95%CI: 2.7-14.9] and OR=3.3 [95%CI:1.4-7.9]) (Table 4). Complementary, blood group non-O, increasing age (per year) and replacement therapy

Table 3. Achieved FVIII levels after clotting factor replacement therapy

	Total cohort		Adults		Children	
	No. Samples (%)	Median deviation [IQR]	No. Samples (%)	Median deviation [IQR]	No. Samples (%)	Median deviation [IQR]
Preoperative: only peak levels	111	1.15 [0.90-1.41]	80	1.23 [0.94-1.50]	31	1.00 [0.82-1.18]
Day 1 (0-24 hours)	308 (100.0)	0.83 [0.65-1.10]	237 (100.0)	0.87 [0.69-1.14]	71 (100.0)	0.76 [0.51-1.09]
FVIII levels outside target range	283 (77.3)	.	181 (76.4)	.	57 (80.2)	.
Above	101 (32.7)	0.23 [0.10-0.40]	81 (34.2)	0.24 [0.10-0.43]	20 (28.2)	0.20 [0.12-0.29]
Below	137 (44.5)	0.17 [0.08-0.33]	100 (42.2)	0.16 [0.08-0.29]	37 (53.6)	0.27 [0.08-0.46]
Day 2-5 (24-120 hours)	510 (100.0)	0.88 [0.69-1.08]	389 (100.0)	0.92 [0.76-1.10]	121 (100.0)	0.66 [0.51-0.93]
FVIII levels outside target range	339 (66.5)	.	270 (69.4)	.	69 (57.0)	.
Above	303 (59.4)	0.23 [0.12-0.41]	262 (67.4)	0.24 [0.12-0.41]	41 (33.8)	0.19 [0.13-0.41]
Below	36 (7.1)	0.17 [0.07-0.24]	8 (2.1)	0.12 [0.03-0.23]	28 (23.1)	0.17 [0.08-0.24]
Day >6 (> 120 hours)	471 (100.0)	0.68 [0.48-0.87]	422 (100.0)	0.70 [0.52-0.89]	49 (100.0)	0.44 [0.26-0.69]
FVIII levels outside target range	383 (81.3)	.	347 (82.2)	.	36 (73.5)	.
Above	343 (74.7)	0.31 [0.15-0.45]	321 (76.1)	0.30 [0.16-0.45]	22 (44.9)	0.19 [0.10-0.30]
Below	40 (8.7)	0.11 [0.05-0.16]	26 (6.2)	0.09 [0.05-0.14]	14 (28.6)	0.12 [0.09-0.20]

No.= Number; IQR = Interquartile range

Table 4. Predictors of underdosing and (excessive) overdosing

	OR		95% confidence interval	
Underdosing				
Age (per year)*	1.03	0.99	-	1.07
Blood group O**	6.30	2.65	-	14.93
Major surgical procedure$^{\$}$	3.30	1.38	-	7.90
Overdosing				
Age	1.02	1.02	-	1.03
Blood group O**	1.47	1.13	-	1.91
Product type (recombinant) $^{\$\$}$	0.52	0.38	-	0.72
Mode of infusion (bolus)***	1.78	1.34	-	2.37
Excessive overdosing				
Age	1.02	1.01	-	1.02
Product type (recombinant)$^{\$\$}$	0.48	0.37	-	0.63
Mode of infusion (bolus)***	1.92	1.45	-	2.54

Stepwise backward logistic regression analysis. OR=Odds Ratio;
CI=Confidence Interval;* Increasing age (per year) ** versus blood group non-O; *** versus continuous infusion; $^{\$}$ versus minor surgical procedure; $^{\$\$}$ versus plasma derived clotting factor concentrate

with a plasma derived product and by bolus infusion were predictive of overdosing (Table 4). Replacement therapy with a plasma derived product and by bolus infusion and increasing age (per year) were associated with excessive overdosing.

Clotting factor VIII concentrate consumption

For the first surgical procedure in each individual, the median total amount of infused FVIII concentrate per kilogram per day during hospitalization was significantly higher in children when compared to adults (children: 93 IUkg^{-1} day^{-1} [IQR: 75-119 IUkg^{-1} day^{-1}] and adults: 57 IUkg^{-1} day^{-1} [IQR: 41-77 IUkg^{-1} day^{-1}]; $p<0.001$) (Table 5). Mode of infusion, type of concentrate (plasma derived or recombinant) and severity of surgical procedures were not associated with the amount of FVIII consumption for both children and adults. As expected, an overall decrease was observed in infused FVIII concentrates over con-

Table 5. Treatment characteristics

	Total cohort			Adults			Children		
	No.	Median [IQR]	p-value*	No.	Median [IQR]	p-value*	No.	Median [IQR]	p-value*
FVIII consumption (IUkg⁻¹ day⁻¹)	119	69.0 [47.5-98.1]		75	57.1 [41.1-76.7]		44	92.7 [75.1-118.8]	
Mode of infusion									
Continuous	62	69.2 [51.9-94.6]	0.60	43	59.2 [46.9-77.2]	0.06	19	89.5 [77.7-117.1]	0.77
Bolus	57	65.8 [39.5-103.9]		32	52.3 [31.0-75.2]		25	97.9 [70.0-129.7]	
Product type									
Plasma derived**	32	58.6 [41.1-79.4]	0.02	28	53.3 [40.0-70.3]	0.32	4	89.2 [68.7-148.5]	0.95
Recombinant***	87	76.7 [54.1-108.1]		47	59.1 [41.9-83.1]		40	92.7 [75.1-118.8]	
Severity risk of surgical procedure[18]									
Minor	66	79.4 [51.7-119.7]	0.05	29	58.0 [35.3-82.7]	0.76	37	91.3 [71.8-119.7]	0.49
Major	53	59.8 [47.3-87.3]		46	55.5 [46.3-74.0]		7	113.9 [85.1-117.5]	

FVIII consumption analysis was performed for the first surgical procedure of each individual patient

* Non-parametric test, Mann-Whitney U Test

** Including: Aafact (Blood Transfusion Council of the Netherlands Red Cross), Hemofil M (Baxter BioScience, Thousand Oaks, CA, USA)

*** Including: Kogenate FS (Bayer, Berkely, Ca, USA), Helixate FS (CSL Behring, Marburg, Germany), and Advate, Recombinate (Baxter BioScience, Thousand Oaks, CA, USA), Refacto (Pfizer, New York, NY USA)

No.=number; IQR=interquartile range; IUkg⁻¹ day⁻¹ =International Units per kilogram per day

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Figure 2. Total amount of FVIII consumption underdosed and overdosed in the perioperative setting
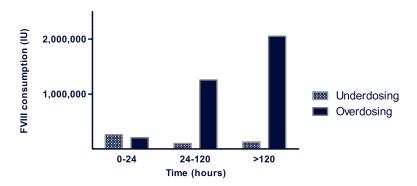

Figure 2 shows the total amount of FVIII consumption underdosed and overdosed in the perioperative setting

Figure 3. Blood group O patients have more bleeding complications

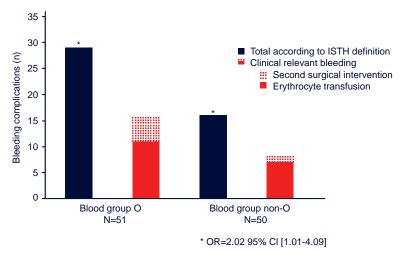* OR=2.02 95% CI [1.01-4.09]

Figure 3 shows that blood group O patients suffer from more bleeding complications in comparison to blood group non O patients.

secutive postoperative days, both in adults and children, as set target range values also decrease accordingly (*p* for trend < 0.001) (Supplemental Figure 1).

Total FVIII concentrate consumption of the whole study cohort during the entire perioperative period amounted to a total of 6,800,000 IU. If predefined FVIII target ranges had been maintained according to the National guidelines this would have led to a reduction of consumption of FVIII concentrate of 44% (Figure 2). This percentage was calculated by subtracting the total amount of FVIII concentrate under lowest target range level e.g. 491,000 FVIII IU from FVIII concentrate consumed above highest target range level e.g. 3,510,000 IU and dividing it by total consumption as defined earlier.

Perioperative blood loss and hemostasis

Forty-five (32%) of the surgical procedures in adults and three (5%) surgical procedures in children were complicated by perioperative bleeding. In patients with blood group O overall more bleeding complications were observed than in patients with blood group non-O (blood group O, n=29 (64%); blood group non-O, n=16 (36%); p=0.047; OR=2.02 95%CI[1.01-4.09]) (Figure 3). These patients also experienced more severe bleeding as 15 (33%) severe bleeding complications were observed in patients with blood group O in comparison to 8 (18%) in blood group non-O patients. Overall, with regard to severity of bleeding, six of the 45 bleeding complications in adult patients and none of the bleeding complications in pediatric patients required a reoperation (Supplemental Table 3 and Table 4). These six reoperations encompassed five for intra-articular bleeding in a total knee replacement and one for bleeding after drain removal. Bleeding complications were overall more common in patients undergoing an orthopedic surgical procedure.

Overall, we did not find an association between bleeding complications and actual FVIII plasma level at the time of the bleeding episode in adults (median FVIII level for patients with a bleeding complication or without a bleeding complication: 0.81 IUmL^{-1} [0.65-0.99 IUmL^{-1}] or 0.82 IUmL^{-1} [0.62-1.07 IUmL^{-1}]; *p*=0.92) and children (median FVIII level for patients with a bleeding complication or without a bleeding complication: 0.66 IUmL^{-1} [0.43-0.92 IUmL^{-1}] vs 0.72 IUmL^{-1} [0.46-0.92 IUmL^{-1}]; *p*=0.66). No thrombotic complications and no deaths were reported.

DISCUSSION

This is presently the largest study evaluating perioperative FVIII concentrate dosing in hemophilia A patients. Our data illustrates the challenges of maintaining FVIII target levels in current perioperative dosing and the magnitude of underdosing and overdosing when targeting prescribed FVIII ranges according to guidelines in a resource rich country. In this study, depending on postoperative day, 7-45% of achieved FVIII plasma levels were under the lowest predefined target range level recommended by National guidelines and 33-75% above the highest predefined target range level.[3] If target ranges had been adequately maintained, an impressive overall reduction of FVIII consumption of 44% would have been possible. Patients with blood group O were at increased risk of underdosing and had a higher rate of both overall bleeding and severe bleeding complications. In this retrospective analysis, we were not able to demonstrate an association between an actual lower FVIII plasma level at the time of a bleeding episode, as FVIII levels were often not available directly during the event. The data, do however suggest that patients with blood group O may have a higher perioperative bleeding risk due to overall lower FVIII levels. Most probably, this is explained by lower VWF levels in patients with blood group O. Unfortunately, VWF antigen and activity levels were only sporadically available in this study, as perioperative VWF testing is currently not common practice, making it difficult to analyze this association. Previous studies, have reported that lower VWF levels lead to shorter FVIII half-life as VWF protects FVIII against proteolytic degradation in the circulation.[20-23] Inversely in this study, overdosing was predicted by blood group non O and older age. This also may be explained by VWF levels, which are generally higher in blood group non-O and higher with increasing age.[26] Further supportive of this hypothesis, are data collected by Kahlon et al. in healthy individuals, describing a decrease of VWF levels 30 minutes after incision and higher VWF levels one day after surgery.[27] If patients with lower baseline VWF levels decrease according to this principle at initiation of surgery and are not able to subsequently increase VWF levels, this may coincide with a higher perioperative bleeding risk. Further predictors of overdosing, other than blood group non O and older age, were replacement therapy with plasma derived clotting factor concentrates and treatment by bolus infusion.

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Strengths and limitations

Strengths of the study are the large number of included patients and surgical procedures, not documented before, as well as the fact that patients were included from numerous treatment centers all working dedicatedly according to one National guideline.[3] The guideline was developed and approved by all hemophilia treatment centers collaborating within the NVHB (Hemophilia Doctors Organization in the Netherlands). In the study, actual dosing regimens and subsequent FVIII plasma samples over the past ten years were collected thoroughly and complications were extensively documented. Data were collected and checked by two independent researchers. The cohort is therefore representative of severe and moderate hemophilia A patients undergoing surgery in a resource rich country.

Study limitations include the retrospective nature of the data. Therefore, not all perioperative patients were monitored as intensively, and analyses of modifiers of consumption were difficult as data were not collected prospectively according to protocol. Major surgical procedures may be overrepresented in the study as these were of course monitored more intensely than minor surgical procedures. However, earlier reports show a similar prevalence of surgical procedures in other hemophilia populations.[28, 29] In addition, quantification and documentation of blood loss is notoriously difficult, especially in retrospective studies. Due to this fact, criteria were applied for blood loss as defined by the ISTH[18], leading to possible over reporting of blood loss as this definition is quite sensitive. Therefore, we additionally reported clinically relevant, severe bleeding as defined simply and reliably by necessary RBCT and/or reoperation.

Potentially, the use of one-stage laboratory assays to measure FVIII plasma levels may lead to biased results with regard to achieved FVIII plasma levels. Especially, as these assays generally lead to higher FVIII levels in higher FVIII ranges than two stage (chromogenic) assays.[30-32] This, with the exception of the measured FVIII levels after infusion of one specific B domain-deleted FVIII concentrate, which was also administered in this study. In this B domain-deleted FVIII concentrate, one stage assays lead to measurement of lower FVIII plasma levels, potentially leading to overdosing specifically in these patients. Due to the latter, consumption was analyzed extensively according to product type in our study cohort. However, no association was found between consumption of FVIII concentrate and specific product type. Prospective studies in perioperative hemophilia A patients are required to verify the data with regard to FVIII levels and type of

FVIII assay. Currently, the one stage assay is overall still the most applied assay and study results depict daily practice in the majority of Hemophilia Treatment Centers.

FVIII consumption and mode of infusion of replacement therapy

In our study, median total amount of infused FVIII concentrates per kilogram per day during hospitalization was comparable to previous reports, both in adults and in children.[13, 33-38] As expected, the amount of infused FVIII concentrate per kilogram was higher in children when compared to adults, which is explained by a higher clearance of FVIII in young children resulting in a shorter half-life[19] and due to a larger volume of distribution in children in comparison with adults.[39] Consequently, variables associated with FVIII consumption were analyzed separately for both children and adults.

The extent and timing of FVIII underdosing and overdosing in the perioperative period have not been reported earlier. Both underdosing, most significant directly after surgery and (excessive) overdosing, most significant more than 6 days after surgery, can clearly be improved. During the entire study period, clinical practice in participating centers with regard to perioperative management of replacement therapy did not change as guidelines were not altered. Patients with preoperative or perioperative FVIII levels that were lower than expected, received additional bolus infusion(s) of FVIII concentrate to achieve target ranges as set by the consensus. Discrepancies between target ranges and actual FVIII plasma levels increased consecutively during the perioperative period. Thus, suggestive of a focus on prevention of bleeding and not on prevention of overdosing.

In two prospective studies by Batarova et al. and Bidlingmaier et al., savings of 30-36% of FVIII concentrate consumption were calculated for continuous versus intermittent bolus infusion.[9, 16] Our data however does not support continuous dosing as more cost reductive when compared to intermittent bolus infusion. This may be due to the following factors. In our study, total amount of FVIII concentrate was corrected for duration of hospitalization, and not only for body weight as in previous studies. Furthermore, confounding by indication, e.g. severity of surgical procedure may have influenced outcome, as continuous infusion was more often used in more severe procedures. Moreover, when intermittent bolus infusion was applied in our study it was often dosed more frequently per day in lower doses, therefore mimicking continuous dosing. All of the above may have led to smaller differences in FVIII concentrate consumption between modes of administration of therapy. Lastly, type of concentrate and severity of surgical

procedure were not associated with the overall amount of FVIII consumption in both children and adults. Most probably due to collinearity between these specific variables.

Complications

In this cohort, representative for surgical patients in Hemophilia Treatment Centers in re-source rich countries[28, 29] bleeding complications were seen in 32% of adult patients and in 5% of pediatric patients. This high percentage seems due to the broad ISTH definition applied in our study for bleeding, not used in comparable studies.[29, 33, 35, 40] Cases were mainly defined by the decrease of hemoglobin of ≥1.24 mmol/l included in the defini-tion, which was not accompanied by hemodynamic problems or low FVIII plasma levels in study patients. Severity of bleeding was similar to earlier reports, as the percentage of study patients requiring a reoperation (3%) was comparable to a previous study, which reported a percentage of 2.7%.[33] We could not demonstrate that FVIII plasma levels were under lowest target range levels in patients with bleeding complications.[33] Although this may be due to a lack of FVIII testing at the bleeding occurrence and FVIII plasma levels measured after acute FVIII concentrate administration.

Theoretically, in our study, optimal maintenance of predefined target FVIII levels by refined dosing would have led to a reduction of FVIII consumption of maximally 44%, with a concomitant reduction of treatment costs. However, when using a strategy of optimal target value maintenance, it is of course not possible to completely eliminate underdosing and overdosing as the logistic delays caused by laboratory monitoring and assessment of FVIII values and adjustment of treatment will persist. Although currently not yet available due to the lack of perioperative PK population models, we believe more optimal treatment will consist of individually dosed FVIII concentrate based on an individual FVIII PK-profile with adaptive dosing according to a perioperative FVIII PK population model. Until recently, most studies on PK-guided dosing were performed in the prophylactic setting.[41-43] In the few studies in which perioperative PK profiling is mentioned it was solely used to establish a preoperative PK- guided loading dose.[9, 11, 13]

CONCLUSION

In conclusion, our findings demonstrate significant underdosing and (excessive) over-dosing of FVIII concentrate and identify its predictors, during the perioperative period with current dosing strategies based on body weight and crude estimations of clearance. Blood group O proved to be predictive of underdosing and was associated with a higher risk of bleeding complications; blood group non-O was demonstrated to be a predictor of overdosing. With regard to excessive overdosing, older age and replacement therapy by bolus infusion were shown to be predictive. Currently available PK population models for FVIII replacement therapy in the prophylactic setting support that age influence FVIII plasma concentrations significantly.[20, 41] These data underline that quality of care and cost-effectiveness can be improved by future refining of dosing strategies based on individual patient characteristics such as the predictors blood group and mode of infusion. However, we also believe that not all variables of influence on dosing and clearance of FVIII concentrate have yet been defined. Therefore, novel developments with regard to pharmacokinetic (PK)-guided dosing based on PK population models and Bayesian analysis, taking both known and unknown modifying factors into account as proposed by Bjorkman et al.[41] are more than promising.

ACKNOWLEGDMENTS

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Supplemental Tables

Supplemental Table 1. Classification of included surgical procedures

Surgical Type	High Risk**	Major	Minor
General			
Laparotomy		Major	
Liver Biopsy		Major	
Cholecystectomy and exploration of common duct		Major	
Colo-Rectal Surgery			
Excision of anal fistula			Minor
Gastro duodenoscopy (biopt)		Major	
Diagnostic laparoscopy		Major	
Vascular			
Amputation of limb		Major	
Cardiothoracic Surgery			
Insertion of defibrillator		Major	
Coronary Angioplasty	High		
Coronary Artery Bypass Graft (CABG)	High		
Excision of mediastinal mass	High		
Neurosurgery			
Craniotomy	High		
Meningioma	High		
Shunt procedures	High		
Orthopedics			
Arthroscopy (shoulder/knee)		Major	
Foot or ankle surgery			Minor
Incision drainage			Minor
Internal fixation of tibia or fibula		Major	
Revision of total hip and knee replacement		Major	
Scoliosis surgery	High		
Total joint replacement (elbow, hip, shoulder, knee)		Major	
Hand or wrist surgery			Minor

Supplemental Table 1. Classification of included surgical procedures (continued)

Surgical Type	High Risk**	Major	Minor
Urology			
Circumcision			Minor
Vasectomy			Minor
Prostatectomy		Major	
Urethroplasty		Major	
Urerthrolithotomy		Major	
Maxillofacial			
Bimaxillary osteotomy		Major	
Craniofacial Surgery	High		
ENT (Ear-Nose-Throat)			
Adenoidectomy			Minor
Adenoido-tonsillectomy		Major	
ENT: insertion of stents			Minor
Tonsillectomy		Major	
Eye Surgery			
Orbital surgery		Major	
Catarract/Virectomy/Retinal surgery			Minor
Miscellaneous			
Dental surgery			Minor
Drainage of abscess			Minor
Excision burns scars			Minor
Excision of lipoma			Minor
Hernia repair (inguinal/umbilical)			Minor
Central venous catheter removal/insertion			**Minor**

*Surgical risk score according to Koshy et al. 1995; **Excluded

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Supplemental Table 2. Frequency of underdosing and overdosing in the perioperative period before 2005 and after 2005

	2000 - 2013	< 2005*	> 2005**
Underdosing (%)			
0-24 hours	45	38	47
24-120 hours	7	10	4
>120 hours	8,5	12	8
Overdosing (%)			
0-24 hours	33	36	31
24-120 hours	59	58	58
>120 hours	73	64	73

Supplemental Table 3. Characteristics of patients with a severe bleeding complication requiring a reoperation

| Patient	Surgical procedure	Day of occurrence of the bleeding complication	Description	FVIII level (IUmL^{-1})	Mode of infusion	Other medication	Blood group
1	Total knee replacement	Day 5	Intra-articular bleed	0.99	Bolus	Heparin	Non-O
2	Total knee replacement	Day 5	Intra-articular bleed	1.03	Continuous	Heparin	O
3	Total knee replacement	Day 4	Intra-articular bleed	0.68	Continuous	Tranexamic acid	O
4	Fixation of hip/humerus	Day 2	Bleed after removal of a drain	0.99	Continuous	Tranexamic acid	O
5	Total knee replacement	Day 7	Intra-articular bleed	0.50	Continuous	Tranexamic acid, heparin	O
6	Total knee replacement	Day 9	Intra-articular bleed	0.64	Continuous	Tranexamic acid, heparin	O
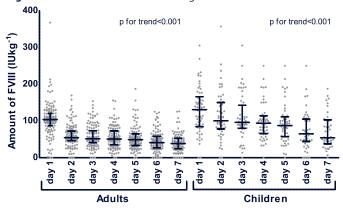
Supplemental Table 4. Surgical and patient characteristics of all bleeding complications and severe bleeding complications

	Bleeding complication*		Severe bleeding complication	
	No	Yes	Reoperation	RBCTF
Type of surgical procedure				
General	4	2	0	0
Colo-rectal	4	1	0	1
Vascular	0	1	0	1
Cardio-thoracic	0	1	0	0
Orthopedic	64	30	6	12
Urology	10	2	0	1
Maxillofacial	1	1	0	1
Ear-Nose-Throat	7	4	0	1
Eye	3	0	0	0
(Re)placement central intravenous catheters	32	0	0	0
Miscellaneous	25	6	0	1
Mode of infusion				
Continuous	83	32	5	12
Bolus	67	16	1	6
Blood group				
O	60	29	5	10
Non-O	67	16	1	7

*according to the ISTH definition; RBCTF=red blood cell transfusion

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Supplemental Figure

Supplemental Figure 1. Amount of infused FVIII clotting factor concentrate.

Figure 1 shows a decrease in total amount of infused FVIII concentrate per kilogram on consecutive days of hospitalization for both adults and children, p for trend is <0.001 (F(1,354)=41.4) tested by one-way ANOVA. IUkg[-1]=International Units per kilogram

Chapter 3

Perioperative replacement therapy in hemophilia B: An appeal to "B" more precise.

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SUMMARY

Background Hemophilia B is caused by a deficiency of coagulation factor IX (FIX) and characterized by bleeding in muscles and joints. In the perioperative setting, patients are treated with FIX replacement therapy striving for physiological FIX levels to secure hemostasis. Targeting of specified FIX levels is challenging and requires frequent monitoring and adjustment of therapy.

Objective We conducted a retrospective international multicenter study to evaluate perioperative management in hemophilia B, including monitoring of FIX infusions (consumption) and observed FIX levels, whereby predictors of low and high FIX levels were assessed.

Methods Hemophilia B patients with FIX<0.05 IUmL^{-1} undergoing elective, minor or major surgical procedures between 2000-2015 were included. Data were collected on patient, surgical and treatment characteristics. Observed FIX levels were compared to target levels as recommended by guidelines.

Results A total of 255 surgical procedures were performed in 118 patients (median age 40 years, median body weight 79 kg). Sixty percent of FIX levels within 24 hours of surgery were below target with a median difference of 0.22 IUmL^{-1} [IQR 0.12-0.36]; while > six days after surgery 59% of FIX levels were above target with a median difference of 0.19 IUmL^{-1} [IQR 0.10-0.39]. Clinically relevant bleeding complications (necessity of a second surgical intervention or red blood cell transfusion) occurred in three procedures (1.2%).

Conclusion This study demonstrates that targeting of FIX levels in the perioperative setting is complex and suboptimal, but despite this bleeding is minimal. Alternative dosing strategies taking patient and surgical characteristics, as well as pharmacokinetic principles into account, may help to optimize and individualize treatment.

INTRODUCTION

Hemophilia B is an X-linked hereditary bleeding disorder characterized by a deficiency of coagulation factor IX (FIX). Treatment consists of prophylactic or on demand replacement therapy with recombinant or plasma derived FIX concentrates. However, replacement therapy with factor concentrates is costly. In the United Kingdom, 60 million international units of FIX concentrates are administered annually in 663 hemophilia B patients.[1] This will most probably increase further in the near future, due to the aging hemophilia patient population and necessity of orthopedic surgery for joint replacement.

In the perioperative setting, patients receive FIX concentrates to normalize FIX levels for 7-10 consecutive days postoperatively. Efficacious perioperative treatment is of importance to prevent underdosing with a risk of bleeding and overdosing with a possible risk of thrombosis and waste of expensive concentrates. However, treatment is complex due to a large interpatient variability which is not taken into account in National guidelines. Recently, we identified both underdosing and overdosing in perioperative hemophilia A patients and the need for optimization of treatment strategies.[2] Collected data were subsequently used to construct a population pharmacokinetic (PK) model, currently being validated in a randomized controlled trial.[3] Few studies have reported on safety and efficacy of perioperative management in hemophilia B.[4, 5] To evaluate perioperative management, we conducted an international multicenter retrospective observational study to collect FIX levels after factor IX concentrate administration during and after minor and major surgery as well as clinical outcome measures (FIX consumption and bleeding/thrombotic complications) in order to identify predictive factors of low and high FIX levels.

METHODS

Patients

In this international multicenter retrospective observational cohort study, patients were included with severe and moderate hemophilia B (FIX <0.05 IUmL^{-1}) who underwent elective minor or major surgical procedures with FIX replacement therapy between January

1st 2000 and December 1st 2015. The procedures were classified by surgical risk score as established by Koshy et al.[6] Patients attended one of ten Hemophilia Treatment Centers in the Netherlands and United Kingdom (Erasmus University Medical Center Rotterdam; Academic Medical Center Amsterdam; University Medical Center Groningen; Leids University Medical Center Leiden and Radboud university medical center Nijmegen; Great Ormond Street Haemophilia Centre, London; Arthur Bloom Haemophilia Centre, Cardiff, Wales; Katharine Dormandy Haemophilia Centre, Royal Free London; Churchill Hospital, Oxford; The Royal London Hospital, London). Patients received recombinant or plasma derived FIX concentrates to normalize FIX levels. Administered recombinant FIX concentrate was Benefix (Pfizer Wyeth Pharmaceuticals Inc, Kent, UK). Plasma derived FIX concentrates included: Alphanine (Grifols Biologicals Inc. Los Angeles, USA), Replenine (BPL Bio Products Laboratory, Hertfordshire, UK); Haemonine (Biotest Pharma GmbH, Dreierich, Germany), Mononine (CSL Behring GmbH, Marbourg, Germany), Nonafact (Sanquin, Amsterdam, the Netherlands). Patients with possible disseminated intravascular coagulation due to sepsis and patients who developed FIX neutralizing antibodies during the perioperative period were excluded. The study was not subject to the Medical Research Involving Human Subjects Act and was approved by all Medical Ethics Committee in the Netherlands. In the United Kingdom, the study was approved by the Research Ethics Committee (NRES committee South Central-Berkshire, REC reference 15/SC/0367); an opt-out consent procedure was used to collect anonymized clinical data.

Objective

Study objective was to evaluate perioperative management of hemophilia B patients by documentation of timing and dosing of FIX infusions, and observed FIX levels, compared to target FIX levels according to National and/or hospital guidelines (Table 1).[7] Moreover, clinical outcome measures were assessed, consisting of FIX consumption and identification of bleeding and thrombotic complications. Also, predictors of low and high levels were identified by collection of data on patient, surgical and treatment characteristics.

Methods

The following information was extracted from the medical notes; patient characteristics, including: age, body weight, baseline FIX level and history of FIX neutralizing inhibiting antibodies. Surgical and treatment characteristics consisted of severity of surgical

Table 1. Specifications of perioperative replacement therapy, definition of bleeding complications and typical surgical procedures

Specified FIX target ranges in the perioperative period*		
Time		**FIX target level (IUmL^{-1})**
Day	**Hours**	
1	0-24	0.80-1.00
2-5	24-120	0.50-0.80
≥6	>120	0.30-0.50

*According to the National and/or hospital guidelines of the Netherlands and United Kingdom
IUmL^{-1} = International Units per milliliter

Definition of bleeding complications$^\$$	Definition of clinical relevant bleeding
Re-operation	Re-operation
Red blood cell transfusion	Red blood cell transfusion
Hemoglobin drop >1,24 mmolL^{-1}	
Bleeding with prolonged hospitalization	

$^\$$According to the International Society of Thrombosis and Haemostasis[6]

Examples of typical minor and major surgical procedures included in the study#	
Minor	**Major**
Dental procedures or surgery	Total knee/ hip and shoulder replacement
Excision of lipoma	Adenoido-tonsillectomy
Insertion/removal of intravenous catheters	Colo-rectal surgery
	Vascular surgery
	Maxillo-facial surgery (bimaxillary osteotomy)

#According to the surgical risk score of Koshy et al.[4]

procedure (minor and major), mode of infusion (continuous and bolus infusion), type of product (recombinant and plasma derived FIX concentrates), FIX concentrate infusion time and dose, and time of FIX level monitoring measured in IUmL^{-1}. FIX levels were monitored daily and measured by one-stage assays in participating centers according to local protocol. Bleeding complications were defined as need of a second surgical intervention, hemoglobin decrease of >1.24 mmolL^{-1} (>20 gL^{-1}) and/or red blood cell transfusion, or bleeding prolonging hospitalization, according to the International Society of Thrombosis and Haemostasis guidelines for major bleeding.[8] Clinically relevant

bleeding complications were defined as bleeding complications requiring a second surgical intervention and/or necessity of a red blood cell transfusion. The duration of the perioperative period in the study was equivalent to duration of hospitalization (day of discharge minus day of surgery and start of infusion of FIX concentrates).

All patients received replacement therapy with FIX concentrate during hospitalization according to National and/or hospital guidelines with daily monitoring of FIX, while aiming for target FIX levels as prescribed (Table 1).[7] Perioperative treatment in severe and moderate hemophilia B patients consisted of FIX bolus infusion of approximately 100 IUkg^{-1}, followed by either continuous infusion or intermittent bolus infusions.[7] Only measured trough and steady state FIX levels were compared to predefined FIX target ranges. Trough FIX levels were measured prior to next FIX bolus infusion, if treatment by bolus was performed. Steady state FIX levels were defined as FIX levels measured when FIX concentrate substitution was equal to clearance in patients with treatment by continuous infusion. In general, it is assumed that steady state is reached after a loading dose is administered and continuous infusion is started. FIX peak levels after FIX bolus infusions were not included in analysis of this data set. Low FIX levels were defined as all FIX levels below lowest predefined target range level. High FIX levels were defined as all FIX levels above highest predefined target range level. FIX levels. A difference of ≥0.20 IUmL^{-1} above the highest FIX target range were defined as excessively high. This cut-off of 0.20 IUmL^{-1} was chosen arbitrarily to overcome inclusion of high FIX levels solely due to logistic delay of adjustment of treatment.

Potential predictors of FIX levels lower or higher than the target range were identified before analysis and based on the potential effects that they may have on PK parameters e.g. clearance and/or volume of distribution of infused FIX concentrate. These consisted of age, body weight, history of FIX neutralizing inhibiting antibodies, type of product (recombinant or plasma-derived FIX), mode of infusion (continuous or bolus infusion), severity of surgical procedure. Also the influence of a clinically relevant bleeding complication was evaluated. In calculations of total perioperative FIX consumption, only FIX concentrate administered during the hospitalization period and during first surgical procedure in each individual patient was included.

Statistical analysis

The non-parametric Mann Whitney U test was used for comparison of FIX consumption between groups. To evaluate trends in FIX consumption a "p for trend analysis by one-way ANOVA" was used. A stepwise forward and backward logistic regression analysis was performed to identify predictors of FIX levels lower or higher than target FIX levels with elimination of variables with p>0.10. A Pearson Chi-Square test was used for comparisons between proportions. General characteristics are presented as median and 25-75% interquartile range (IQR) and as number and percentages for respectively continuous and categorical variables. Data management and statistical analysis were performed with SPSS for Windows, version 21.0 (SPSS Inc, Chicago, IL, USA). A P-value of <0.05 was considered statistically significant.

RESULTS

A total of 118 severe and moderate hemophilia B patients who underwent a total of 255 surgical procedures were included. Of these, 85 (72%) were severe hemophilia B patients, of which 36 were on prophylactic treatment. Patient characteristics are shown in Table 2. Eighty-two adult patients underwent a total of 201 surgical procedures (median age 46 years; median body weight 85 kg) and 36 children underwent a total of 54 surgical procedures (median age 6 years; median body weight 19 kg). Twenty-five patients with 51 surgical procedures were included from Hemophilia Treatment Centers in the Netherlands and 91 patients with 208 surgical procedures from Hemophilia Treatment Centers in the United Kingdom. Only six patients were documented to have had a FIX neutralizing antibody in the past. Several patients underwent multiple surgical procedures; with 28 (34%) adult patients undergoing ≥ three surgical procedures. In children, 25 (46%) of all surgical procedures consisted of an insertion or removal of a central intravenous catheter; adult patients underwent an orthopedic surgical procedure most frequently (n=92; 46%). Most patients (n=199; 78%) received their replacement therapy by bolus infusion therapy. In 201 (79%) surgical procedures, patients were treated with recombinant factor concentrates. Children had a higher FIX consumption than adults (children: 145 IUkg^{-1} day^{-1} [IQR 71-234 IUkg^{-1} day^{-1}]; adults: 68 IUkg^{-1} day^{-1} [IQR 34-97 IUkg^{-1} day^{-1}]; p<0.001). In accordance with guidelines, FIX consumption was highest on day 1 in both adults and children. Strikingly, FIX consumption did not decrease as prescribed during hospitalization from day two until day seven (p for trend = 0.92) (Figure 1).

Table 2. General characteristics

	Total cohort		Adults		Children	
	No. (%); or Median [IQR]					
Patient characteristics						
No. of patients	118		82		36	
Age (years)	40	[22-58]	46	[34-59]	6	[2-11]
Body weight (kg)	79	[65-92]	85	[73-95]	19	[13-39]
Severe hemophilia B (<0.01 IUmL^{-1})	85	(72)	57	(70)	28	(78)
On prophylaxis	36	(31)	28	(34)	8	(22)
Blood group O*	33	(28)	24	(29)	9	(25)
Neutralizing antibodies (historically)	6	(5)	5	(6)	1	(3)
Chronic hepatitis C	47	(40)	46	(56)	1	(3)
Surgical characteristics						
No. of surgical procedures	255		201		54	
Total no. of patients undergoing:						
1	55		33		22	
2	31		21		10	
≥3	42		28		4	
Major surgical procedure	120	(47)	105	(52)	15	(28)
Type of surgical procedure						
General	19	(7)	16	(8)	3	(6)
Colo-rectal	16	(6)	14	(7)	2	(4)
Vascular	9	(4)	9	(4)	0	(0)
Cardio-thoracic	3	(1)	2	(1)	1	(2)
Orthopedic	99	(39)	92	(46)	7	(13)
Urological	11	(4)	11	(5)	0	(0)
Maxillofacial	1	(0)	1	(0)	0	(0)
Ear-Nose-Throat	9	(4)	5	(2)	4	(7)
Neurosurgery	1	(0)	1	(0)	0	(0)
Eye surgery	2	(1)	2	(1)	0	(0)
(Re)placement central intravenous catheters	27	(11)	2	(1)	25	(46)
Dental extractions	31	(12)	25	(12)	6	(11)
Miscellaneous	27	(11)	21	(10)	6	(11)

Table 2. General characteristics (continued)

	Total cohort		Adults		Children	
	No. (%); or Median [IQR]					
Replacement therapy with factor concentrate, hospitalization and blood loss						
Mode of infusion						
Continuous	56	(22)	54	(27)	2	(4)
Bolus	199	(78)	147	(73)	52	(96)
Product type						
Recombinant[$]	201	(79)	150	(75)	51	(91)
Plasma derived[#]	54	(21)	51	(25)	3	(6)
Duration of hospitalization (days)	4	[2-9]	5	[2-11]	4	[2-5]
Complications during perioperative period						
No. of patients suffering from a complication						
Bleeding						
Re-operation	2	(2)	2	(2)	0	(0)
Hemoglobin drop >1,24 mmolL[-1]	23	(19)	17	(21)	6	(17)
Red blood cell transfusion	1	(1)	1	(1)	0	(0)
Thrombosis	0	(0)	0	(0)	0	(0)

No. = number; IQR = inter-quartile range; kg = kilogram; IUmL[-1] = international units per milliliter; * Blood group available in 80 patients; [$] including BeneFix (Pfizer Wyeth Pharmaceuticals Inc., Kent, UK); [#] Including AlphaNine (Grifols Biologicals Inc. Los Angeles, USA); Replenine (Bio Products Laboratory, Hertfordshire, UK); Haemonine (Biotest Pharma GmbH, Dreierich, Germany); Mononine (CSL Behring GmbH, Marbourg, Germany); Nonafact (Sanquin, Amsterdam, the Netherlands).

Perioperative complications

In only three (1.2%) surgical procedures clinically relevant bleeding complications were observed. Two of these three patients underwent total knee replacements followed by hemarthrosis requiring a second intervention. One of these three patients received a red blood cell transfusion after surgery. No association between FIX levels and occurrence of a bleeding complication was found. However, FIX testing was limited during bleeding events. No predictors of clinically relevant bleeding complications could be established. Although one patient was suspected for deep vein thrombosis (DVT), a compression ultrasonography was negative.
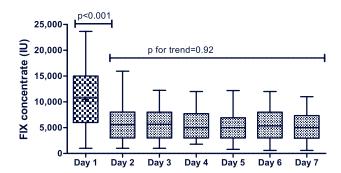
Figure 1. Perioperative FIX consumption on consecutive days

FIX consumption on consecutive days postoperatively. The amount of FIX administered factor concentrates was higher on day 1 in comparison to following days. P-for trend analysis using one-way ANOVA showed no differences between amount of FIX concentrates administered postoperatively.

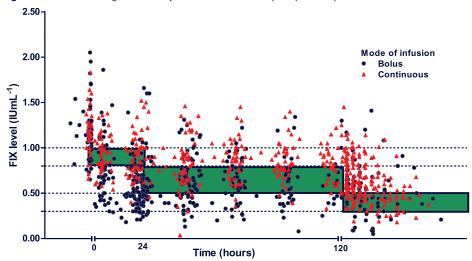## Observed FIX levels and comparison to target ranges

No differences were observed between observed FIX levels between treatment centers and between countries. Daily monitoring of FIX levels revealed that most perioperative FIX levels were outside specified target ranges (Figure 2). More specifically, 60% of trough or steady state FIX levels were below target range with a median difference of 0.22 IUmL^{-1} [IQR 0.12-0.36 IUmL^{-1}] within 24 hours of the surgical procedure. Relative under dosing decreased over time with only 9% of values under target range at six days after surgery (median difference 0.09 IUmL^{-1} [IQR 0.05-0.20 IUmL^{-1}]. Conversely, an increase in proportion of FIX levels above target range was observed over time, with 59% of FIX levels above target range with a median difference of 0.19 IUmL^{-1} [IQR 0.10-0.39 IUmL^{-1}] six days after surgery.

Predictors of lower and higher FIX levels than target range

When analyzing the complete perioperative period in the total study population, both treatment by bolus infusion and minor surgical procedures were predictive of lower FIX levels than required by guidelines (respectively OR=5.4 95%CI 3.5-8.3, OR=2.0 95%CI 1.2-3.2). During the first 24 hours after surgery, only bolus infusion was predictive of lower FIX levels in comparison to continuous infusion (OR=6.1 95%CI 2.8-13.4) (Table

3). Occurrence of a clinically relevant bleeding complication and treatment with continuous infusion were associated with excessively high FIX levels ($\geq$0.20 IUmL^{-1} above target). No differences were observed between achieved FIX levels between treatment centers or between countries (data not shown).

Figure 2. Achieved trough and steady state FIX levels in the perioperative period

Frequency of lower and higher FIX levels than target range and median difference of target range

	0-24 hours	24-120 hours	>120 hours
	Median difference (IUmL^{-1}) [IQR]	Median difference (IUmL^{-1}) [IQR]	Median difference (IUmL^{-1}) [IQR]
Total no. of samples	232	381	273
Lower FIX levels	140 (60) 0.22 [0.12-0.36]	81 (21) 0.11 [0.05-0.19]	25 (9) 0.09 [0.05-0.20]
Higher FIX levels	41 (18) 0.15 [0.08-0.28]	148 (39) 0.16 [0.09-0.32]	162 (59) 0.19 [0.10-0.39]

Achieved trough and steady state FIX levels are shown of both patients treated by bolus infusion replacement therapy (blue) and by continuous infusion (red). Bolus infusion therapy was predictive of lower levels in the first 24 hours after surgery in comparison to replacement therapy by continuous infusion. Frequency of lower and higher FIX levels than target range with median difference in IUmL^{-1} and corresponding 25-75% interquartile range (IQR) during the perioperative period are shown corresponding to specified target ranges (green) as defined by National and/or hospital guidelines.

Table 3. Predictors of lower and (excessive) higher FIX levels than target range*

	OR	95%CI
Lower FIX levels (0-24 hours)		
Bolus infusion (versus continuous)	6.1	[2.8-13.4]
Age (increasing per year)	1.0	[1.00-1.03]
Lower FIX levels (total perioperative period)		
Minor surgical procedure (versus major)	2.0	[1.2-3.2]
Bolus infusion (versus continuous)	5.4	[3.5-8.3]
Age (increasing per year)	1.0	[1.00-1.02]
Higher FIX levels		
Continuous infusion (versus bolus)	3.1	[2.2-4.5]
Age (decreasing per year)	1.0	[1.0-1.0]
Excessive higher FIX levels		
Continuous infusion (versus bolus)	1.6	[1.03-2.5]
Bleeding complication (versus not present)	2.8	[1.4-5.8]

*Stepwise forward and backward logistic regression analysis. OR=Odds Ratio; CI=Confidence Interval

DISCUSSION

This is the largest cohort of perioperative hemophilia B patients described to date with a total of 255 surgical procedures in 118 patients. This study demonstrates the challenges of perioperative FIX concentrate dosing as most perioperative FIX levels were outside the predefined target ranges recommended by National and/or hospital guidelines. Importantly, 60% of trough and steady state FIX levels were below the target level in the first 24 hours after surgery, while 59% of FIX levels were above target more than six days after surgery. Despite the lower FIX levels clinically relevant bleeding complications were uncommon (3/255, 1.2%).

The lower FIX levels observed immediately after surgery in our study, are most likely due to increased clearance of FIX concentrate during and directly after surgery[4] as well as increased consumption of FIX due to activation of hemostasis by tissue damage and

blood loss. Bolus infusion therapy was predictive of FIX levels lower than target range, most prominently in the first 24 hours after surgery. This is in accordance to pharmaco-kinetic principles as bolus infusions generally lead to overall lower trough levels when frequency of dosing is not sufficient. In addition, the somewhat higher FIX levels in patients treated by continuous infusion may be attributed to overall lower FIX clearance rates due to saturation of FIX binding sites and additional extravascular localization of FIX.[5] Moreover, it should be considered that clinicians may have neglected to adapt con-tinuous infusion rates and may have tolerated or aimed for higher FIX levels in patients undergoing major surgical procedures. This is further supported by the observation, although not remarkable, that minor surgical procedures were predictive of underdos-ing, when the total perioperative period was evaluated. Minor surgical procedures are often treated for a shorter period of time, with possible aiming of lower FIX levels. Also, guidelines do not distinguish between severity of surgical procedure.[7] Furthermore, as may be expected, patients with a clinically relevant bleeding complication showed excessively high FIX levels, due to repetitive bolus infusions and/ or increased infusion rates in cases of continuous infusion.

Study strengths and limitations

The large number of patients and variety of surgical procedures included from ten Aca-demic Hemophilia Treatment Centers in two countries makes this study representative for perioperative management in high income countries in severe and moderate severe hemophilia B. Moreover, no differences were observed between observed FIX levels and FIX consumption between these treatment centers and between countries. This study is one of the few studies evaluating perioperative management in hemophilia B with identification of predictors of FIX levels lower and higher than target ranges specified by guidelines. Study limitations include the retrospective nature of the data. However, treatment characteristics, including FIX timing and dosing and timing of FIX sampling were collected thoroughly, and complications were extensively documented. Yet, docu-mentation of blood loss remained difficult, although we do feel that clinically relevant bleeding defined as necessity of a second surgical intervention and/or necessity of a red blood cell transfusion depicts noteworthy bleeding in this cohort of perioperative patients. Patients with an established neutralizing antibody to FIX were excluded from analysis as these influence FIX clearance due to other, immunological mechanisms. This

study may lead to both refinement of current guidelines with regard to target ranges. In addition, these data underline the potential of alternative dosing strategies based on pharmacokinetic principles which are more specific than body weight and crude estimations of clearance currently applied.

Perioperative bleeding

Overall in our study population, perioperative bleeding in hemophilia B in both countries was rare (1.2%), and was not correlated with low FIX levels. However, FIX testing was limited during bleeding events. In literature, in two case series consisting of 36 and 25 surgical procedures respectively[4, 5], higher percentages of clinically relevant bleeding events as defined in our study have been reported (4-8.3%). In addition, most of these included patients underwent an orthopedic surgical procedure. Contrastingly, in a cohort of 74 hemophilia B patients undergoing 81 surgical procedures, no red blood cell transfusions were reported and hemostatic efficacy was rated as excellent by surgical teams.[9] In this study, also different minor and major surgical procedures were included, which was similar compared to our cohort. Exceptions are made for certain surgical procedures as a recent report by Kapadia et al. showed that lower extremity total joint arthroplasty leads to significantly more red blood cell transfusions in hemophilia patients (15.1%) in comparison to a large matched cohort without a known bleeding history (9.8%); OR 1.60 (95% CI 1.11-2.31).[10]

Current guidelines and possible refinements

Although target ranges in most National and/or hospital guidelines do not differ between hemophilia A and B[7, 11-13], other international guidelines such as set by the World Federation of Hemophilia (WFH), prescribe lower FIX levels in the perioperative setting.[14] In developing countries with scarce resources, even lower FIX levels are advised (FIX levels of 0.20-0.50 for 1-5 days postoperatively).[14] A low frequency of perioperative bleeding under replacement therapy with lower FVIII and FIX target levels was reported by Srivastava et al. in a single center respective study of 11 hemophilia A and seven hemophilia B patients.[15] In this study, FIX trough levels were set at 0.15-0.30 IUmL^{-1} on day 1-3 postoperatively and at 0.10-0.20 IUmL^{-1} more than four days postoperatively, until the wound had healed and sutures had been removed. Only one of these seven hemophilia B patients experienced postoperative bleeding due to surgical reasons as

verified by the surgeon. Our study supports these last findings, as in only three of 255 surgical procedures (1.2%) a clinically relevant bleeding complication was documented despite underdosing within 24 hours after surgery in 60% of FIX levels. We conclude that there may be growing evidence that it may be possible to maintain lower FIX target ranges in the perioperative setting.

Perioperative FIX consumption and individualization of therapy

Although a significant proportion of the study population was underdosed without bleeding, a significant proportion was overdosed, especially >6 days after surgery with 59% of trough and steady state FIX levels above target. Current costs of health care for society warrant avoidance of excessive dosing without a clinical effect. Overdosing may be prevented by more individualized dosing strategies that take patient, and surgical characteristics as well as individual pharmacokinetics of concentrates into account.

Children had a higher FIX consumption when compared to adults, which is explained by a large volume of distribution and higher clearance.[16]

In prophylactic treatment, it has been proven that FIX consumption can be significantly reduced by individualization of dosing based on pharmacokinetic modelling.[17-20] Several studies have also shown that preoperative dosing based on an individual pharmaco-kinetic profile is safe, effective and applicable.[5, 21] However, the real challenge is to implement iterative pharmacokinetic-guided FIX concentrate dosing in the periopera-tive period. This has not been possible to date, as a reliable perioperative population pharmacokinetic model has been lacking. Widespread application of such a model will help to implement individualization of dosing, thereby increasing the proportion of patients with FIX levels within the target range.

This study shows that targeting of FIX levels in the perioperative setting is complex and results are suboptimal as both lower and higher levels than targeted are observed. Individualization of dosing by identification of predictors of volume of distribution and clearance of FIX concentrate may improve outcomes. In addition, a critical assessment of current FIX target ranges seems warranted as few bleeding complications occurred in patients with lower levels than prescribed by National and/or hospital guidelines. Phar-macokinetic-guided dosing may help attain this goal, as lowering of FIX target ranges as specified ranges can be achieved reliably. Moreover, this may also decrease overdosing in the last days of the perioperative period. Therefore, we suggest that construction of

population pharmacokinetic models and dosing according to these models will lead to refinement of current target ranges in hemophilia B and towards overall optimization of perioperative management.
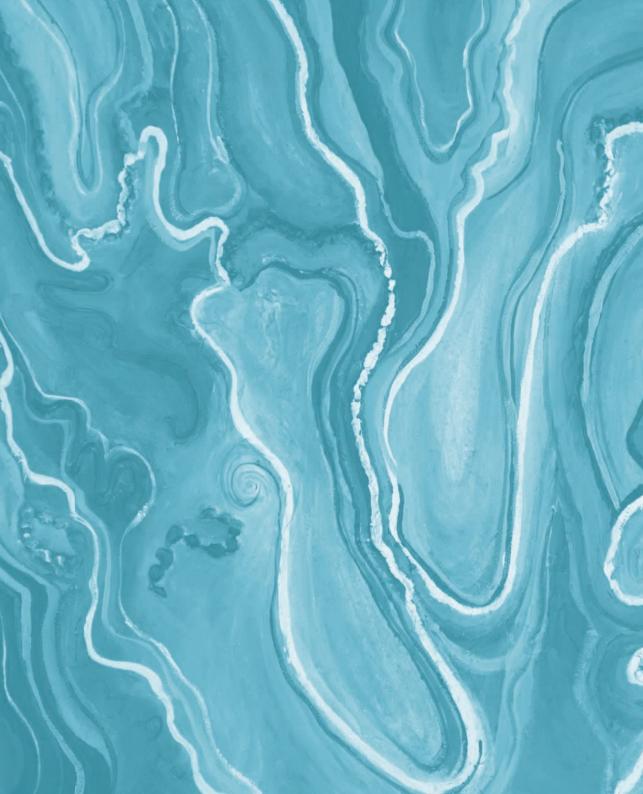
ACKNOWLEDGMENTS

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Chapter 4

Perioperative management of VWF/
FVIII concentrate in patients with von
Willebrand disease: a lot to "WiN" by
individualization of treatment?

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SUMMARY

Background Von Willebrand disease (VWD) patients are regularly treated with factor concentrates in cases of acute bleeding, trauma or surgical procedures.

Objective In this multicenter retrospective study current perioperative management with von Willebrand factor (VWF)/Factor VIII (FVIII) (Haemate P®) concentrate in VWD patients was evaluated.

Methods VWD patients undergoing minor or major surgery between 2000-2015 and treated with VWF/FVIII concentrate (Haemate P®) were included. Achieved VWF:Act/FVIII:C during FVIII:C-based treatment regimens were compared to predefined target levels in National guidelines.

Results In total, 103 VWD patients (148 surgeries) were included: 54 type 1 (73 surgeries), 43 type 2 (67 surgeries) and 6 type 3 (8 surgeries). Overall, treatment resulted in high VWF:Act/FVIII:C levels, defined as ≥ 0.20 IUmL^{-1} above predefined levels. In type 1 VWD patients, respectively 65% and 91% of trough VWF:Act and FVIII:C levels were higher than target levels. In type 2 VWD and type 3 respectively, 53% and 57% of trough VWF:Act and 72% and 73% of trough FVIII:C levels were higher than target level. Furthermore, FVIII accumulation over time was observed, with significantly higher levels than VWF:Act.

Conclusion High VWF:Act and accumulation of FVIII:C levels was observed after perioperative FVIII:C-based replacement therapy in VWD patients, both underlining the necessity of more efficient and individualized therapy in order to optimize treatment.

INTRODUCTION

Von Willebrand Disease (VWD) is the most common inherited bleeding disorder with a prevalence of 0.5-1%.[1] It is caused by a quantitative or qualitative defect of von Willebrand Factor (VWF) and is characterized by mucocutaneous bleeding.[2] In more severe VWD, factor VIII (FVIII) can also be very low, as VWF prevents FVIII from clearance due to proteolysis.[3] Generally, VWD patients are treated "on demand" with desmopressin (DDAVP) or factor concentrate when acute bleeding or trauma occurs, or to prevent bleeding in the surgical setting. The aim of treatment is to correct VWF deficiency, and to correct FVIII deficiency if this is also present. When patients do not respond adequately to DDAVP or have contra-indications for its use, treatment usually consists of combined VWF/FVIII factor concentrates amongst which the ratios of VWF activity (VWF:Act) over FVIII (FVIII:C) may differ.[4, 5]

Although clinical symptoms are generally milder than in hemophilia, treatment in VWD is more challenging due to variation in VWD disease types and mutations[2, 6], interpatient variability of residual endothelial VWF production, VWF secretion and clearance, as well as heterogeneity in types of factor concentrates with different ratios of VWF:Act/FVIII:C and VWF:Act/VWF:Ag.[4, 5] Previous studies have reported that surgical procedures can be performed safely in VWD patients and that treatment with VWF/FVIII concentrate is efficacious.[7-16] In many countries, specific target levels are defined in guidelines to safeguard hemostasis during surgery. These target values are based on expert opinion and limited observational research (Figure 1).[17]

VWF:Act/ VWF:Ag ratio of available concentrates corresponds with presence of high molecular weight multimers (HMWM) and therefore with hemostatic potential. Worldwide, the most frequently used VWF/FVIII concentrate is Haemate P® and is considered as gold standard for the management of VWD patients.[18] VWF/FVIII concentrates can be classified into three different groups according to VWF:Act/FVIII:C and VWF:Act/VWF:Ag ratios.[4] More specifically, products with a VWF:Act/FVIII:C ratio of approximately 1 (1.2:1; low and high content of HMWM). Secondly, with a ratio of >1 (2.4:1 and high content of HMWM) and lastly VWF concentrates with a ratio of >10 (10:1 and high content of HMWM). The latter, are scarcely applied in the perioperative setting, as FVIII:C is only minimally supplemented with these concentrates.[19] Moreover, it has been suggested that FVIII:C is crucial to prevent surgical bleeding due to its importance in thrombin
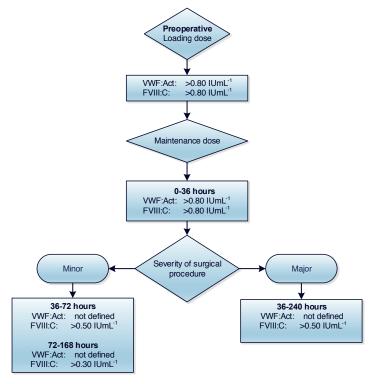
Figure 1. Target VWF:Act and FVIII:C in VWD patients in the perioperative setting*

* According to National guidelines[17]. Guidelines describe a standard perioperative dosing regimen of VWD patients undergoing minor and/or major surgery. A loading dose of VWF/FVIII factor concentrate of 50IUkg^{-1} FVIII (30-50 IUkg^{-1} in case of minor surgery) followed by maintenance doses of 15-25 IUkg^{-1} FVIII twice daily, depending on FVIII:C measurements. Both, VWF:Act and FVIII:C are targeted at trough and/or steady state levels.

generation and consolidation of the fibrin plug.[16] Furthermore, it has been reported that repetitive dosing of concentrates with a VWF:Act/FVIII:C ratio >1 results in less accumulation of FVIII:C than concentrates with a ratio of approximately 1.[7]

Intensity of perioperative treatment in VWD is dependent on type and extent of the surgical procedure, as target levels vary; but is also dependent on type and severity of VWD due to varying residual VWF and FVIII levels. In addition, treatment may differ due to interindividual differences in pharmacokinetic (PK) parameters such as clearance

and half-life of both exogenous and endogenous VWF/FVIII. Studies report that perioperative VWF/FVIII concentrate consumption indeed varies substantially, from 27 to 146 VWF:Act IUkg^{-1} day^{-1}.[7, 16] As achieved VWF and FVIII levels have rarely been evaluated and reported in literature in relation to efficacy[20], we aimed to evaluate current perioperative management of VWF/FVIII concentrate in VWD patients. This was done by assessing to what extent predefined VWF:Act and FVIII:C target levels were actually achieved as well as by analyzing predictors of higher or lower VWF:Act and FVIII:C levels than targeted. Insight in these factors will help realize more efficacious and individualized treatment in VWD in the near future.

MATERIALS AND METHODS

This multicenter retrospective observational cohort study was conducted in five Academic Hemophilia Treatment Centers in the Netherlands (Erasmus University Medical Center Rotterdam (n=51); Academic Medical Center Amsterdam (n=15); University Medical Center Groningen (n=14); Leiden University Medical Center (n=12), Radboud university medical center (n=11). This study was not subject to the Medical Research Involving Human Subjects Act, as retrospective anonymized data were analyzed, and therefore, according to Dutch law, review by the Ethical Committee and informed consent were not required.

Subject selection

Patients with a clinical and laboratory diagnosis of VWD (historically lowest levels of VWF antigen (VWF:Ag) ≤0.30 IUmL^{-1} and/or VWF:Act ≤0.30 IUmL^{-1} and/or FVIII:C ≤0.40 IUmL^{-1}) were included. Patients who underwent a minor or major surgical procedure as defined by Koshy et al.[21], under replacement therapy with a plasma derived VWF/FVIII concentrate (Haemate P®) between January 1st 2000 and January 1st 2015 were eligible. Monitoring of minimally two VWF:Act and FVIII:C levels was obligatory. Patients with other known hemostatic disorders and patients lacking accurate documentation were excluded.

Study objective

The study objective was to evaluate current perioperative management with a specific VWF/FVIII factor concentrate (Haemate P®) in VWD patients by specification of concentrate administration and subsequently achieved peak and trough levels of VWF:Act and FVIII:C in comparison to target VWF and FVIII levels as prescribed by National guidelines (Figure 1).[17] In this study, both potential predictors of low and high levels of VWF:Act/FVIII:C as well as variables associated with VWF/FVIII concentrate consumption were collected and evaluated.

Figure 2. Number and type of surgical procedures

Number (No.) and type of surgical procedures

Laboratory assessment

VWF:Act and FVIII:C were generally monitored daily during hospitalization. Immediately before surgery, peak levels were assessed, in the days after surgery trough levels were measured. In all cases, perioperative dosing was based on FVIII:C levels as VWF:Act results were standardly not rapidly available. FVIII:C was measured by one-stage clotting assays in all participating centers. In various centers, VWF activity (VWF:Act) assays were performed according to local protocol.

Data collection

Patient, surgical and treatment characteristics during the hospitalization period were collected retrospectively. Patient characteristics included age, body weight, gender, type of VWD, historically lowest baseline VWF:Ag, VWF:Act and FVIII:C, ABO blood group, and VWF gene mutation if available. Surgical characteristics consisted of procedure severity as classified by surgical risk score,[21] duration of surgery, perioperative blood loss and postsurgical bleeding complications. Bleeding complications were assessed according to definition by the International Society of Thrombosis and Hemostasis[22] and defined as necessity of second surgical intervention, hemoglobin decrease of ≥20 gL^{-1} and/or requiring red blood cell transfusion, or bleeding prolonging patient hospitalization. A clinically relevant bleeding complication was defined as a bleeding complication requiring a second surgical intervention and/or red blood cell transfusion. Treatment characteristics included: timing and dosing of VWF/FVIII concentrate administration and achieved VWF:Act and FVIII:C during and after surgical procedure; mode of infusion (continuous or bolus infusion) of VWF/FVIII concentrate and co-medication with effect on hemostasis (desmopressin, tranexamic acid, low molecular weight heparin, non-steroidal anti-inflammatory drugs) as well as duration of hospitalization. Duration of hospitalization was defined as day of discharge minus day of surgical procedure and initiation of replacement therapy with VWF/FVIII concentrate.

National guideline and evaluation of perioperative VWF/FVIII concentrate management

National guidelines prescribe a FVIII-based regimen with a loading dose of VWF/FVIII concentrate (ratio of 2.4:1) of 50 IUkg^{-1} FVIII for major surgery and 30-50 IUkg^{-1} FVIII for minor surgical interventions followed by maintenance doses of 15-25 IUkg^{-1} FVIII twice daily with regular monitoring of VWF:Act and FVIII:C. Dosing is adjusted according to VWF:Act and FVIII:C target levels specified in guidelines and depicted in Figure 1.[17] In general, patients are treated 7-10 days in case of a major surgical procedure, and 4-7 days in case of a minor surgical procedure. This is in accordance to the UKHCDO and Nordic guidelines.[23, 24] Perioperative dosing was left to discretion of treating physician. Most patients received thromboprohylaxis using low molecular weight heparin.

Perioperative management of VWF/ FVIII concentrate after first peak values, was evaluated by comparing achieved VWF:Act and FVIII:C trough and steady state levels to target

VWF:Act and FVIII:C levels. Trough levels were defined as measurements prior to bolus infusion or measurements at least 12 hours after infusion, when no subsequent factor concentrate infusion was given. Redundantly, no peak levels after bolus infusion were included in these analyses. Steady state samples were defined as VWF and FVIII levels sampled when concentrate substitution is expected to equal elimination of VWF/FVIII concentrate when administered continuously. In general, it is assumed that steady state will be reached after a loading dose is administered and continuous infusion is started. Analysis of predictors of low and high levels of VWF:Act/FVIII:C could only be performed in type 1 and type 2 VWD disease patients, due to limited numbers of patients with type 3 VWD. A stepwise forward and backward logistic regression analysis was performed with low levels defined as VWF:Act or FVIII:C below predefined target levels stated by guidelines and high levels of VWF:Act/FVIII:C, as all VWF:Act or FVIII levels above the predefined target level with a deviation of ≥ 0.20 IUmL^{-1}. Potential predictors included in the analysis, were severity of surgical procedure, blood group O versus non-O, body weight, age, mode of infusion and treatment center.

Statistical analysis

Descriptive data are presented as numbers with percentages for categorical variables and as medians with an interquartile range (IQR) for continuous variables, as data were not normally distributed. The non-parametric Mann-Whitney U test was used to compare VWF/FVIII concentrate consumption between surgical procedures of different severity. If a patient was subjected to two or more surgeries, calculations were only performed for the first surgical procedure. Potential predictors of lower and higher VWF:Act/FVIII:C levels than aimed for were analyzed by stepwise backward and forward logistic regression analysis with elimination of variables with P>0.10. A linear regression analysis was performed to calculate if FVIII accumulation occurred after repetitive dosing of VWF/FVIII concentrate, whereby regression coefficients were compared between both VWF:Act and FVIII:C. Data management and statistical analysis were performed with IBM SPSS statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, USA). A P-value of <0.05 was considered statistically significant.

RESULTS

The study population consisted of 103 patients undergoing a total of 148 surgical procedures; 54 type 1 VWD patients (73 surgical procedures), 43 type 2 VWD patients (67 procedures) and 6 type 3 VWD patients (8 surgical procedures) (Table 1). Half of patients had blood group O (51%). Median historical baseline VWF:Ag level and VWF:Act level was 0.30 and 0.22 IUmL^{-1} for VWD type 1 patients; 0.29 and 0.10 IUmL^{-1} for VWD type 2 and 0.05 and <0.10 IUmL^{-1} for VWD type 3 patients. Some patients in the study population underwent multiple surgical procedures (Table 1). Procedures were mainly orthopedic (n=36; 24%), general (n=26; 18%) and gynecological (n=24; 16%) (Figure 2). No differences in number and type of surgical procedures between VWD types were observed. Almost all patients received replacement therapy by bolus infusion (90%). Median duration of hospitalization was six days and did not differ between the different types of VWD (Table 1). Eleven (29%) and 52 (47%) patients with respectively a minor and major surgical procedure received thromboprophylaxis with low molecular weight heparin.

Actual VWF:Act and FVIII levels compared to predefined target levels

No differences were observed in achieved VWF:Act and FVIII:C levels between type 1, type 2 and type 3 VWD patients (Figure 3) after replacement therapy. In all VWD types, most perioperative VWF:Act and FVIII:C levels were well above predefined target levels. Postoperatively, accumulation of FVIII was observed after repetitive dosing of VWF/FVIII concentrates, resulting in increased FVIII:C in comparison to VWF:Act (p<0.01) (Figure 4). No differences in FVIII accumulation were observed between type 1 and type 2 VWD patients (data not shown). Thirteen (8%) FVIII:C trough levels were above 2.70 IUmL^{-1}.
In the 54 type 1 VWD patients, *in the first 36 hours* after surgery, median trough *VWF:Act* was 1.48 IUmL^{-1} (IQR 1.03-1.87). Eighty-four percent of trough and steady state levels were above predefined target level with a median deviation of 0.80 IUmL^{-1} (IQR 0.38-1.11). Seven levels were below target level (median deviation: 0.24 IUmL^{-1} [IQR 0.03-0.38]). All these patients underwent a major surgical procedure, and received an additional bolus infusion with VWF/FVIII concentrate to correct lower levels. With regard to *FVIII:C*, median trough and steady state was 1.46 IUmL^{-1} (IQR 1.14-1.82) in this time period. Ninety-two percent of measured levels were above predefined target level with

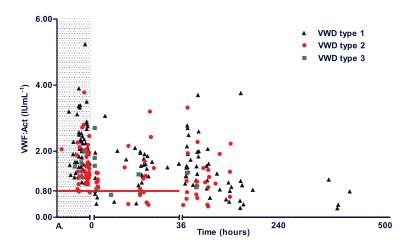**Table 1.** General characteristics of study population

	Total cohort	Type 1 VWD	Type 2 VWD	Type 3 VWD
	N (%) or median [IQR]			
Patient characteristics				
No. of patients	103 (100)	54 (100)	43 (100)	6 (100)
Female gender	69 (67)	38 (70)	27 (63)	4 (67)
Age (years)	51 [36-62]	52 [40-61]	53 [36-66]	22 [16-33]
Height (cm)	175 [167-180]	173 [166-179]	175 [165-183]	179 [168-180]
Body weight (kg)	77 [65-85]	79 [68-89]	75 [62-83]	74 [65.7-78.5]
Body mass index (kgm^{-2})	24.9 [22.7-28.1]	25.4 [23.6-29.1]	24.2 [21.7-25.7]	22.5 [21.2-26.2]
Blood group O	51 (50)	32 (59)	16 (37)	3 (50)
Baseline VWF/FVIII levels *				
Antigen (IUmL^{-1})	0.28 [0.21-0.38]	0.30 [0.22-0.38]	0.29 [0.22-0.39]	0.05 [0.01-0.06]
Activity (IUmL^{-1})	0.14 [0.10-0.25]	0.22 [0.13-0.30]	0.10 [0.05-0.15]	0.10 [0.04-0.10]#
FVIII:C (IUmL^{-1})	0.44 [0.28-0.60]	0.54 [0.34-0.69]	0.42 [0.24-0.57]	0.03 [0.02-0.08]
Surgical characteristics				
No. of surgical procedures	148 (100)	73 (100)	67 (100)	8 (100)
Total number of patients undergoing				
1 procedure	75 (73)	41 (76)	29 (67)	5 (83)
2 procedures	16 (15)	7 (13)	9 (21)	0 (0)
3 procedures	10 (10)	6 (11)	3 (7)	1 (17)
≥ 4 procedures	2 (2)	0 (0)	2 (5)	0 (0)
Severity of surgical procedure				
Minor	38 (26)	13 (18)	18 (27)	7 (88)
Major	110 (74)	60 (82)	49 (73)	1 (12)
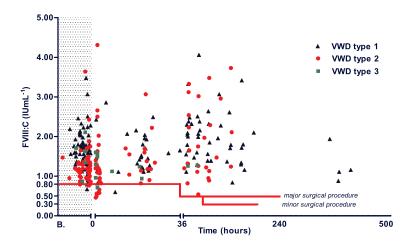
Table 1. General characteristics of study population (continued)

	Total cohort	Type 1 VWD	Type 2 VWD	Type 3 VWD
Treatment characteristics				
Duration hospitalization (days)	6 [4-8]	6 [4-8]	6 [3-9]	7 [3-8]
Type of infusion				
Bolus infusion	133 (90)	64 (88)	62 (93)	7 (88)
No. of complications				
Bleeding	20 (14)	12 (16)	8 (12)	0 (0)
Re-operation	1 (5)	0 (0)	1 (11)	0 (0)
Hemoglobin drop and/or RBCTF	19 (95)	12 (100)	7 (89)	0 (0)
Prolonged hospitalization	0 (0)	0 (0)	0 (0)	0 (0)
Thrombosis	0 (0)	0 (0)	0 (0)	0 (0)

*Historically lowest measured VWF/FVIII levels. #VWF:Act measurements were lower than the limit of detection 0.10 IUmL[-1] in a number of VWD type 3 patients. No.=number (percentages); Median [IQR=Inter quartile range 25-75%]; cm=centimeter; kg=kilogram; kgm[-2]=kilogram per square meter; VWF=von Willebrand factor; IUmL[-1]= international units per milliliter; RBCTF=red blood cell transfusion

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Figure 3. Achieved VWF:Act and FVIII:C levels in the perioperative period

The red lines indicate predefined target VWF:Act and FVIII:C according to National guidelines[17]. Preoperative peak VWF:Act and FVIII:C levels are shown < 0 hours. Postoperative trough and steady state VWF:Act and FVIII:C measurements are shown after surgery. Time of surgical procedure was defined as t=0 hours. A) Achieved VWF:Act and B) Achieved FVIII:C levels. No differences in achieved VWF:Act and FVIII:C are observed between types of VWD.
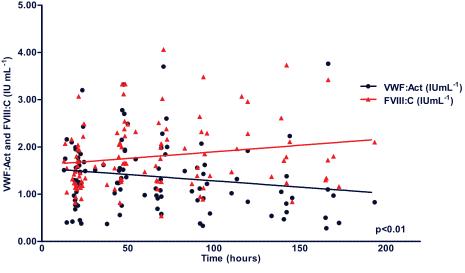
Figure 4. Accumulation of FVIII:C after repetitive dosing of VWF/FVIII concentrate*

Accumulation of FVIII was present after repetitive dosing of VWF/FVIII concentrates, resulting in increased FVIII:C in comparison to VWF:Act (p<0.01) (F=6.90 DFn=1, DFd=209); *Haemate P®

a median deviation of 0.70 IUmL^{-1} (IQR 0.43-1.07) above target level. Only five patients (9%) had a *FVIII:C* below the predefined target level. All were administered additional treatment: in four patients this consisted of VWF/FVIII concentrate, and in one patient of intravenous desmopressin. In the period *36 hours until 72 hours after surgery*, all trough and steady state *FVIII:C* levels were above FVIII target level (median FVIII:C 1.80 IUmL^{-1} [IQR 1.35-2.11]).

Overall, no differences in achieved VWF:Act and FVIII:C were observed for minor versus major surgical procedures, blood group non-O versus O, adults versus children and between modes of infusion (data not shown). Moreover, high VWF:Act and FVIII:C levels (defined as >0.20 IUmL^{-1} above target) were predominant as illustrated by the fact that 65% of trough and steady state VWF:Act levels and 91% of FVIII:C values were above target.

In the 43 type 2 and 6 type 3 VWD patients, 62% and 71% of trough *VWF:Act* levels were above predefined target level in the *first 36 hours after surgery* (not significantly different from type 1 VWD). Median *VWF:Act* in this period was 1.07 IUmL^{-1} [IQR 0.68-1.50] and 1.30 IUmL^{-1} [IQR 0.82-1.68], respectively. Eighty-six percent and 89% of trough *FVIII:C* were

above target in the first 36 hours with a median deviation of 0.40 IUmL^{-1} [IQR 0.26-0.85] and 0.47 IUmL^{-1} [IQR 0.28-0.71], respectively for type 2 and type 3 VWD patients. In addition, all *FVIII:C* were above target *after 36 hours* of hospitalization for both major and minor surgical procedures. High VWF:Act and FVIII:C (≥0.20 IUmL^{-1}) were present in 53% and 57% of VWF:Act and in 72% and 73% of FVIII:C for type 2 and type 3 VWD patients respectively.

Complications

Overall, occurrence of bleeding complications was not associated with a low trough VWF:Act and/or low FVIII:C (p=0.95 and 0.25 respectively). Exception was one patient, undergoing a craniotomy with excessive blood loss with need for blood cell transfusions and presenting with lower trough VWF:Act (0.40 IUmL^{-1}) and FVIII:C (0.60 IUmL^{-1}) levels (Table 2). Clinically relevant bleeding only occurred in 5 (3.4%) surgical procedures, as four surgical procedures required red blood cell transfusion postsurgery and only one a second surgical intervention (Table 2). Despite excessive FVIII:C levels, no thrombotic complications were reported.

Treatment

Two patients with VWD type 1 received desmopressin prior to surgery in order to achieve VWF:Act and FVIII:C target levels. After surgery, trough VWF:Act and FVIII:C were 0.56/0.55 and 0.59/0.48 IUmL^{-1}, respectively. Consequently, treating physician administered VWF/FVIII concentrate on following postoperative days.
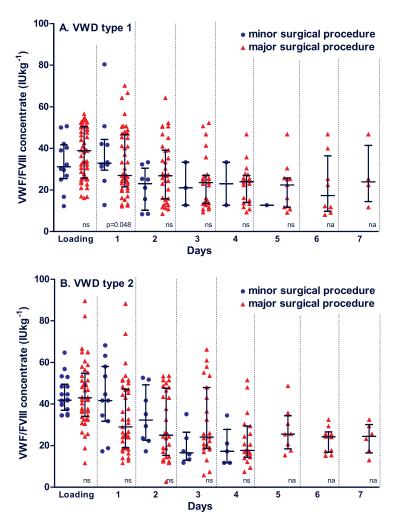
In VWD type 1 patients, median loading dose for minor and major surgical procedures did not differ as these were 32 IUkg^{-1} and 38 IUkg^{-1} respectively (Figure 5). Strikingly, maintenance dose on day 1 (0-24 hours) after surgery differed between minor and major procedures with a significantly higher dose in cases of minor surgery (33 IUkg^{-1} and 26 IUkg^{-1} respectively). Patients who underwent a minor procedure were generally treated with VWF/FVIII concentrate for a median of 48 hours. Median duration of hospitalization for patients undergoing a minor or major surgical procedure did not differ significantly (respectively 4 [IQR 4-8] versus 6 [IQR 4-8] days, p=0.88). Loading dose and maintenance doses did not differ between type 1 and type 2 VWD patients; median 36 IUkg^{-1} [IQR 27-49] and 43 IUkg^{-1} [IQR 37-52], p=0.12 for loading dose and median maintenance doses ranged from 22-27 IUkg^{-1} versus 21-35 IUkg^{-1}. No differences between minor and major surgical procedures were observed for loading and maintenance doses in type 2 VWD.

Table 2. Characteristics of VWD patients with a clinically relevant bleeding complication in the perioperative setting

Patient	VWD type	Age (years)	Surgical procedure	Complication (No.)	Day of complication	Hb drop (mmolL⁻¹)	Preoperative peak VWF:Act (IUmL⁻¹)	Preoperative peak FVIII (IUmL⁻¹)	Trough* VWF:Act (IUmL⁻¹)	Trough* FVIII:C (IUmL⁻¹)	Surgical blood loss (mL)	Other medication	Blood group
1	2	50	Cervical conization	Re-operation	Day 1	8.0 - 6.7	1.63	1.19	NA	NA	0	TXA	Non-O
2	1	14	Craniotomy	RBCTF (6)	Day 0	7.5 - 4.8	NA	3.07	0.40	0.60	2800	DDAVP	Non-O
3	1	46	Adrenalectomy	RBCTF (5)	Day 0	6.1 - 4.5	1.60	1.12	NA	NA	4000	Heparin	O
4	1	34	Aortic Valve replacement & resection aneurysm	RBCTF (3)	Day 0	7.4 - 4.3	NA	NA	1.84	1.14	0	TXA, DDAVP	Non-O
5	1	61	Total hip replacement	RBCTF (1)	Day 2	7.4 - 5.6	1.04	1.18	1.99	1.51	425	None	O

No.=number; mmolL⁻¹ = millimol per liter; IUmL⁻¹ =international units per milliliter; VWF:Act= VWF activity; FVIII:C = FVIII plasma level; RBCTF=red blood cell transfusion; NA=not applicable; TXA=tranexamic acid; DDAVP=desmopressin; *Trough VWF:Act and FVIII:C measurements at time of occurrence of the bleeding complication.

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Figure 5. Loading and maintenance doses in minor and major surgical procedures in type 1 and type 2 VWD patients

Loading and maintenance doses in minor and major surgical procedures are shown using a scatter dot plot with median and 5-95% quartile ranges for A. Type 1 and B. Type 2 VWD patients. The non-parametric Mann-Whitney U test was used to compare VWF/FVIII concentrate consumption between minor and major surgical procedures.

Predictors of low and high VWF:Act and FVIII:C levels

It was only possible to evaluate predictors in VWD type 1 and type 2 patients, due to a limited number of type 3 patients. This was performed for both VWF:Act and FVIII:C by both stepwise backward logistic regression analysis as well as stepwise forward logistic regression analysis. In type 1 VWD, in the total postoperative period, only blood group O was predictive of high VWF:Act levels (VWF:Act levels ≥0.20 IUmL^{-1} above target) (OR 2.9; 95%CI [1.3-6.6]); not for FVIII:C. No other predictors were found for low and high VWF:Act and FVIII:C levels in both type 1 and type 2 VWD patients.

DISCUSSION

This study is the largest so far evaluating perioperative management of VWD patients in a resource rich country. We present data that underline the complexity of VWF/FVIII concentrate dosing in this patient population, as illustrated by the fact that in type 1 VWD patients, 65% of trough and steady state VWF:Act and 91% of FVIII:C levels were ≥0.20 IUmL^{-1} above predefined target levels. In type 2 and type 3 VWD respectively 53% and 57% for VWF:Act and 72% and 73% for FVIII:C were ≥0.20 IUmL^{-1} above predefined target levels. In contrast to results in perioperative severe and moderate hemophilia A patients[25], only a small percentage of type 1 VWD patients experienced low levels in the first 36 hours after surgery, as only 16% of VWF:Act levels and only 8% of FVIII:C levels were under prescribed target level. This is probably due to FVIII:C-based dosing per-formed according to National guidelines applied in this study. Although both VWF:Act and FVIII:C were measured perioperatively, VWF:Act was not directly available in most cases and could not be used to monitor perioperative VWF/FVIII concentrate manage-ment. In our cohort, prevalence of clinically relevant bleeding complications was low (3.4%) and not associated with achieved VWF:Act and/or FVIII:C. This is supported by others[8, 12, 14, 15, 26] and confirms that other causal factors for bleeding than VWF:Act and FVIII:C, either hemostatic or surgical must be involved. In this study, no predictors of bleeding could be identified. Strikingly, blood group O was predictive of high VWF:Act levels (≥0.20 IUmL^{-1} above target) in type 1 VWD in the total postoperative period. Most probably this is explained by lower endogenous baseline VWF:Act and FVIII:C levels resulting in administration of higher dosages of VWF/FVIII concentrates.

Analyses were performed for the total VWD population as well as separately for each type of VWD, as it has been shown that clearance mechanisms of the endogenous VWF differ between VWD types.[2, 6] However, no differences were found in achieved VWF:Act and FVIII:C after preoperative loading and subsequent maintenance doses between type 1 and type 2 VWD. Also, VWF/FVIII consumption did not differ between types of VWD. Strikingly, on day 1 (0-24 hours) after surgery, a significantly higher VWF/FVIII concentrate consumption was observed for minor surgical procedure when compared to major surgical procedures. This is probably explained by the fact that patients undergoing a minor surgical procedure received less frequent but higher dosed bolus infusions within a shorter period of time. This finding is supported by a previous study in 29 VWD patients of types, in which no differences in consumption between patients undergoing minor or major surgical procedures was observed.[12]

In this perioperative study, accumulation of FVIII:C was observed after repetitive dosing of VWF/FVIII concentrates with median FVIII:C values increasing with time (Figure 4). Increasing FVIII:C levels, due to concomitant increase of both endogenous and exogenous FVIII, were significantly higher than VWF:Act levels (p<0.01). This may be partly explained by findings by Kahlon et al.[27] who observed an intraoperative decrease and postoperative increase of VWF and FVIII levels in 30 individuals without a bleeding disorder undergoing surgery. In these healthy individuals, mean VWF:Act and FVIII:C levels were greater than 1.00 IUmL^{-1} at all intra- and postoperative time points. This physiological response to surgery may reflect an increased need of VWF in the perioperative period. Current guidelines are not in line with these physiological responses to surgery, as perioperative target VWF:Act and FVIII:C levels are >0.80 IUmL^{-1} (0-36 hours postoperatively) and >0.30/0.50 IUmL^{-1} (36-240 postoperatively) and thus below 1.00 IUmL^{-1}. Although we observed high FVIII:C levels that confer a risk for thrombosis[28-30], no thrombo-embolic complications were observed. Previously Wells et al. demonstrated that FVIII:C levels above 2.70 IUmL^{-1} are associated with a higher risk of thrombosis in non-surgical patients.[31] In our study, 8% of trough levels of FVIII:C were above 2.70 IUmL^{-1}. Also, observed postoperative VWF:Act and FVIII:C levels were increased for only a brief period of time and coincide with physiological levels in healthy individuals without a bleeding disorder.[27] Mannucci et al. also reported this scarcity of thrombosis in perioperative VWD patients on replacement therapy.[28] In our study, it must also be taken into

account that almost half of patients undergoing a major surgical procedure received thromboprophylaxis with low molecular weight heparin.

As reported, plasma derived VWF/FVIII concentrate in this study (Haemate P ®), has a VWF:Act/FVIII:C ratio of 2.4:1 and contains large amounts of HMWM. Earlier, in vivo recovery (IVR) studies have demonstrated a median IVR of 2.0 for VWF:Act and 2.0 for FVIII:C, implying a rise of 0.02 IUmL^{-1} in VWF:Act and FVIII:C for each infused IUkg^{-1} for VWF:Act or FVIII:C. Theoretically, for each infused IUkg^{-1} of FVIII:C an increase of approximately 0.05 IUmL^{-1} VWF:Act will be observed (2.4*0.02 IUmL^{-1}). Currently, it is common practice to apply IVR to dose and monitor replacement therapy.[12, 14] However, dosing based on body weight and IVR does not take interindividual differences in clearance and volume of distribution into account that are associated with half-life of VWF/FVIII concentrates. Individualized perioperative dosing based on IVR deducted from a preoperative PK profile is not possible, as PK profile is not representative for clearance during surgery as shown by Di Paola et al.[11] In this study, only a weak correlation was shown between IVR values of VWF:Act obtained 1 week prior to surgery and IVR values obtained directly after surgery (n=41; r=0.41).[11] Both the changes of IVR following surgery and differences in half-life between VWD types demonstrate the complexity and importance of development of alternative dosing algorithms to individualize treatment for each VWD patient. Hypothetically, VWD population PK models will be able to incorporate these differences between VWD types due to: mutational variation, differences in baseline values of endogenous VWF:Act and FVIII:C, higher FVIII:C levels with a longer half-life[32], differences in clearance of endogenous and exogenous VWF:Ag and VWF:Act, and differences in composition of administered VWF/FVIII concentrates. Also, other known and unknown modifying factors that influence clearance and volume of distribution in an on demand-, perioperative setting can be incorporated. The development of such models will lead to Bayesian adaptive dosing to predict VWF:Act/FVIII:C and effects of treatment more precisely. In the long run, we believe such an approach will optimize patient care and minimize overdosing and potentially reduce overall costs of treatment.[12, 28, 33-35] Therefore, PK-guided dosing forms a promising approach for more efficient and individualized replacement therapy in VWD with considerable clinical and economic impact due to the frequency of this bleeding disorder.

In conclusion, although perioperative replacement therapy in VWD patients is successful with few bleeding complications, it can be optimized as patients are currently over

treated with accumulation of FVIII:C levels, fortunately without thrombotic complications. The complexity of treatment in VWD, makes population PK models which incorporate known and unknown modifying factors of clearance and other PK parameters of VWF/FVIII concentrates into account, a promising tool to individualize replacement therapy in all VWD patients.
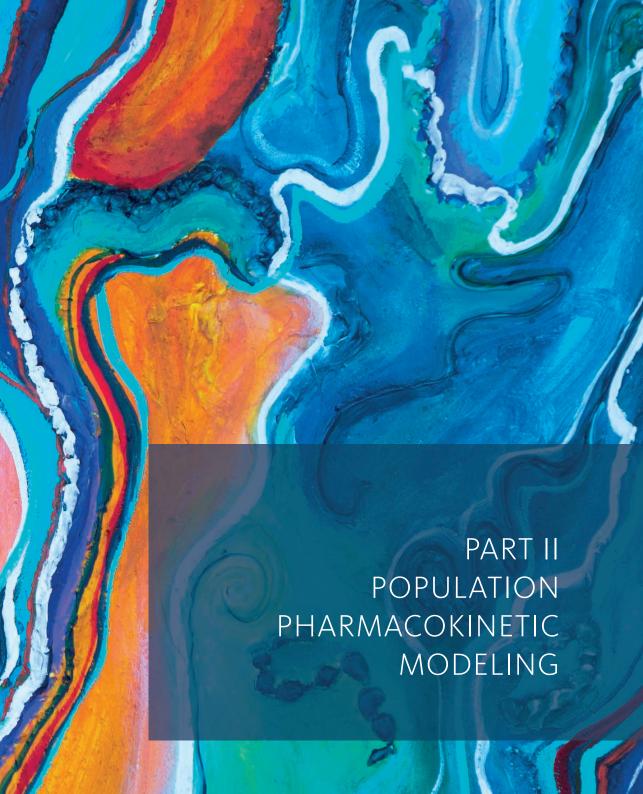
ACKNOWLEGDMENTS

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PART II
POPULATION
PHARMACOKINETIC
MODELING

Chapter 5

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

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SUMMARY

Background The role of pharmacokinetic-guided dosing of factor concentrates in hemophilia is currently subject of debate and focuses on long-term prophylactic treatment. Few data are available on its impact in the perioperative period.

Objective 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.

Methods Retrospective data was collected on FVIII treatment, including timing and dosing, time point FVIII sampling and all achieved FVIII plasma concentrations (trough, peak and steady state), brand of concentrate, as well as patient and surgical characteristics. Population pharmacokinetic modeling was performed using nonlinear mixed-effects modeling.

Results 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 0.15L/h/68 kg, 0.16L/h/68 kg, 2.81L/68 kg and 1.90L/68 kg. Inter-patient variability in clearance and central volume was 37% and 27%. Clearance decreased with increasing age (p<0.01) and increased in case of 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).

Conclusion The developed population model describes the perioperative pharmacokinetic of various FVIII concentrates, allowing individualization of perioperative FVIII therapy for severe and moderate hemophilia A patients by Bayesian adaptive dosing.

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 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 updated by combining PK information (e.g. dose, concentration, time) from the individual patient with a priori PK information (e.g. average clearance, variability) from the population. The latter does not currently exist and has therefore never been performed.

In order to construct such a perioperative population PK model facilitating 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 and data collection

Severe and moderate hemophilia A patients of all ages with FVIII plasma concentration <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], and 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 >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), patient and surgical characteristics, and concomitant medication with a possible effect on hemostasis (i.e. tranexamic acid, heparin, desmopressin and nonsteroidal anti-inflammatory drugs). Patient characteristics included: 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 bleed-ing 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 ac-cording 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 Medical Research Involving Human Subjects Act, as patient data were analysed anonymously. Moreover, the study was approved by all local Medical Ethics Committees; one center requiring 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 pharmacokinetics (PK) is defined as the study of sources of variability in drug concentrations after dosing that occurs within and between patients.[20] In the present population analysis, all plasma concentration time points were analyzed simultaneously using non-linear mixed-effects modelling software (NONMEM (version 7.2.0), Globomax LLC, Ellicott City, Maryland, USA).[21] All PK related abbreviations and terminology are described in supplementary Table 1. More specifically, first-order conditional estimation (FOCE) method with interaction was applied, allowing interaction between structural and residual variance components. The statistical package R, version 2.14.2 (The R Foun-dation for Statistical Computing) and Xpose version 4[22] were used for data set checkout, 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 χ2 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-values of 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 compart-ment (V1), intercompartment 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:

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

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

In this expression, CL_i and V_i are the typical clearance and central volume of distribution for an individual i with body weight BW_i θ_{CL} and θ_{V1} are the respective parameter values for a subject with a body weight of 68 kilogram.
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 sym-metrically 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 patient and surgical 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-values <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]
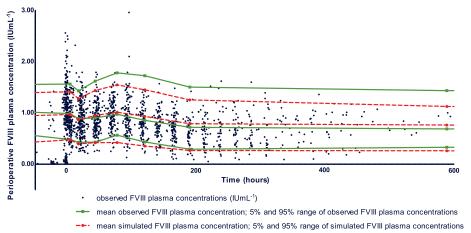
RESULTS

Patients and treatment in the perioperative setting

Our cohort consisted of 119 hemophilia A patients 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 preoperative bolus infusion of approximately 50 IUkg^{-1} followed by a treatment scheme with either bolus infusions or continuous infusion therapy based on a clearance rate of 3-4ml 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 three percent 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).

Figure 1. Perioperative FVIII plasma concentrations and visual predictive check for observed FVIII plasma concentrations

- observed FVIII plasma concentrations (IUmL^{-1})
- mean observed FVIII plasma concentration; 5% and 95% range of observed FVIII plasma concentrations
- mean simulated FVIII plasma concentration; 5% and 95% range of simulated FVIII plasma concentrations
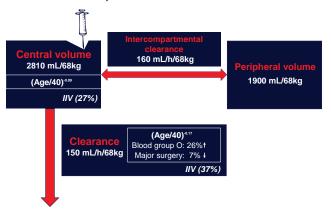
Perioperative FVIII plasma concentrations consists of trough, peak and steady state concentrations for both modes of therapy (continuous infusion and bolus infusion therapy); Visual predictive check for the observed FVIII plasma concentrations, given the final model; observed FVIII plasma concentrations and mean, 5th percentile and 95th percentile observed and simulated FVIII plasma concentrations.

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 >40%.[25] Although this may suggest that inter-patient variability in Q and V2 is absent, this is due to the fact that available data was not informative enough. The IIV for CL and V1 were respectively 45% and 29%, underlining the importance of individualization of therapy. Estimation of IOV on CL and V1 resulted in high shrinkage values for both parameters (respective value 34% and 46%); consequently IOV was not included in the model. Inclusion of individual endogenous baseline FVIII plasma concentrations and inclusion of a structural under prediction of plasma concentrations using a B-domain deleted product improved the model. A proportional under prediction of 0.34 (34%) in FVIII plasma concentration was estimated for this product. The residual error was described using a combined error model.

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 2. Population characteristics

	Total cohort	Adults	Children
	No. (%); or Median [minimum; maximum]		
Patient characteristics			
No. 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			
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 no. of surgical procedures	198	140	58
No. 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)

Table 2. Population characteristics (continued)

	Total cohort		Adults		Children	
	No. (%); or Median [minimum; maximum]					
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						
No. 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)

No.=number; %= percentages; kg=kilogram; FVIII=coagulation factor VIII; IUmL^{-1}=international units per milliliter; BU=Bethesda Units; VWF=von Willebrand factor; gL^{-1}= gram per liter; *Blood group known of 101 patients

5

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 compartment 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

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

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						
θ1 - Clearance (CL; mL/h/68 kg)	190	(5)	150	(8)	160	(5)
θ2 - Volume of central compartment (V1; mL/68 kg)	3030	(3)	2810	(4)	2810	(3)
θ3 - Inter-compartmental clearance (Q; mL/h/68kg)	170	(17)	160	(20)	170	(15)
θ4 - 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						
θ5 - CL – Age (change with increasing age)			-0.17	(22)	-0.16	(13)
θ6 - CL – Blood group O (% difference)			26	(7)	27	(22)
Θ7 - CL – Major surgical procedure (% difference)			-7	(6)	-7	(34)
Θ8 - 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						
Additive residual error (SD; IUmL^{-1})						
Center 1,2,3			0.15	(12)	0.14	(9)
Center 4,5			0.05	(28)	0.05	(20)
Proportional residual error (% CV)						
Center 1,2,3			0.18	(15)	0.18	(9)
Center 4,5			0.23	(9)	0.23	(7)

RSE indicates relative standard error; and CV coefficient of variation

changes in clearance during the perioperative period; no differences were observed however. 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.

Table 5. Model equations describing the perioperative population PK model

CL	$CL\ (\frac{mL}{h}) = 150 \times (\frac{Body\ weight}{68})^{0.75} \times (\frac{Age}{40})^{-0.17} \times 1.26^{Blood\ group}$ $\times 0.93^{Severity\ of\ surgical\ procedure}$
V1	$V1\ (mL) = 2810 \times (\frac{Body\ weight}{68}) \times (\frac{Age}{40})^{-0.09}$
Q	$Q\ (mL/h) = 160 \times (\frac{Body\ weight}{68})^{0.75}$
V2	$V2\ (mL) = 1900 \times (\frac{Body\ weight}{68})$

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
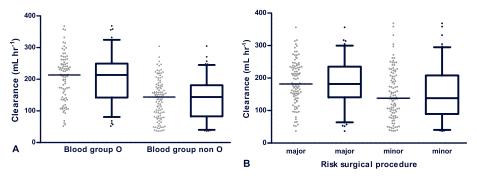
According to the equation, clearance was 214, 169, 150 and 142 ml/h/68 kg for a typical patient (with blood group non-O undergoing a minor surgical procedure) with an age of 5, 20, 40 and 55 years, respectively. In case of a major surgical procedure, a small decrease in CL was observed of 7% (Table 4). 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 -2 to +2 range 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 predictive check was conducted by 1000 simulations based on the final model as shown in Figure 1. It con-
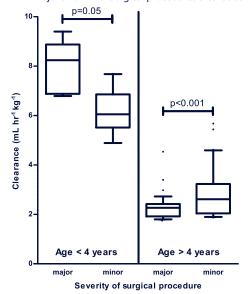
Figure 3. Graphical visualization of variability of the clearance and covariates

Visualization of variability of the clearance; a. as a function of blood group O versus blood group non O; b. as a function of risk of surgical procedure.

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.
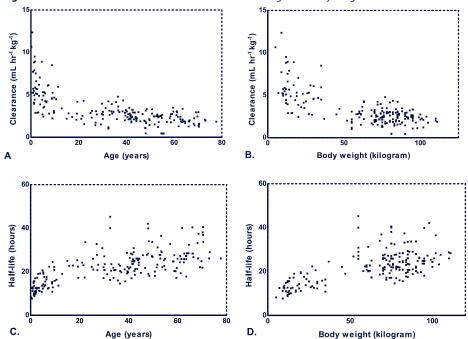
Figure 5. Clearance and elimination half-life as functions of age and body weight

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.

firmed, adequateness of the model, as seven percent of the measured concentrations were calculated above the 95th percentile of the simulated concentrations and nine percent 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 currently used FVIII concentrates. These factor VIII concentrates were in majority
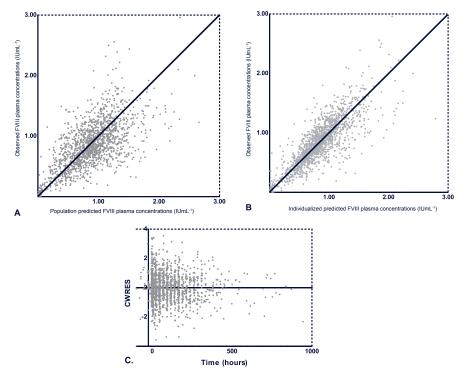
Figure 6. Observed and model-predicted FVIII plasma concentrations

NONMEM 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

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. Earlier, only a few studies have reported application of PK-guided dosing during the perioperative period. Unfortunately, in all studies only the FVIII loading dose was based on an individual PK-profile derived several days before surgery.[30-35] Iterative perioperative FVIII dosing-adjustments after first loading dose could not be performed as a population PK model was lacking. The perioperative population PK model presented, will now make Bayesian adaptive dosing in this setting possible. Moreover, it will take all important patient characteristics associated with clearance in the surgical setting into account.

The presented model consists of a two-compartment model with allometric scaling of the PK parameters for 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 risk 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 following sections. Although it should be underlined that this population PK model is 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.

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 continuous 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 as 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, to be able 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 under prediction of perioperative FVIII concentrations <1.00 IUmL^{-1} as well as an overprediction of FVIII concentrations >1.00 IUmL^{-1}. In other words, actual FVIII plasma concentrations were higher and respectively lower than predicted by prophylactic population PK model (data not shown). Therefore, it was concluded that prophylactic population PK models cannot 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 been applied earlier.[12] CL, V1 and Q were actually in accordance when a comparison was made between perioperative and prophylactic PK population model (CL: 150 versus 222 mL/hr/68 kg; V1: 2810 versus 3520 mL/68 kg; and Q: 160 versus 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 (respectively 4 hours and 25 hours versus 0.6 hours and 12 hours). These calculated half-lifes 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 (respectively 9.6 and 17.8 hours) 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 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] Additionally, 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 Bjorkman et al.[12] However, we are not informed if VWF levels were available for those analyses. Contrastingly, higher VWF levels may also help explain the unexpected overall lower clearance found in patients undergoing major surgical procedures. In the ongoing prospective randomized controlled "OPTI-CLOT" trial (RCT), which is described in more detail elsewhere[45], insight will be gained into the pathophysiology of VWF in hemophilia patients during the perioperative setting and the relationship between VWF levels and estimates of FVIII PK parameters, among others. These data will further validate the now presented

perioperative PK population model, refining its applicability and further defining the influence of possible modifying factors of PK parameters. Moreover, extension of this population PK model, in combination with extended half-life (EHL) products in the near future, could be of great value. However, firstly, studies are needed to extensively document 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 information 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 patient characteristics known to influence clearance and other PK parameters, but also currently unidentified patient 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 achieved FVIII plasma concentrations. Incorporation of the patient's 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 with experience with this methodology and iteratively updated, leading to calculated dose adjustments. Currently, we are 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 a decrease of underdosing and overdosing, and therefore both a decrease of bleeding risk and an expected overall reduction of factor concentrate consumption with concomitant cost reduction.

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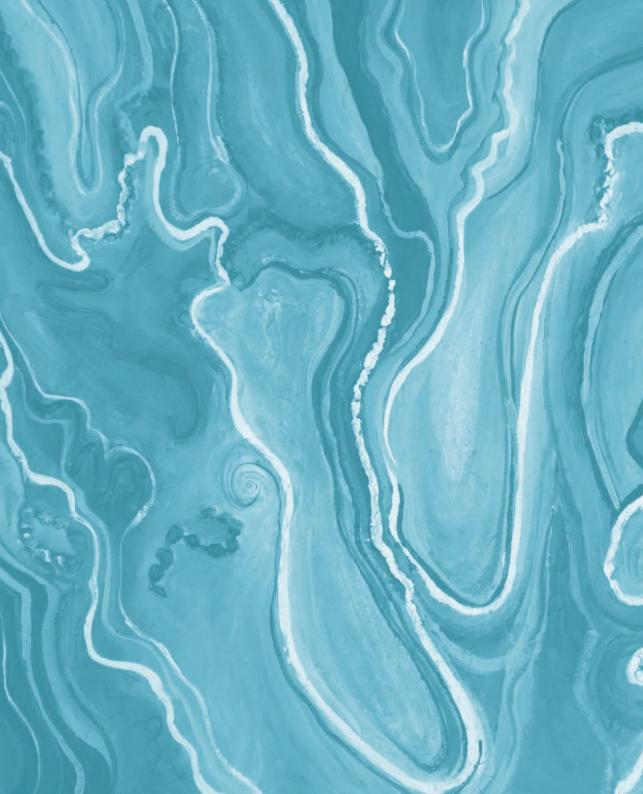
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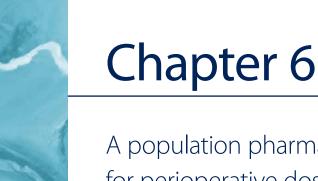30. Batorova A, Martinowitz U. Continuous infusion of coagulation factors. Haemophilia. 2002;8:170-7.

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Supplemental Table

Supplementary Table 1. Terminology and definitions used to develop population PK models

Terminology	Definitions
NONMEM®	Non-linear mixed-effects modelling software to construct a population analysis, where all plasma concentration time points are analyzed simultaneously
OFV	Objective function value; a measurement of goodness of fit of the model. OFV is proportional to minus two times the logarithm of the likelihood (-2log likelihood) of the data
PK parameters	Pharmacokinetic parameters (e.g. CL, V1, Q, V2)
CL	Clearance
V1	Volume of distribution of the central compartment
Q	Intercompartment clearance
V2	Volume of distribution of the peripheral compartment
Allometric scaling	PK parameters are allometrically scaled to account for the wide range of body weights of both adults and pediatric patients
IIV	Inter-individual variability; variability between patients
IOV	Inter-occasion variability; variability within patients

Chapter 6

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

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SUMMARY

Background Hemophilia B is an X-linked bleeding disorder characterized by a deficiency of coagulation factor IX (FIX). In the perioperative setting, patients receive replacement therapy with factor concentrate to normalize FIX activity levels (FIX) according to physiological levels. Due to high inter-patient pharmacokinetic (PK) variability, PK-guided dosing can be used to individualize dosing of FIX.

Objective In this study, we aimed to construct a population PK model to describe FIX and inter-patient variability in the perioperative period, during FIX replacement therapy.

Methods Retrospective data of 118 patients (age/weight: median plus range) undergoing 255 surgical procedures was available from ten hemophilia treatment centers in the Netherlands and the United Kingdom. Average PK parameters and their variability were estimated using nonlinear mixed effect modeling in NONMEM. Relationships between patient characteristics and PK parameters were evaluated to explain variability.

Results FIX versus time profiles were adequately described using a three-compartment model Average clearance (CL), inter-compartmental clearance (Q2, Q3), distribution volume of the central compartment (V1) and peripheral compartments (V2, V3), plus inter-patient variability (%) were: CL: 251 $mLh^{-1}70kg^{-1}$ (13%), V1: 4950 $mL70kg^{-1}$ (13%), Q2: 91.3 $mLh^{-1}70kg^{-1}$ (99%), V2: 7900 $mL70kg^{-1}$ (57%), Q3: 831 $mLh^{-1}70kg^{-1}$, V3: 1600 $mL70kg^{-1}$. With increasing age, CL and V1 increased 1.2% and 1.9% per year, respectively, until the age of 32 years ($p<0.001$, $p<0.01$). Compared to patients treated in the United Kingdom, CL and V1 were 20.1% and 28.3% higher ($p<0.01$, $p<0.01$) than in patients treated in the Netherlands. Furthermore, a 9.8% decrease for V1 was associated with the use of tranexamic acid during a surgical procedure.

Conclusion Measured perioperative FIX were described adequately by the established population PK model. The estimated population PK parameters were significantly different from those reported for prophylactic treatment. The present population PK analysis will be continued to develop a model that can be used prospectively to perform PK-guided dosing of FIX concentrates during surgery.

INTRODUCTION

Hemophilia B is an X-linked bleeding disorder characterized by a deficiency of coagulation factor IX (FIX). Severity is categorized according to a patient's endogenous FIX coagulant activity level (FIX). Severe, moderate-severe and mild patients have an endogenous FIX of <0.01 IUmL^{-1}, 0.01 to 0.05 IUmL^{-1} and >0.05 IUmL^{-1}, respectively.[1] Treatment consists of replacement therapy with plasma-derived or recombinant FIX concentrates.[2, 3] These are administered 'on demand', in case of an acute bleed, or prophylactically, in patients with a severe bleeding phenotype, to prevent spontaneous joint bleedings. Prophylaxis is aimed at increasing trough FIX >0.01 IUmL^{-1}[4], as moderate severe patients have significantly less spontaneous bleeds than severely affected patients. However, to ensure hemostasis during a surgical procedure, trough FIX are prescribed which range from 0.30 to 1.00 IUmL^{-1}.[5]

Current guidelines specify FIX dosing according to body weight for prophylaxis, "on demand" treatment and in the perioperative setting. However, due to a heterogeneous treatment response and inter-patient variability in pharmacokinetics (PK), these doses are generally tailored to an individual's need based on measured FIX levels. In situations of high risk of bleeding, monitoring is applied to ensure appropriate FIX. Fortunately, PK of plasma-derived FIX (pdFIX) and recombinant FIX (rFIX) is well documented.[6, 7] Several population PK models, describing the PK of FIX concentrates for a cohort of patients rather than individual patients, have been reported.[4, 8-10] So far, however, these models have all been constructed using data collected during prophylactic dosing of FIX. During the perioperative setting, it is suspected that the PK of FIX may be altered due to hemostatic challenges and consumption or loss of FIX.

In a retrospective study, Hazendonk et al.[11] reported that 60% of hemophilia B patients have a FIX below specified target range during the first 24 hours of the surgical procedure. Subsequently, six days after surgery 59% the of the patients have a FIX above the specified target range. In this study, it was suggested that dosing of FIX during surgery may be individualized by PK guidance of dosing. Using a Bayesian technique, PK of an individual patient can be calculated iteratively, as subsequent FIX are collected.[12, 13] This Bayesian approach allows calculation of individual PK parameters by using a population PK model which also takes patient's achieved plasma concentration after an administered dose into account. By means of PK-guided dosing, target attainment can be opti-

mized and bleeding risk, due to low inappropriate dosing, can be prevented. To date, no studies have been reported describing PK-guided dosing of FIX in hemophilia B patients undergoing elective surgical procedures.

In this study, we aimed to develop a population PK model describing perioperative FIX concentrations in hemophilia B patients using detailed retrospective perioperative FIX dosing data.[11]

METHODS

Patients and data

A multicenter observational cohort study was performed in which retrospective data was collected from 118 severe and moderate (defined as baseline FIX <0.05 IUmL^{-1}) hemophilia B patients from five Hemophilia Treatment Centers in the Netherlands and five Hemophilia Treatment Centers in the United Kingdom. Patients of all ages, who had undergone a minor or major elective surgical procedure, were included. Details of the study have been reported previously.[11]

Clotting factor IX products

To ensure hemostasis during the surgical procedure, patients received replacement therapy with FIX concentrates. The following plasma-derived FIX products [AlphaNine® SD (Grifols Biologicals Inc., Los Angeles, USA), Replenine® (Bio Products Laboratory, Hertfordshire, UK), Haemonine® (Biotest Pharma GmbH, Dreierich, Germany), Mononine® (CSL Behring GmbH, Marbourg, Germany), Nonafact® (Sanquin, Amsterdam, the Netherlands)] and the following recombinant FIX products [BeneFix® (Pfizer Wyeth Pharmaceuticals Inc., Kent, UK) and IXinity® (Aptevo BioTherapeutics LLC, Berwyn, US)] were administered.

Pharmacokinetic modeling

In population PK modeling, PK is assessed in a cohort of patients rather than in an individual patient.[14] In the development of a population model, typical (average) PK parameter values and their intra- and inter-patient variability are estimated in combina-

tion with residual variability. After this process, it is evaluated to what extent covariates explain these different kinds of variability.

In this study, a perioperative FIX population PK model was built by means of nonlinear mixed-effects modeling.[15] Perioperative FIX dosing and FIX measurement data was analyzed simultaneously using NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD, USA).[16] First-order conditional estimation (FOCE), in which the first-order Taylor expansion of the PK model is used, was applied to obtain all model parameter estimates. For PK parameters estimation, a transform-both-sides approach was used. Hereby, the FIX measurements from the data as well as the model predicted FIX are both logarithmically transformed.

PsN version 4.6.0 was used to aid model development and Pirana served as a model management tool. Data modification and model diagnostics were performed using R version 3.2.2 (R Development Core Team, 2015) with software-package Xpose version 4.5.3.[17-19]

To evaluate the ability of the established models to describe the data, diagnostic evaluation was performed using the obtained precision of the estimated model parameters, goodness-of-fit plots, condition number and visual predictive checks (VPC).[20, 21] In the latter method, simulated concentrations from the established model are compared to the actual obtained plasma concentrations.

An objective function value (OFV), which depicts the fitting ability of the model, was calculated by minus two times the logarithm of the likelihood (-2LL) of the model to describe the data. To discriminate between hierarchical models, the difference of the OFVs (dOFV) was calculated. This value is known to be described by a c^2 distribution, in which the degrees of freedom (df) are calculated by the difference in the number of parameters between the evaluated (nested) models. Therefore, a dOFV of >3.84, >5.99 and >7.81 corresponds to 1, 2, and 3 df, respectively, associated to an p-value of <0.05.

Structural model development

In literature, the population PK of FIX is mostly described by a three-compartment model.[4, 8, 9, 22] In our study, however, it was uncertain whether the data would allow to estimate all parameters for a three-compartment model with adequate precision, since the precision of these estimates is determined by the timing of blood sampling. Therefore, development of the model was initiated by fitting a two-compartment model to the

data. Subsequently, it was evaluated if addition of an extra compartment to the model would improve the fit. Hereby, model building was performed in a stepwise manner.

For a two-compartment model, estimated PK parameters were clearance from the central compartment (CL), inter-compartmental clearance (Q2), and volume of the central compartment (V1) and second peripheral compartment (V2). For a three-compartment model, inter-compartmental clearance between the central and the third peripheral compartment (Q3) and volume of the third peripheral compartment (V3) were added to the model. Inter-individual variability (IIV) was estimated using an exponential model (see equation 1 below). Furthermore, different residual error models were evaluated, including an additive, proportional and combined (additive and proportional) error model. In case a proportional or combined error model was applied to the model, interaction between residual and IIV was allowed for the FOCE method.

First, a structural model was developed, consisting of estimated population PK parameters, for which interpatient variability can be estimated as well, and residual variability. Because various patients underwent more than one surgical procedure, inter-occasion (between-surgery) variability (IOV) of the PK parameters was also estimated. An exponential model was used to estimate IIV and IOV, as described by the following equation:

$(1)\ \theta_{ik} = \theta_{TV}\ x\ exp^{\eta}{}_{i} + \kappa_{ik}$

in this expression, the subscripts i and k denote the number of the individual and occasion, respectively, θ_{TV} is the estimated typical (average) value for a population PK parameter, θ_{ik} is the estimated individual PK parameter, and η and κ are the random effects accounting for IIV and IOV, respectively. Both random effects describe individual deviation from the typical value and are assumed to follow a Gaussian distribution with a mean of zero and an estimated variance of ω^2 and π^2, respectively. In case dosing information was missing before the first FIX measurement, all model-compartments were initialized using this value. This would allow all model parameters to describe the disposition from this time-point onwards, instead of using only the terminal elimination half-life to correct for pre-dose measurements.[23]

PK parameters were allometrically scaled *a priori* (i.e. no evaluation of scaling performance was conducted) using body weight, which is described by the following equation:

$(2)\qquad \theta_{TV} = \theta_i\ x\ (\frac{BW}{70})^{\theta_p}$

in which θ_i is a population PK parameter, θ_{TV} is the typical value for this parameter, BW is body weight and θ_p is the allometric exponent. Allometric exponents were fixed to 1 in case of a volume parameter (V1, V2, V3) and to 0.75 for all clearance parameters (CL, Q2, Q3). A median body weight of 70 kg was used to describe the PK parameter typical values.

For every patient age was known at each surgical procedure. However, body weight was missing in 40 surgical procedures (16%). Therefore, we developed a linear model in NONMEM to impute body weight using age as a predictor. First, by graphical exploration of distribution of age and body weight a piecewise linear model was selected to predict the missing values. The following equation was used to impute missing body weight:

$$(3) \qquad \theta_{BW} = \beta_1 + \beta_2 xAGE + \beta_3 x(AGE - \beta_4) \, x \, \beta_5 \left\{ \begin{array}{l} AGE \leq \beta_4 : \beta_5 = 0 \\ AGE > \beta_4 : \beta_5 = 1 \end{array} \right.$$

in which θ_{BW} is the imputed body weight, β_1 is the estimated y-intercept of the linear model, β_2 the estimated coefficient of the predictor age for all ages, β_3 the estimated coefficient for the predictor age after the inflexion point estimated using β_4. Since β_3 only describes body weight after this inflexion point, β_5 is 0 below this age and 1 in other cases.

Covariate analysis

After the final structural model was established, relationships between covariates and PK parameters were evaluated. Based on clinical relevance, graphical evaluation and covariate correlations a pre-selection on eligible relations was conducted. These relations were evaluated on their ability to explain the IIV of the PK parameters or residual variability. A stepwise covariate modeling (SCM) procedure from PsN was applied to evaluate pre-selected covariate relationships to the model parameters.[24] In this procedure, the covariate relations are evaluated using a forward inclusion step, in which all eligible covariate relations are tested using a univariate analysis. After this step, the covariate relation with the lowest p-value (minimum of 0.05) is included in the (new) model in the consecutive step. This procedure is performed until all significant covariate relations are included. Likewise, the backward elimination evaluates if the covariate relations, included by the final forward step, retain in the model using a more conservative p-value of 0.01.

Final model evaluation

In the final model, all covariate relations are included. By means of a bootstrap-analysis, the robustness of the final model in terms of stability and estimation performance is evaluated.[25] In the bootstrap-analysis, 1000 bootstrap data sets are created from the original data set in which the data from all patients are randomly sampled using permutation with replacement. From this procedure, standard errors can be calculated amongst all obtained estimates from all bootstrap datasets. These standard errors depict the influence of the input data on the obtained model parameter estimates.
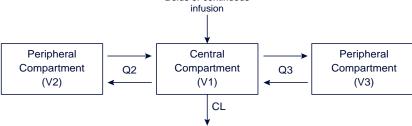
RESULTS

Patients and data

In total, 118 severe and moderate-severe hemophilia B patients were included in the cohort undergoing 255 surgical procedures. Surgical and patient characteristics are shown in Table 1.

Body weight was not recorded in 16% of all occasions. Therefore, a piecewise linear model was developed, from which body weight could be calculated using age. Parameter estimates for the piecewise linear model, describing the relationship between age and body weight, are shown in Supplementary Table 1. The relationship between age and body weight is shown in Supplementary Figure 1; the line depicts the predictions from the model used to calculate values for missing body weight.

Pharmacokinetic modeling

A three-compartment population PK model provided a better fit to the data than a two-compartment model, according to the drop in OFV (Table 2). In Figure 1, a general presentation of a three-compartment model is shown. NONMEM subroutine ADVAN11 with TRANS4 was applied, comprising estimates for CL, V1, Q2, V2, Q3 and V3. Model building was conducted using a stepwise approach and models were evaluated separately for their ability to describe the data. In Table 2, the decrease in OFV is shown for several building steps. The individual residual endogenous FIX were obtained from the patient's chart and were subtracted from each observed FIX.

Figure 1. Depiction of a three-compartment population PK model

Intravenous doses of clotting factor are administered into the central compartment. From this compartment disposition occurs to the other compartments. In the pharmacokinetic model, FIX:C represents the plasma levels of FIX in the central compartment (V1). CL: clearance from central compartment; Q2: inter-compartmental clearance between central en second compartment; V2: distribution volume of second (peripheral) compartment; Q3: inter-compartmental clearance between central en third compartment; V3: distribution volume of third (peripheral) compartment.

In the structural model, the typical PK parameters were allometrically scaled *a priori*. All PK parameters were scaled to a body weight of 70 kg and were estimated with high precision (<25% relative standard error). In comparison with an additive residual error model, application of a proportional residual error or combined residual error model did not improve the fit of the structural model to the data.

In the final base model, inter-patient variability for CL, V1, V2 and Q2 could be estimated, as shown in Table 2. Furthermore, covariance between inter-patient and inter-occasion variability was evaluated. Correlation between inter-patient variability for CL and V1 was high (100%), which negatively influenced model convergence. Therefore, we constrained the inter-patient variability estimates on CL and V1 to be the same using following equations:

(4) $\quad \theta_{CL,ik} = \theta_{CL,TV} * exp^{(\eta_1 + \kappa_{ik})}$

(5) $\quad \theta_{V1,ik} = \theta_{V1,TV} * exp^{(\eta_1 \, x \, \theta_\eta + \kappa_{ik})}$

in which *i* and *k* denote the number of individual and occasion, respectively, η_1 describes the IIV of parameters CL as well as V1, and θ_η is used to estimate the ratio between the (shared) IIV of CL and V1. Hereby, correlation of IIV for CL and V1 was constrained to 100%.

Table 1. General characteristics of the study population

	Total cohort	Adults		Children
	No. (%); or Median [IQR]			
Patient characteristics				
No. of patients	118	82		36
Age (years)	40 [22-58]	46 [34-59]		6 [2-11]
Body weight (kg)	79 [65-92]	85 [73-95]		19 [13-39]
Severe hemophilia B (<0.01 IUmL^{-1})	85 (72)	57 (70)		28 (78)
On prophylaxis	36 (31)	28 (34)		8 (22)
Blood group O*	33 (28)	24 (29)		9 (25)
Neutralizing antibodies (historically)	6 (5)	5 (6)		1 (3)
Chronic hepatitis C	47 (40)	46 (56)		1 (3)
Surgical characteristics				
No. of surgical procedures	255	201		54
Total no. of patients undergoing:				
1	55	33	33	22
2	31	21	21	10
≥3	42	28	28	4
Major surgical procedure	120 (47)	105 (52)		15 (28)
Type of surgical procedure				
General	19 (7)	16 (8)		3 (6)
Colorectal	16 (6)	14 (7)		2 (4)
Vascular	9 (4)	9 (4)		0 (0)
Cardio-thoracic	3 (1)	2 (1)		1 (2)
Orthopedic	99 (39)	92 (46)		7 (13)
Urological	11 (4)	11 (5)		0 (0)
Maxillofacial	1 (0)	1 (0)		0 (0)
Ear-Nose-Throat	9 (4)	5 (2)		4 (7)
Neurosurgery	1 (0)	1 (0)		0 (0)
Eye surgery	2 (1)	2 (1)		0 (0)
(Re)placement central intravenous catheters	27 (11)	2 (1)		25 (46)
Dental extractions	31 (12)	25 (12)		6 (11)
Miscellaneous	27 (11)	21 (10)		6 (11)

Table 1. General characteristics of the study population (continued)

	Total cohort	Adults	Children
	No. (%); or Median [IQR]		
Replacement therapy with factor concentrate, hospitalization and blood loss			
Mode of infusion			
Continuous	56 (22)	54 (27)	2 (4)
Bolus	199 (78)	147 (73)	52 (96)
Product type			
Recombinant[$]	201 (79)	150 (75)	51 (91)
Plasma derived[#]	54 (21)	51 (25)	3 (6)
Duration of hospitalization (days)	4 [2-9]	5 [2-11]	4 [2-5]
Complications during perioperative period			
No. of patients suffering from a complication			
Bleeding			
Re-operation	2 (2)	2 (2)	0 (0)
Hemoglobin drop >1,24 mmolL^{-1}	23 (19)	17 (21)	6 (17)
Red blood cell transfusion	1 (1)	1 (1)	0 (0)
Thrombosis	0 (0)	0 (0)	0 (0)

No. = number; IQR = inter-quartile range; kg = kilogram; IUmL^{-1} = international units per milliliter; * Blood group available in 80 patients; [$] including BeneFix (Pfizer Wyeth Pharmaceuticals Inc., Kent, UK); [#] Including AlphaNine (Grifols Biologicals Inc. Los Angeles, USA); Replenine (Bio Products Laboratory, Hertfordshire, UK); Haemonine (Biotest Pharma GmbH, Dreierich, Germany); Mononine (CSL Behring GmbH, Marbourg, Germany); Nonafact (Sanquin, Amsterdam, the Netherlands).

The fit of the established structural model to the data was evaluated by using goodness-of-fit plots, as shown in Figure 2. Figure 2B shows a slight overprediction of the highest FIX. However, few data is present in this concentration region. For the largest part of the concentration region, data are randomly distributed around the y=x axis. Figure 2A demonstrates that the model is able to describe the measured FIX for all individuals. Nevertheless, this figure should be considered with caution, because the described IIV showed marked shrinkage (IIV$_{CL}$: 35%, IIV$_{V1}$: 31%, IIV$_{Q2}$: 38%, IIV$_{V2}$: 66%) for all estimates, whereas the ε-shrinkage was small (10.5%). High shrinkage indicates that values for individual PK parameters cannot be estimated accurately. As a consequence, these individual estimates are closer to their average value than in reality.[26]

Table 2. Model-building steps

	NOP	OFV
Structural model		
1 Two-compartment model with IIV on V1 and CL	7	-2313.7
2 Baseline FIX:C measurements added to model 1	7	-2343.1
3 IOV for both CL and V1 added to model 2	9	-2522.5
4 IIV for both V2 and Q2 added to model 3	11	-2612.3
5 Three-compartment model with IIV on CL, V1, V2, and Q2 and Baseline	13	-2657.8
Univariate relationships (covariates added to model 5)		
4 AGE on V1	14[a]	-2667.2
5 Country on V1	15	-2673.7
6 Tranexamic acid on V1	16	-2679.6
7 Country on CL	17	-2686.9
8 AGE on CL	18[a]	-2713.8

NOP = number of estimated parameters; OFV = objective function value; IIV = inter-individual variability; CL = Clearance; V1 = distribution volume of the central compartment; V2 = distribution of the second compartment; Q2 = inter-compartmental clearance between central and second compartment. [a] For these models, the coefficients for covariate age on both CL and V1 were estimated using a hockey-stick model. However, the coefficients for all ages above median age were fixed to 0. Therefore, the NOP is only lowered by 1.

Covariate analysis

In the pre-selection of covariate relationships, the distinction between severe or moderate hemophilia, age, the use of tranexamic acid during surgery, the use of recombinant versus plasma-derived products, country of treatment and brand of product were evaluated on CL and V1. For V1, a difference between treatment centers was evaluated as well. For V2, age, the use of tranexamic acid and the distinction between severe and moderate hemophilia, and for Q2, the use of plasma-derived versus recombinant products, age, the use of tranexamic acid, the presence of hepatitis C, the country of treatment and the severity of the surgical procedure (see Table 1, Major surgical procedures) were evaluated.

Using the SCM method, age was found to be significantly associated to the population PK parameters CL and V1, as shown in Table 3. In Figure 3, age versus individual parameter values for CL and V1 are shown. In both cases, a piecewise-linear model was chosen to describe the relationship between age and the PK parameter:

$$(6) \quad \theta_i = \theta_{TV} * ((\theta_1 * (AGE - AGE_{med}))^{\theta_2} + (\theta_3 * (AGE - AGE_{med}))^{(1-\theta_2)})$$
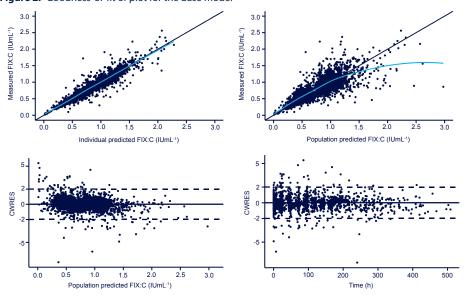
Figure 2. Goodness-of-fit of plot for the base model

FIX:C = FIX activity level. 3A. Individual predicted versus measured FIX:C. 3B. Population predicted versus measured FIX:C. 3C. Conditional weighted residuals (CWRES) versus population predicted FIX:C. 3D. CWRES versus time, in which time is defined as the time of first measured or first dosing, whichever occurs first.

in this expression, θ_2 is 1 if age of an individual is less than or equal to its population median and 0 otherwise, θ_1 and θ_3 are the coefficients for age below or equal to its population median and above, respectively, θ_{TV} the parameter typical mean value and θ_i the individual PK parameter. Median age calculated for this population was 32.2 years. Other significant covariate relationships provided by the SCM method were country and the use of tranexamic acid during a surgical procedure. Both covariate relations were additively associated to CL or V1, which was described by the following equation:

(7) $\theta_i = \theta_{TV} * (1 + \theta_{cov})$

in which θ_{cov} is the fraction of the typical PK parameter θ_{TV}, which was calculated in case a patient was treated in the Netherlands or used tranexamic acid during a surgical procedure, respectively. In other cases θ_{cov} was 0, meaning θ_{TV} was not altered. V1 was 9.8% higher than the associated population typical value in case tranexamic acid was

Table 3. Estimated population PK parameters for the structural model, final model and bootstrap analysis

	Structural model		Final model		Bootstrap analysis	
	Estimate	(%RSE)	Estimate	(%RSE)	Estimate	(%RSE)[a]
Structural model						
Clearance (CL; mLh^{-1}70kg^{-1})	286	3	251	3	251	4
Volume of central compartment (V1; mL70kg^{-1})	5550	4	4950	3	4935	3
Distribution CL to compartment 2 (Q2; mLh^{-1}70kg^{-1})	92.7	14	91.3	11	92.2	14
Volume of compartment 2 (V2; mL70kg^{-1})	7880	21	7900	14	7756	29
Distribution CL to compartment 3 (Q3; mLh^{-1}70kg^{-1})	1580	54	831	8	847	72
Volume of compartment 3 (V3; mL70kg^{-1})	1810	17	1600	12	1659	17
Inter-individual variability (%CV)						
IIV on CL	17.4	12	12.5	19	12.2	39
IIV on V1$^{\Delta}$	19.6	14	13.3	21	12.9	25
IIV on Q2	84.9	14	98.9	12	98.6	30
IIV on V2	48.7	27	56.8	27	51.1	83
Inter-occasion variability (%CV)						
IOV CL	18.9	11	18.8	11	18.6	23
IOV V1	16.5	14	15.8	13	15.9	29
Covariance between IOV on CL and V1	68.3	14	68.6	13	70.2	27
Residual variability						
Additive residual error (SD; IUmL^{-1})§	0.192	5	0.192	5	0.192	5
Covariate relations						
CL – Age (change with increasing age for age <32 years)			-0.012	21	-0.012	22
CL – Country			0.202	31	0.204	31
V1 – Age (change with increasing age for age <32 years)			-0.019	18	-0.019	17
V1 – Country			0.283	23	0.280	24
V1 – Tranexamic acid use during surgical procedure			-0.098	49	-0.093	50

[†] IIV: Inter-individual variability; [‡] RSE: relative standard error; [§] Additive error estimated on log-scale; [Δ] Parameter was estimated using a ratio estimator on shared inter-individual variability parameter; CV: coefficient of variation. SD: standard deviation. [a] Relative standard errors for parameter estimates obtained from bootstrap analysis.
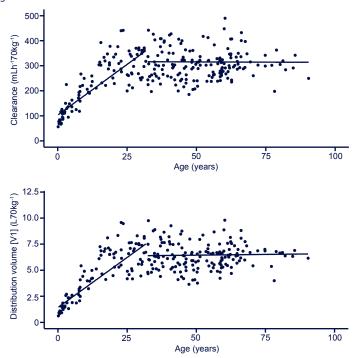
Figure 3. Age versus distribution volume and clearance

In both plots the empirical Bayesian estimates for distribution volume (V1) and clearance (CL) versus age is shown. It can be seen that there is a steep increase for ages below 32 years. Likewise, for ages above 32 years there is (on average) no change in the parameter values. Therefore, age was associated using a piece-wise linear model (equation 6). In both graphs, trend lines were added using a linear model for ages below 32 years and a (separate) linear model describing age above 32 years.

used during the surgical procedure. In case a patient was treated in the Netherlands, CL and V1 were 20.1% and 28.3% higher, respectively, than their corresponding population typical values (Table 3).

Product brand was evaluated as a categorical covariate and found to be significantly associated to V1. However, when associated to the model parameters using equation 7 for each specific brand, high uncertainty for the estimated coefficients were found. Moreover, due to a high condition number (>1000), indicating over-parameterization, product brand was not used as a covariate relationship on V1.

Using all covariate relations from the SCM method, except for product, IIV for CL and V1 decreased from 17.5% to 12.5% and from 19.6% to 13.3%, respectively, in comparison with the structural model.

Final model evaluation

To evaluate the final model, a visual predictive check was performed using 1000 Monte Carlo simulations from the established model, as shown in Figure 4. The simulated concentrations described the median of the observed data well. The observed median (solid red line) and 5th quantile (lower red dashed line) were within their respective 95% prediction intervals (grey area), whereas the 95th quantile of the observed FIX (upper red dashed line) is slightly below its prediction interval. This suggests that the model slightly over-predicts variability.

A bootstrap analysis was performed to evaluate the stability of the model regarding parameter estimation. Using this method, 1000 bootstrapped datasets were created, from which 78% converged. Obtained parameter estimates were similar to the estimates from
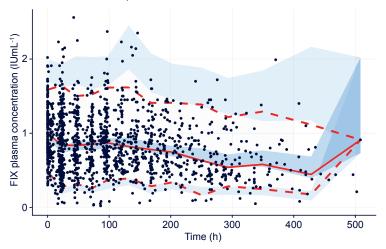
Figure 4. Prediction-corrected visual predictive check of the final model

Time is defined as the time after first FIX activity levels (FIX:C) measurement or first dose administration, whatever comes first, each surgical procedure of a patient. Dashed red lines depict the 5th and 95th quantiles of the measured FIX:C and the solid red line the 50th quantile. The grey areas surrounding the red quantile lines depict the 95% prediction interval for the simulated values from the final model.

Table 4. Population PK parameter estimates from published models

	Model 1[a]		Model 2[b]		Model 3[c]	
	Estimate	**(%RSE)**	**Estimate**	**(%RSE)**	**Estimate**	**(%RSE)**
Structural model						
Clearance (CL; mLh^{-1}70kg^{-1})	319.8	7.2	290	3.7	560	3.1
Volume of central compartment (V1; mL70kg^{-1})	5922	7.0	5710	3.6	6090	14
Distribution CL to compartment 2 (Q2; mLh^{-1}70kg^{-1})	1049	20.3	1990	35	22400	28
Volume of compartment 2 (V2; mL70kg^{-1})	828.9	50.7	810	19	4160	17
Distribution CL to compartment 3 (Q3; mLh^{-1}70kg^{-1})	160.4	8.1	170	6.7	430	15
Volume of compartment 3 (V3; mL70kg^{-1})	2234	73.9	2890	10	3900	7.7
Inter-individual variability (%CV)$^\Delta$						
IIV on CL	36.8	36.8	23	64	19	18
IIV on V1	41.2	34.2	19	37	46	36
IIV on V2	97.4	72.6	63	30	28	44
IIV on V3	133.2	34.5	78	81	19	71
Inter-occasion variability (%CV)						
IOV CL	48.8	10.1	15	36	-	-
IOV V1	47.2	17.8	12	24	-	-
Residual variability						
Additive residual variability (SD; IUmL^{-1})	0.0067	3.1	0.0037	10	0.0064	12
Proportional residual variability (CV; %)	6.95	1.5	9.2	11	8.7	4.9
Calculated half-life$^\ulcorner$						
First phase (t$_{1/2,\alpha}$, h)	0.48		0.25		0.08	
Second phase (t$_{1/2,\beta}$, h)	6.2		6.7		4.1	
Elimination phase (t$_{1/2,\gamma}$, h)	23		28		20	

[a] Brekkan, 2016. [b] Björkman, 2012. [c] Björkman, 2013. $^\Delta$ Calculated for FOCE with interaction. $^\ulcorner$ Half-life was calculated (without precision) using a closed-form solution for three compartments, using the population PK parameter typical values. Since only the structural part of the models with the random-effects were compared, allometric coefficients and covariate relations are not shown. Furthermore, correlations for IIV and IOV are not shown.

the final model, as shown in Table 3. Comparing the relative standard errors obtained from the bootstrap analysis, values for PK parameter Q3 and IIV for V2 were large (72% and 83%). This indicates these parameters can vary amongst the bootstrapped datasets and therefore are suspected to be more unstable estimates.

DISCUSSION

In this study, a population PK model was established which describes the time profile of FIX in hemophilia B patients during surgery. Inter-patient and inter-occasion variability was modest and could be explained on basis of patient characteristics.

A three-compartment model adequately fitted the data, which is in agreement with pre-viously published population PK models.[8, 9, 22] However, these models were constructed using data from the prophylactic (non-surgical) setting. Population parameter estimates for these models are summarized in Table 4. In this study, an elimination half-life of 88 hour and a second phase half-life of 12.7 hours were calculated. These are markedly higher compared to the elimination half-life for each of the models in Table 4. These differences are caused mainly due to the differences in PK parameters estimates of first peripheral compartment (Q2, V2). In Figure 5, the performance to predict the periopera-tive FIX is shown and underprediction is seen for each model. This finding is counter intuitively, since it was expected that perioperative FIX would be overpredicted by each model due to lower FIX resulting from endogenous consumption. These findings clearly show that perioperative FIX PK is different from regular prophylaxis.

FIX is believed to distribute rapidly to the interstitial fluids due to its small molecular size[7], which is supported by the estimates for the peripheral clearance terms in Table 4. However, the estimate for Q2 in this study was markedly lower, suggesting a less rapid first phase disposition to the interstitial fluids during the perioperative period. A tenta-tive explanation for this finding is that endogenous consumption and complexation of FIX with FVIII during hemostatic challenge causes a lower distribution towards the in-terstitial fluids. Therefore, a dedicated population PK model is needed when PK-guided dosing is performed in the perioperative period.

As body weight is known to be correlated with age, especially for children, estimation of an allometric exponent would interfere with estimation of the association between age
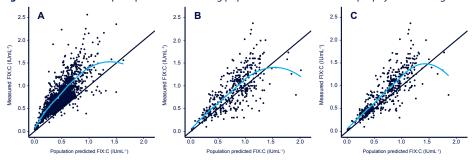
Figure 5. Predictions of perioperative FIX:C using population PK models for the prophylactic setting

Population predictions, obtained using Bayesian analysis, for the perioperative data using three different models from literature. If a model was constructed using recombinant FIX data, the predictions were obtained only for perioperative recombinant FIX data and likewise for plasma-derived FIX data. A: Predictions using model [Björkman, 2013]. B: Predictions using model [Björkman, 2012]. C: Predictions using model [Brekkan, 2016]. Black line is the line of identity (y=x). Blue line depicts the loess line. In each case, an under-prediction of the perioperative FIX:C is shown for the models constructed using solely prophylactic data.

and the PK parameters. In this study, however, allometric exponents were fixed to 0.75 (CL, Q2, Q3) and 1 (V1, V2, V3).[27] Therefore, the relation between age and PK parameters, which were normalized using body weight, was investigated. In our study, an increase in age was associated to a decrease in CL as well as V1 until an age of 32 years. These findings are in accordance with a study with only adult patients, in which this relationship was absent[9]. In Björkman et al.[28], a similar piecewise linear relation was obtained compared to our findings (see Figure 4). In their results, clearance and (steady-state) distribution volume increased per rising age, for ages below 20 years. Above 20 years, there was virtually no change in clearance or distribution volume. In our study, covariate coefficients for ages above 32 years were fixed to 0, as virtually no change in parameter value was observed.

In previous studies, differences in PK were reported between plasma-derived and recombinant FIX products.[4, 29, 30] The clearance of recombinant FIX products is found to be higher compared to plasma-derived products.[4] In this study, a dichotomous covariate was used to evaluated the relationship between these product types and the estimated PK parameters. However, this covariate relationship was not retained in the final model using SCM. Therefore, further investigations should be focused towards confounding

factors for this covariate relationship, since findings from literature suggests a relationship for clearance terms should be detected.

The final model indicated that CL and V1 differed between countries. CL and V1 were found to be 20.1% and 28.3% higher, respectively, when a patient was treated in the Netherlands. Due to preferences in choice of clotting factor concentrate brands between countries, further investigations should be focused towards the interference of combined or masked covariate effects of product and country on the mentioned PK parameters. However, the final backward model from the SCM method contained both covariate effects associated to CL, suggesting both covariate relations can be estimated simultaneously. Furthermore, the use of tranexamic acid decreased V1 by 9.8% and thus obtaining a lower V1. This corresponds to achieving higher FIX directly after dosing, when tranexamic acid is applied during a surgical procedure. However, to date there are no studies which demonstrate this pharmacodynamic effect. Besides, a decrease of 10% would not be marked as clinically relevant. Therefore, further study is necessary to demonstrate this covariate relationship is established by a true covariate relationship instead of an association due to confounding.

A prerequisite for PK-guided dosing during regular prophylaxis is a low inter-occasion variability compared to the inter-individual variability. In this study, the estimates for IIV and IOV were similar. Compared to the perioperative PK of FVIII, IIV was comparable when IOV was also taken into account for describing the total variability of CL and V1 in the patient population.[31] However, in the perioperative setting the variability described within an individual (between occasions) may be influenced by the types of surgical procedure. For all occasions of a specific individual, these types can vary between minor and major surgical interventions. Nevertheless, no relationship between type of surgery and the PK parameters estimated was found in this study.

In all efforts to prevent the occurrence of bleeding events in hemophilia B using doses of factor IX concentrates, the exact relationship between hemostasis and achieved FIX is unknown. During perioperative treatment, patients are 'normalized' towards physiological concentrations for FIX to ensure hemostasis. While irrefutable evidence for perioperative target concentrations is missing, PK-guided dosing may be used to obtain the desired FIX. In this study, a population PK model was developed, which can be used to individualize and optimize FIX dosing using a Bayesian approach. In this approach, individual information (dose, concentration) is combined with population information

(fixed, random-effects) to estimate individual PK parameters. Using these parameters, doses can be tailored to achieve target concentration attainment for a specific individual. Using Bayesian analysis, this model can be used to individualize FIX replacement therapy in the perioperative setting. Application of perioperative PK-guided FIX dosing allows more optimal and adequate FIX dosing. Hazendonk et al. have demonstrated that improvement is possible as 60% of achieved trough and steady-state FIX were below required target concentration range during the first 24 hours after the start of the surgical procedure.[11] However, these ranges were not evidently associated to bleeding complications. Therefore, it was suggested that target attainment during the perioperative period is complex and target ranges may potentially be lowered.[11] Nevertheless, PK-guided dosing may enable to reliably lower perioperative doses for hemophilia B patients without raising risk of bleeding.

CONCLUSIONS

This study provides a preliminary PK analysis of FIX dosing for hemophilia B patients undergoing surgery. A three-compartment perioperative population PK model was established using FIX levels obtained during the perioperative period. Age, country of treatment and the use of tranexamic acid during a surgical procedure were associated to the model as covariate relations. A relationship between the PK parameters from the model and the different brand of product could not be established. However, the model was constructed using both pdFIX and rFIX dosing information. Therefore, the model is suitable to describe both mentioned types of FIX concentrates.

Inter-patient differences in FIX PK should be taken into account when optimizing treatment regimens. These differences are accounted for by means of patient tailored dosing, in which individual PK parameters obtained from an appropriate population PK model is essential.

PK parameter estimates for the established final model clearly demonstrates that the PK of FIX in the perioperative period is different from dosing during the regular prophylactic setting. Therefore, it has been advocated that attainment of target plasma activity levels should be considered using iterative Bayesian adaptive dosing, which comprises the use of a population PK model in lieu of body weight for calculation of individualized

doses. Since this is a preliminary study, the established structural model and associated covariate relations should be further investigated.

ACKNOWLEDGEMENTS

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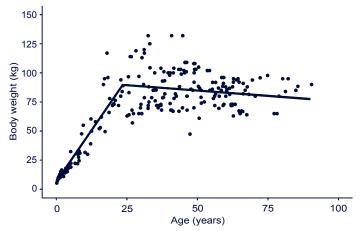
Supplemental Table/Figure

Supplemental Table 1. Model for body weight imputation using age

Parameter	Unit	Mean	(%RSE)[‡]
β_1 – y-intercept	kg	6.3	(7)
β_2 – coefficient for all ages	kg year^{-1}	3.6	(5)
β_3 – coefficient for age > β_4	kg year^{-1}	-3.73	(7)
β_4 – Inflexion point	year	23.5	(8)
Residual variability			
Proportional error (CV)[§]	%	19.1	(6)
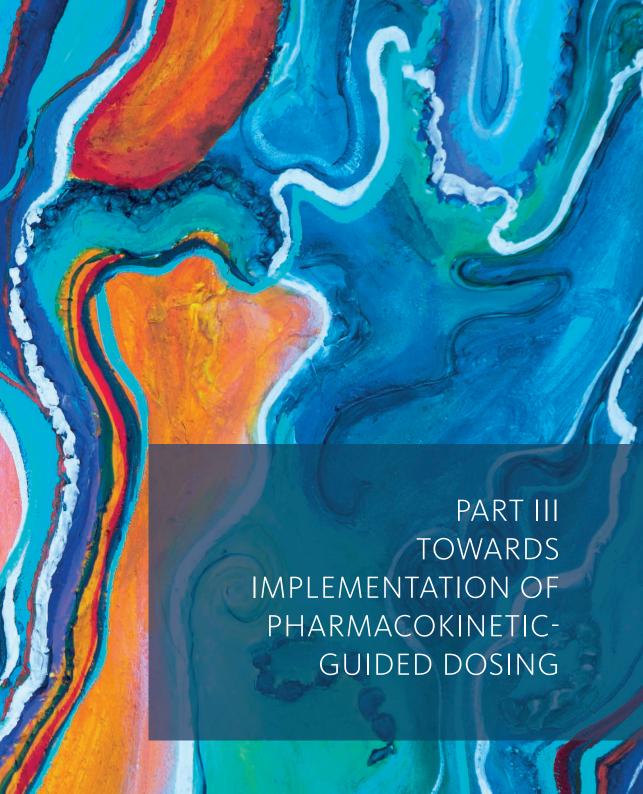
[‡] RSE: relative standard error; Kg = kilogram; [§] measured on normal scale; CV: coefficient of variation.
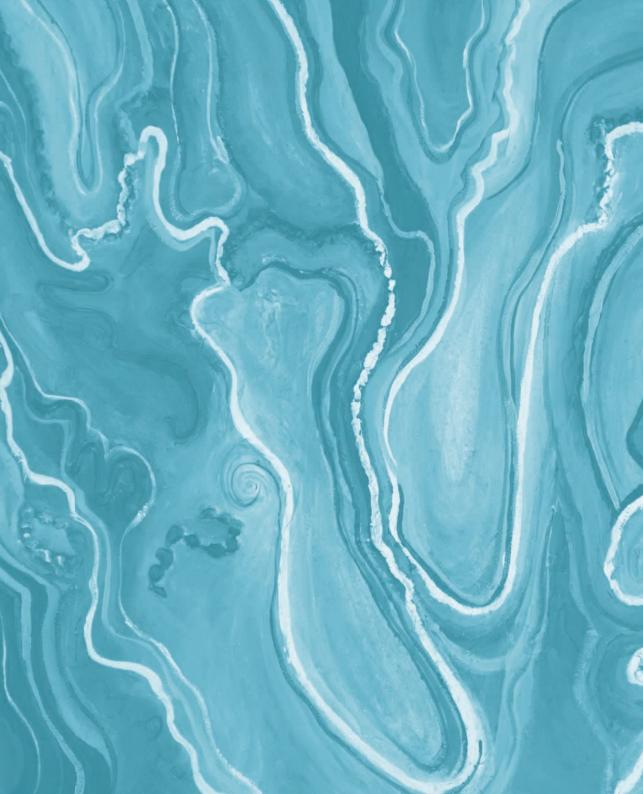
Supplemental Figure 1. Imputed weight based on age from all individuals

Black dots are individual body weights plotted versus age for all patients. The black line depicts the predicted body weight with age as predictor, described by the piecewise linear model (equation 3 in the method section).

PART III
TOWARDS
IMPLEMENTATION OF
PHARMACOKINETIC-
GUIDED DOSING

Chapter 7

The "OPTI-CLOT" trial A randomized controlled trial on periOperative PharmacokineTIc-guided dosing of CLOTting factor concentrate in hemophilia A.

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SUMMARY

Background Hemophilia A is an X-linked inherited, rare bleeding disorder, caused by a deficiency of coagulation factor VIII (FVIII). Previous studies in prophylactic dosing have demonstrated that FVIII consumption can be significantly reduced by individualizing dosing based on combined analysis of individual pharmacokinetic (PK) profiling and population PK data (Bayesian analysis). So far, no studies have been performed that address perioperative concentrate consumption using iterative PK-guided dosing based on a PK population model.

Methods The "OPTI-CLOT" trial is an open-label, prospective, multicenter randomized controlled superiority trial (RCT), aiming to detect a 25% difference in perioperative FVIII concentrate consumption with iterative Bayesian PK-guided dosing in comparison to the standard dosing procedure. Sixty hemophilia A patients ≥ 12 years of age, with FVIII plasma levels ≤ 0.05 IUmL^{-1} will be included requiring FVIII replacement therapy administered either by continuous or bolus infusion for an elective, low or medium risk surgical procedure.

Discussion The proposed study aims to investigate a novel perioperative iterative PK-guided dosing strategy, based on a recently constructed perioperative PK population model. This model will potentially decrease underdosing and overdosing of clotting factor concentrate and is expected to overall reduce FVIII consumption by minimally 25%. Moreover, participating hospitals will gain experience with PK-guided dosing, facilitating future implementation of this intervention which is expected to optimize current care and reduce costs of treatment.

Trial registration: NTR4121

INTRODUCTION

Hemophilia A is an X-linked inherited bleeding disorder, caused by a deficiency of coagulation factor VIII (FVIII). Patients with severe (FVIII <0.01 IUmL^{-1}) and moderate severe (FVIII 0.01-0.05 IUmL^{-1}) hemophiliac A experience spontaneous bleeding, mainly in muscles and joints, or bleeding after minor trauma. Prophylactic substitution of FVIII concentrate intravenously, several times a week, aiming for a trough level of above 0.01 IUmL^{-1}, generally prevents severe joint damage and subsequent long term disability. Surgery necessitates an intensive regimen of factor replacement therapy, as factor levels are normalized for 7-14 days. Therefore, overall in the perioperative period, a patient may consume up to 15% of his regular annual use of clotting factor concentrate. Annually, overall costs of hemophilia treatment In the Netherlands are estimated at €130 million, of which more than 90% consists of costs for concentrates.[1-3]

In the perioperative period, target trough levels dictated by National and International Guidelines are exceeded in the perioperative setting. This seems due to difficulties in targeting these levels but also due to the fact that doctors are inclined to dose generously in order to avoid low factor activity levels and subsequent bleeding risk.[4-6] Treatment is extremely effective as perioperative bleeding is rare in hemophilia patients in countries where concentrates are adequately available. Refining of perioperative dosing strategies seems warranted to optimize replacement therapy in the individual hemophilia patient and to increase quality of care by avoiding both under dosing and overdosing.

Rationale: Pharmacokinetic-guided dosing may be cost-reductive

Large inter-individual differences in the pharmacokinetics (PK) of FVIII concentrates have been demonstrated, making PK-guided dosing a potential strategy to improve clinical outcome and possibly cost-effectiveness of dosing in prophylactic, on demand and perioperative settings.[7] Bayesian PK-guided dosing is the combined analysis of individual PK parameters in regard to the population parameters. Using this approach only three samples are needed to describe a complete PK curve.[8]

Using a Bayesian approach in the prophylactic setting, Carlsson et al.[9] reported a dose reduction of 30% without an increase in bleeding in a randomized cross-over study of two six months' periods, comparing PK-guided dosing with standard dosing. However, prophylactic population PK models cannot be extrapolated to the perioperative situa-

tion, as surgery forms an incomparable hemostatic challenge. Moreover, Longo et al. reported excessive FVIII consumption and clearance in 50% of surgical hemophilia patients due to unidentified factors.[10]

Current perioperative management in hemophilia

In surgery, earlier studies on perioperative management in hemophilia have compared continuous infusion with intermittent bolus infusions. Batorova et al.[11] reviewed eleven case series and concluded that continuous infusion of FVIII and factor IX is safe and effective in situations requiring intensive replacement therapy such as surgery and major bleedings. Strikingly, there was a wide variation in targeted hemostatic levels, dosage regimens, modes and duration of therapy. Eight of these studies concluded that continuous infusion is more cost-effective than intermittent bolus administration by reduction of total clotting factor consumption.[12-19] In two studies, bolus injections were prospectively compared to adjusted continuous infusions, demonstrating 30-36% reduction of FVIII consumption in the latter.[12, 19] Preoperative PK profiling was reported in 3 out of 8 hemophilia A case series, but was not specified.[13-15, 17, 19, 20] A perioperative study by Batorova and Martinowitz[12] showed that if targeted FVIII levels are actually maintained, a reduction of consumption and therefore costs of up to 70% may be attained. Mulcahy et al.[15] retrospectively evaluated adjusted continuous FVIII infusions in a single center study and concluded that close monitoring of FVIII levels in itself with strict regulation of infusion rate alone, may significantly reduce FVIII consumption.

So far, iterative Bayesian PK-guided perioperative dosing has not been performed as perioperative PK population models for clotting disorders have not been available. Recently, we have however constructed a population PK model from retrospective perioperative FVIII data[21], facilitating Bayesian adaptive dosing of FVIII in the perioperative setting. We hypothesize that application of this approach may improve quality of hemophilia care as both underdosing and overdosing are avoided. Potentially, it will also decrease FVIII consumption and lower costs of treatment.

OBJECTIVE

The objective of this study is to investigate whether perioperative PK-guided dosing of FVIII concentrate in hemophilia A patients receiving FVIII replacement therapy using a Bayesian approach, leads to a significant reduction in perioperative clotting factor consumption.
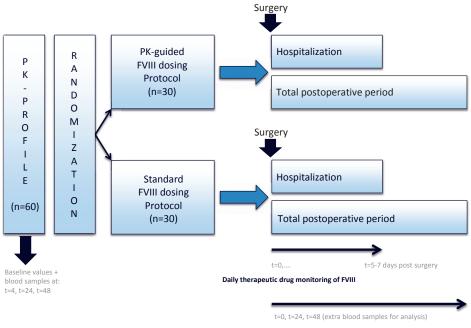
METHODS

Trial design

The "OPTI-CLOT" trial is a prospective, multicenter randomized controlled superiority trial (RCT), aiming to detect a difference in perioperative FVIII consumption with iterative PK-guided dosing in comparison to the standard dosing procedure, the latter primarily based on body weight. FVIII levels will be targeted in the middle of each target range defined in the perioperative guidelines of the National Hemophilia Consensus, unless stated otherwise by treating physician.

In all patients six weeks before surgery, a preoperative PK profile will be constructed using only three blood samples without a wash out period but with exact notation of prior doses in the week before PK profiling; individual PK parameters will be assessed by Bayesian analysis (Figure 1). Subsequently, patients will be randomized after stratification according to mode of FVIII administration (continuous or bolus), type of surgical procedure (minor or major) and treatment center as is usual in a multicenter trial and subsequently allocated to one of two perioperative treatment arms: (A) the intervention arm in which dosing is adjusted on basis of the individual preoperative PK parameter estimates and iterative perioperative Bayesian analysis; or (B) the standard treatment arm in which dosing regimen is established by the physician according to the standard dosing regimen. At least 60 patients will be needed to detect a difference of minimally 25% in consumption of FVIII concentrate during the perioperative period between treatment arms. Safety is guarded by generally daily monitoring of FVIII levels, as is now standard procedure. Perioperative hemostasis will be assessed during the entire perioperative period.

Figure 1. Flowchart

After inclusion a PK profile will be constructed preoperatively prior to stratified randomization; individual PK parameters will be assessed using Bayesian analysis. In the intervention arm dosing will be administered based on the individual PK parameter estimates. With daily FVIII levels available the Bayesian approach will be used to iteratively adjust the daily dose. In the standard treatment arm dosing will be set by the treating physician according to the standard dosing regimen described in the National Hemophilia Consensus in the Netherlands based primarily on bodyweight with target plasma FVIII values as set in the Consensus, unless otherwise specified. Adjustments will be performed by the treating physician without knowledge of the preoperative profile of the patient.

Study population

Patients will be included from six large Academic Hemophilia Treatment Centers in the Netherlands: Erasmus University Medical Center Rotterdam, Academic Medical Center Amsterdam, Radboud university medical center, University Medical Center Utrecht, University Medical Center Groningen and Leiden University Medical Center.

Inclusion criteria:
–   Severe and moderate hemophilia A patients with FVIII levels ≤0.05 IUmL^{-1};
–   ≥ 12 years of age at inclusion date;
–   Undergoing elective, minor or major surgery as defined by surgical risk score (Koshy et al.[22]);
–   Under replacement therapy with FVIII concentrate, (plasma derived or recombinant) by continuous or bolus infusion;
–   Written informed consent, according to METC guidelines.

Exclusion criteria:
–   Patient with other congenital or acquired hemostatic abnormalities.
–   Withdrawal of (parental) informed consent.
–   Due to additional effect on FVIII clearance: detectable FVIII inhibiting antibodies (>0.2 Bethesda Units) at study inclusion.
–   General medical conditions which may interfere with participation in the study.

Outcome measures

Primary endpoints are:
1. Total amount of infused FVIII concentrate (IU per kilogram) during the perioperative period per postoperative day (from 72 hours before surgery up to 14 days after surgery);
2. Achieved FVIII levels (IUmL^{-1}) after FVIII infusion.

Secondary endpoints are:
1. Duration of hospitalization (day of release - day of surgery/ start of continuous or bolus FVIII infusion);
2. Perioperative hemostasis as quantified by standardized form;
3. Effects of baseline VWF antigen, propeptide values and blood type on FVIII clearance and identification of other potential modifiers;
4. Economic analysis of costs in both treatment arms.

Interventions

Overall treatment protocol in all patients, independent of treatment arm

In all patients, a PK profile will be constructed six weeks before surgery prior to stratified randomization. After a standard bolus of FVIII of 50 IU per kilogram, FVIII levels will be measured in three blood samples of 1.8 mL citrate blood, withdrawn at t=4, t=24 and t=48 hours after FVIII clotting factor concentrate infusion, according to Björkman et al.[8] The individual PK parameters are assessed by Bayesian analysis. During PK profiling, exact information on three prior FVIII doses before the standardized FVIII infusion will be gathered to predict residual FVIII level in each individual patient. Treating physicians and nurses will be blinded for PK profile results in both arms.

In both treatment arms, target ranges for FVIII values will be applied as set by the National Hemophilia Consensus aiming for the middle of each range, unless stated otherwise by treating physician (Table 1)[4]. In all patients in both treatment arms, FVIII levels will be monitored as is momentarily standard clinical practice, which is generally daily, during the perioperative period.

Table 1. Target trough levels of FVIII in the perioperative period according to the National Hemophilia Consensus[4]

Time postoperative		Target range FVIII levels (IUmL^{-1})	OPTI-CLOT Target FVIII level (IUmL^{-1})
Day 1	0-24 hours	0.80-1.00	0.90
Day 2-5	24-120 hours	0.50-0.80	0.65
Day >6	> 120 hours	0.30-0.50	0.40

FVIII values as set in the Consensus, unless otherwise specified. Adjustments will be performed by the treating physician without knowledge of the preoperative profile of the patient.

Specification of treatment arms

Trial/ Intervention arm:

The FVIII dose prior to the start of the surgery will be based on the required FVIII target level according to the National Consensus and individual PK parameters as obtained from the preoperative PK profile according to Björkman et al.[8] and exact information of three prior doses of FVIII concentrate preceding the date of surgery. Subsequent doses will be adjusted iteratively using Bayesian analysis on basis of daily therapeutic monitor-

ing of FVIII using our own perioperative population PK model based on retrospective data of severe and moderate severe hemophilia patients undergoing surgery.[21]

Daily therapeutic monitoring of FVIII is part of current standard clinical care and FVIII values will be analyzed locally. Results will be blinded for the treating physician and nurses. The FVIII levels and administered FVIII doses will be communicated by the laboratories of each specific site with the clinical pharmacologist. The clinical pharmacologist is responsible for the calculation of the individual dose using the Bayesian approach. The clinical pharmacologist will send the FVIII dosing recommendations to the treating physician, who will subsequently adjust dosing. Target levels according to Consensus or otherwise set by the treating physician will be safeguarded by an unblinded hematologist with experience in hemophilia treatment.

Trial/ Standard treatment arm:

The standard perioperative dosing regimen, as described by the Consensus, consists of a FVIII bolus dose directly prior to surgery of 50 IUkg^{-1}, followed by either continuous infusion or intermittent daily bolus infusions. The rate of infusion (IU hour^{-1}) is obtained by multiplying the patient's bodyweight (kg) with clearance (3-4 mL kg^{-1} hour^{-1}) and target FVIII level (IUmL^{-1}). Subsequent FVIII clotting factor concentrate dosing will be based on daily monitoring of FVIII levels and adjusted according to doctor's opinion, based on a standard clearance of 3-4 mL kg^{-1} hour^{-1} and FVIII levels are targeted in the middle of each target range as set by the National Hemophilia Consensus, which decrease per postoperative day (Table 1).[4] Dosing adjustments will be performed by the treating physician on basis of the daily monitored FVIII levels, without knowledge of PK parameters collected in the individual preoperative PK profile.

Bayesian-analysis

In the treatment arm individual PK parameters will be assessed iteratively by application of Bayesian analysis as implemented in the NONMEM® software (Icon, Dublin, Ireland). For Bayesian analysis a population PK model will be used constructed on the basis of the PK data from an earlier retrospective perioperative study.[21] Based on the derived individual Bayesian PK parameters an optimal dosing scheme will be calculated during perioperative use, taking mode of administration of concentrates (continuous or bolus infusion) and desired target FVIII value into account. As for continuous infusions, indi-

vidual estimates for clearance are needed. With regard to intermittent bolus infusions, estimates for both clearance and volume of distribution are needed.

Sample size

Based on earlier data and economic relevance, we aim to detect a difference in mean FVIII concentrate use in IUkg^{-1} which equals 150 IUkg^{-1} or a 25% reduction in use of clotting factor. To study this with a power of 80% and a two-sided α of 0.05, a sample size of minimally 60 patients is necessary. To allow for dropouts, 65 patients will be included in the total study. One patient per center, except Erasmus MC (n=5) will be treated according to protocol to test local logistical processes. These patients will not be evaluated with regard to primary endpoints, only with regard to secondary endpoints.

Economic analysis will be performed from a health care perspective taking all health care costs into account. We will calculate and compare the costs of PK profiling consisting of: bolus of 50 IUkg^{-1} FVIII minus prophylactic doses required, time invested by hemophilia caretakers, two and three FVIII test samples (in standard clinical practice, usually one in vivo recovery FVIII level is performed), generation of PK profile by Bayesian analysis and perioperative iterative Bayesian analysis to the standard dosing procedure consisting of: establishment of treatment protocol by hemophilia expert, and perioperative dosing adjustment calculations by hemophilia expert. Theoretical consequences of PK profiling on prophylactic dosing regimen in the following years, at one year after surgery, both reduction and increase of dosing, will also be taken into account in this economic evaluation. Actual medical costs will be calculated by multiplying volume of health care use with corresponding unit prices. Costs will be valued using the National guidelines for economic evaluation studies.[23]

CONCLUSION

The proposed study aims to investigate an innovative individualized perioperative PK-guided dosing strategy, which is expected to reduce FVIII consumption and therefore costs by minimally 25%. Strengths of the study are the number of participating centers and study design. The application of both perioperative Bayesian guided dosing and a specific perioperative population PK model has not been performed before. Further-

more, the inclusion of children is important, as inter-individual clearance of clotting factor is exceptionally variable at younger ages. As a direct consequence of the study, participating hospitals will gain experience with PK-guided dosing facilitating future implementation of this promising intervention.

Ethical considerations

The study protocol was approved by the Medical Ethics Board of the Erasmus University Medical Center Rotterdam, the Netherlands and approved by all boards of participating hospitals.

Registration

The trial is registered at the Dutch Trial registry, number NTR4121 (www.trialregister.nl) This research is funded by ZonMW (grant number 80-83600-98-10098), the Dutch organization for Health Research and Development, and an unrestricted investigator initiated research grant from Baxter. The funding source has no involvement in the study and the author's work is independent.
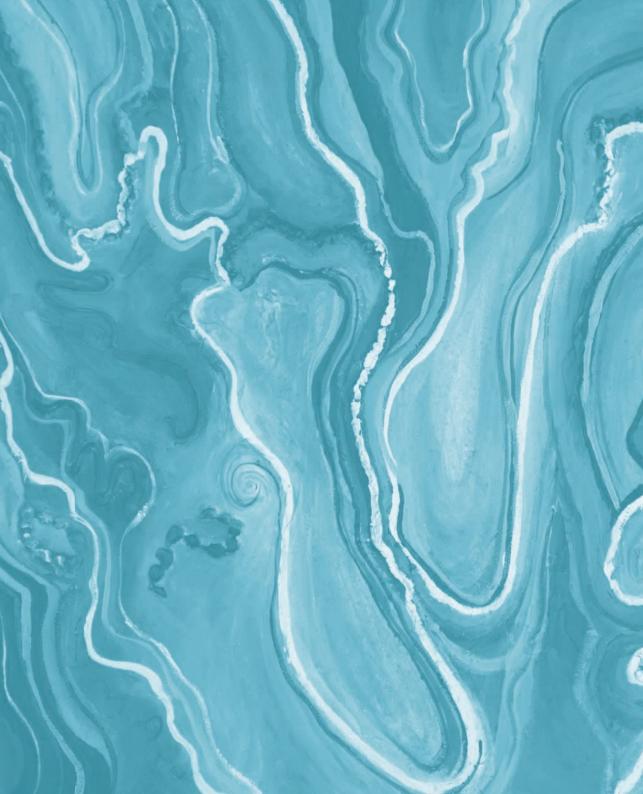
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Chapter 8

Obesity and dosing of replacement
therapy in hemophilia; How to optimize?

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M.H. Cnossen, for the "OPTI-CLOT" study group

SUMMARY

Background Treatment in hemophilia A is based on body weight and an in vivo recovery (IVR) of 2.0 which equals an increase of 2.0 $IUdL^{-1}$ per unit of factor VIII (FVIII) per kilogram. Overweight/obese patients have significantly higher IVR values, resulting in overestimation of FVIII doses.

Objective To explore the potential of PK-guided dosing of factor VIII concentrate in overweight/obese hemophilia A patients and to evaluate the use of alternative body size descriptors for dose calculation, e.g. ideal-, adjusted- and lean body weight.

Methods Twenty-two hemophilia A patients (baseline FVIII <0.05 $IUmL^{-1}$) were classified according to body mass index (BMI), normal: < $25kgm^{-2}$(n=5), overweight: 25-30 kgm^{-2}(n=12) and obese: > 30 kgm^{-2}(n=5). All patients received ±50 $IUkg^{-1}$ FVIII, with FVIII sampling after 4, 24 and 48 hours. Population PK models were applied to calculate FVIII plasma concentration over time.

Results The population PK model by Bjorkman et al. did not correctly predict FVIII levels in the overweight/obese. A modified model was constructed, describing PK parameters and FVIII levels adequately. Median IVR was significantly higher in overweight (2.65) and obese (3.00) patients when compared to those with a normal BMI (2.17) (p<0.05). IVR was independent of BMI when ideal body weight was applied. IVR-based dosing resulted in FVIII trough levels below set target levels for bleeding events.

Conclusion When PK-guided dosing of factor VIII concentrate is performed, the population PK model should represent the specific patient population, in this case: obese/overweight patients. In contrast to what is generally hypothesized, alternative body size descriptors are not able to substitute PK-guided dosing.

INTRODUCTION

Hemophilia A is an X-linked inherited bleeding disorder characterized by a deficiency in coagulation factor VIII (FVIII). Treatment with FVIII concentrate replacement therapy is administered prophylactically or "on demand", in case of bleeding or in the perioperative setting. Various guidelines prescribe specified target levels for different circumstances[1-3], for example a bolus infusion of 50 IUkg^{-1} followed by twice a day 25 IUkg^{-1} in case of a life-threatening bleeding event. To achieve the prescribed target plasma level the required dose is calculated based on baseline FVIII, actual body weight in kilograms (kg), and a crude estimation of clearance. In these calculations FVIII in vivo recovery (IVR) is assumed to be 2.0, defined as an increase of 2.0 IUdL^{-1} per unit of infused FVIII concentrate per kilogram (kg) body weight.[4] The crude FVIII half-life, generally assumed to be 12 hours, is subsequently applied to predict FVIII trough levels. As large interindividual variation in IVR and half-life exist, the lack of precision of these estimates can be overcome by frequent monitoring of FVIII plasma concentrations in critical situations. In order to predict FVIII plasma concentrations over time, it may be more efficient to dose based on a population PK model.

Both overweight and obesity are highly prevalent in the hemophilia population with a prevalence of respectively 35% and 8%.[5] Previous studies have shown that obese patients have significantly higher IVR values when dosed according to body weight, suggesting that these doses can be decreased.[6-8] This is probably due to the fact that the intravascular plasma volume (in which factor concentrate is infused) does not linearly increase with body weight.[9] The increased IVR in overweight and obese hemophilia A patients has led to hypotheses that alternative parameters for dose calculations such as ideal body weight (kg) or lean body mass (kg) instead of actual body weight (kg) may be more adequate.[6, 7, 10, 11] Until now, the effect of the use of these alternative parameters on adequate prediction of trough FVIII plasma concentrations has not been evaluated. Therefore, we aimed to explore the potential of PK-guided dosing based on FVIII population PK models in overweight and obese hemophilia A patients and to evaluate the use of alternative body size descriptors instead of actual body weight for dose calculation.

PATIENTS AND METHODS

Patients

In this cross-sectional study, severe and moderate hemophilia A patients were included (baseline FVIII <0.05 IUmL^{-1}) from four Academic Hemophilia Treatment Centers in the Netherlands (Erasmus University Medical Center Rotterdam, University Medical Center Groningen, Radboud university medical center Nijmegen, Leids University Medical Center). Patients with FVIII neutralizing antibodies were excluded. Written informed consent was obtained from all patients according to the declaration of Helsinki.

Methods

Patient characteristics were collected; including baseline FVIII plasma concentration, DNA mutation, inhibitor status, age (years), actual body weight (kg), and height (cm). These parameters were used to calculate the following body size descriptors for each patient: body mass index (BMI, kgm^{-2}), ideal body weight (kg), adjusted body weight (kg), and lean body weight (kg) (Table 1).[8, 12, 13] These body size descriptors are believed to take percentages of fat mass into account and therefore may be more precise descriptors of body size in association with clearance and volume of distribution when compared to actual body weight. FVIII plasma concentrations were measured by means of an one-stage clotting assay, using FVIII-deficient plasma (Siemens Healthcare, Marburg, Germany) and reference plasma (Cryocheck, Precision Biologic, Kordia, Leiden, The Netherlands) on an automated coagulation analyzer (Sysmex CA1500, Siemens, Breda, The Netherlands).

Table 1. Calculation of body size descriptors

Body size descriptor	Formula
Ideal body weight (IBW) (kg) *Devine et al. 1974*	0.9 * H -88
Adjusted body weight (ABW) (kg) *Devine et al. 1974*	IBW + 0.4 (BW-IBW)
Lean body weight (LBW) (kg) *Janmahasatian et al. 2005*	$(9.27 *10^3 * BW)/(6.68*10^3+(216*BMI))$
Body mass index (BMI) (kgm^{-2}) *Garrow et al. 1985*	$BW / (HT^2)$

kg= kilogram; H= height in centimeter; BW = body weight in kilograms; BMI= body mass index; HT= height in meter

Pharmacokinetic modeling

All patients received a FVIII bolus infusion of approximately 50 IUkg^{-1} with FVIII blood sampling at baseline, t=4, t=24 and t=48 hours. Individual PK profiles were constructed by Bayesian analysis using the FVIII population PK model, developed for the prophylactic setting, as published by Björkman et al.[14] Actual FVIII plasma concentrations were compared to predicted FVIII plasma concentrations obtained using this model.[14]

Furthermore, a novel modified FVIII population PK model was developed for this study population using nonlinear mixed-effects modeling software (NONMEM version 7.3.0, Globomax LLC, Ellicott City, Maryland, USA)[15], including both the normal, overweight and obese study patients. A two-compartment model was constructed. The endogenous baseline FVIII plasma concentration, collected for each individual, was incorporated into the model. The following PK parameters were estimated: clearance (CL), intercompartmental clearance (Q), central volume of distribution (V1) and peripheral volume of distribution (V2). PK parameters were not scaled allometrically, allowing evaluation of the relationship with various body size descriptors. Inter-individual variability (IIV) and their correlation was estimated for clearance and central volume of distribution using an exponential function. Residual variability in FVIII plasma concentration was described by an additive error model. In order to perform these calculations, R version 3.2.22 (The R Foundation for Statistical Computing) and R-package Xpose version 4.5.3[16] were used for data check-out, exploration and model diagnostics. In addition, Pirana software was used as an interface between NONMEM, R and Xpose.[17]

Estimated individual PK parameters from the modified FVIII population PK model were used to simulate FVIII plasma concentration-time curves using the four body size descriptors e.g. actual body weight, ideal body weight, adjusted body weight and lean body mass (Table 1). Moreover, the simulated FVIII peak plasma concentrations were used to recalculate IVR according to the formula: body size descriptor (kg) x observed FVIII increase (%) / FVIII dose (IU).[4] In addition, simulated FVIII trough levels achieved with FVIII doses based on the different the body size descriptors were compared to predefined FVIII target trough levels for a life threatening bleeding event (Table 2).

Statistical analysis

Hemophilia patients were divided into three subgroups according to BMI; <25 kgm^{-2}, overweight: 25-30 kgm^{-2}, and obese: >30 kgm^{-2}. Descriptive statistics are presented as

Table 2. General patient characteristics and pharmacokinetic parameters

	Total cohort	BMI <25 kgm^{-2}	BMI 25-30 kgm^{-2}	BMI >30 kgm^{-2}
No. of patients (%)	22	5 (23)	12 (54)	5 (23)
Age (years)	51 [33-65]	24 [19-48]	54 [41-69]	53 [35-67]
Severe hemophilia A	17 (77)	5 (100)	7 (58)	5 (100)
Body weight (BW) (kg)	87 [73-96]	68 [61-77]	87 [78-99]	95 [94-104]
Calculated morphometric variables$^{#}$				
Ideal body weight (IBW) (kg)	71 [65-79]	72 [67-79]	73 [65-82]	65 [65-77]
Adjusted body weight (ABW) (kg)	76 [72-85]	72 [66-76]	79 [70-88]	77 [76-87]
Lean body weight (LBW) (kg)	63 [56-69]	55 [52-61]	65 [58-72]	64 [63-72]
Body mass index (BMI) (kgm^{-2})	28 [25-30]	23 [19-23]	28 [26-28]	32 [31-33]
Individual PK parameters				
Clearance (mLhr^{-1})	258 [193-314]	287 [209-377]	258 [128-318]	250 [193-296]
Central volume of distribution (mL)	3898 [2416-3794]	3164 [2322-3697]	2898 [2240-4589]	2516 [2416-3457]
Intercompartmental clearance (mLhr^{-1})	89	89	89	89
Peripheral volume of distribution (mL)	799	799	799	799
Half-life (hours)	12.6 [11.8-14.5]	12.6 [10.3-14.2]	14.1 [11.8-18.3]	12.3 [11.6-14.1]

Data presented as no. (percentages) and/or median [25-75% interquartile range].$^{#}$see table 1 for formula of calculation of morphometric variables.

median and interquartile range [IQR] for continuous variables and as number (No.) and percentages (%) for categorical variables.

The relationship of IVR with body size descriptors was evaluated. To test differences between groups and significant trends, the Kruskal Wallis-test and Jonckheere Terpstra test were used, which are non-parametric independent tests using SPSS statistics for Windows, version 21.0 (IBM Corp, Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

In total, we included 22 severe and moderate hemophilia patients (median body weight 87 kg [IQR 73-96]; median age 51 years [IQR 33-65]). Twelve patients (54.5%) were overweight (BMI 25-30 kgm^{-2}) and five (22.7%) were obese (BMI >30 kgm^{-2}). General patient characteristics and individual PK parameters are depicted in Table 3. Comparison of measured and predicted FVIII plasma concentrations, calculated using the FVIII population PK model developed by Björkman et al.[14], demonstrated underprediction of FVIII measurements at t=4 hours (with concentrations greater than 0.8 IUmL^{-1}) in overweight and obese hemophilia patients (Figure 1A). Therefore, it was concluded that individual PK parameters using this model could not describe FVIII plasma concentrations versus time curves adequately.

Table 3. Dose recommendations and specified FVIII target levels for a life-threatening bleeding event

	FVIII bolus	FVIII target
Consensus*	Initial: 50 IUkg^{-1} bd: 25 IUkg^{-1}	1.00 IUmL^{-1} *(peak)* >0.50 IUmL^{-1} *(trough)*

* according to the National guideline of the Netherlands[3]; bd= twice daily

Average parameter estimates of the newly constructed modified FVIII population PK model were: CL: 258 mLhr^{-1}, Q: 89 mLhr^{-1}, V1: 3898 mL and V2 799 mL. Inter-patient variability in CL and V1 was 44% and 34%, respectively. Residual variability was 14%. The modified FVIII population PK model was able to describe PK parameters of all study patients adequately, and to correctly predict observed FVIII plasma concentrations (Figure
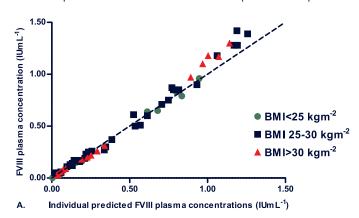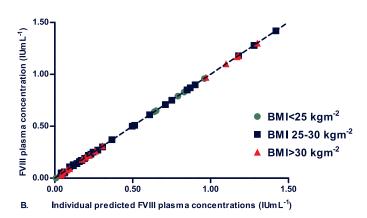
Figure 1. Goodness of fit plot with both measured and individual predicted FVIII plasma concentrations

*According to the population pharmacokinetic model of A. Bjorkman et al. and B. the modified model including overweight and obese patients; in all figures patients are categorized to body mass index (BMI), in green patients with a BMI <25 kgm^{-2}, in black BMI 25-30 kgm^{-2}, and red BMI >30 kgm^{-2}.

1B). No differences were observed for clearance and volume of the central compartment between different subgroups when classified according to BMI (p=0.40 and p=0.66 respectively, Table 2).

For each patient with individual PK parameters obtained from the modified population PK model, FVIII concentration versus time profiles were simulated. Four time profiles

were simulated following a dose of 50 IUkg^{-1}, using the four body size descriptors e.g. body weight, ideal body weight, adjusted body weight, and lean body weight (Table 1). Subsequently, IVR was calculated using these simulated FVIII plasma concentrations generated according to body size descriptor (Figure 2). A significant trend was observed towards higher IVR with increasing BMI when dosing was performed according to body weight (p=0.049). When ideal body weight was used as a body size descriptor, IVR was independent of BMI, as expected. In contrast, dosing according to adjusted body weight and lean body weight showed a non-significant trend of increasing IVR for subgroups with increasing BMI (Figure 2).
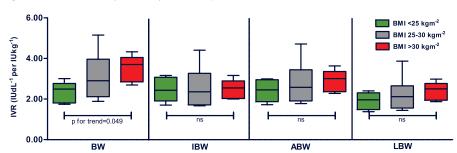
Figure 2. In vivo recovery and body size descriptors

In vivo recovery according to body mass index (BMI) for each body size descriptor; BMI <25 kgm^{-2}; BMI 25-30 kgm^{-2}; BMI >30 kgm^{-2}; IVR= in vivo recovery; IUdL^{-1}= International units per deciliter; IUkg^{-1}= International units per kilogram; BW= actual body weight; IBW= ideal body weight; ABW= adjusted body weight; LBW= lean body weight. Comparison and ordered pattern between groups was analyzed by the non-parametric Jonckheere-Terpstra test.

Prediction of FVIII peak and trough levels in case of a life threatening bleeding event
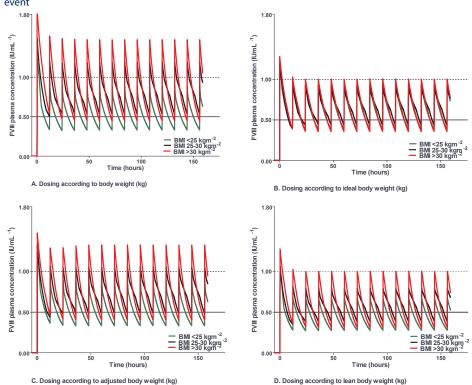
As treatment for a life threatening bleeding event requires both minimal FVIII peak values as well as minimal FVIII trough levels (Table 3), we used the individual PK parameter estimates from the modified FVIII population PK model to simulate FVIII peak values and FVIII trough levels.

As expected, high peak FVIII plasma concentrations were observed for overweight and obese patients dosed according to body weight, with mean peak FVIII plasma

concentrations of 1.60 and 1.80 IUmL^{-1} respectively (Figure 3). However, predictions of FVIII plasma concentrations resulted in trough FVIII levels below specified minimal FVIII target plasma concentration of 0.50 IUmL^{-1} in both normal and obese patients. The simulated peak FVIII plasma concentrations were significantly lower after dosing according

Figure 3. Individual estimations of FVIII plasma concentrations when dosing for a life threatening bleeding event

A. Dosing according to body weight (kg)

B. Dosing according to ideal body weight (kg)

C. Dosing according to adjusted body weight (kg)

D. Dosing according to lean body weight (kg)

Individual estimations of FVIII plasma concentrations after dosing according to different body size descriptors in case of a life threatening bleed; BMI=body mass index; A. Dosing according to body weight (kg), which resulted in high peak FVIII plasma concentrations, but also trough levels below specified target FVIII ranges; B. Dosing according to ideal body weight (kg); C. Dosing according to adjusted body weight (kg); D. Dosing according to lean body weight (kg); Dosing according to ideal body weight, adjusted body weight and lean body weight, results in FVIII trough levels below specified minimal FVIII target plasma concentration. Data presented as median of all groups, BMI <25 kgm^{-2}, BMI 25-30 kgm^{-2}, BMI >30 kgm^{-2}.

to ideal body weight in all patients (all BMI subgroups). However, corresponding FVIII trough plasma concentrations were below specified target ranges. Furthermore, dosing according to the other body size descriptors e.g. adjusted body weight and lean body weight showed similar results (Figure 3).

DISCUSSION

This cross-sectional study including overweight and obese hemophilia A patients confirms that current body weight-based dosing strategies are inadequate in these patient groups. As expected, a significant higher IVR was observed with increased BMI, as has been published by Henrard et al. and Blanchette et al.[6-8, 11] Furthermore, the FVIII population PK model by Bjorkman et al. did not correctly predict FVIII plasma concentrations in overweight and obese patients.

The data collected for this study was used to construct a modified FVIII population PK model which was able to adequately predict achieved FVIII levels for all patients. The inadequacy of the current prophylactic FVIII population PK model underlines the fact that these models should be representative for the hemophilia population as a whole. The necessity of such enriched population PK models, in this case including sufficient overweight and obese patients, is underlined by the growing number of overweight and obese hemophilia patients.[5]

A Bayesian approach was used, in which observations from individual patients and the modified population PK model were combined, in order to obtain individual PK parameter estimates. These parameter estimates were subsequently used to simulate FVIII plasma concentration-time dosing curves according to four body size descriptors e.g. actual body weight, ideal body weight, adjusted body weight and lean body mass. IVR was independent of BMI when ideal body weight was applied as a body size descriptor. Nevertheless, calculations according to IVR-based dosing resulted in FVIII values below prescribed FVIII trough values for bleeding events. This suggests that individualized dosing cannot be achieved by application of body size descriptors. Moreover, that dosing by PK-guidance using a representative population PK model seems best practice.

Study strengths and limitations

The strength of this study is the inclusion of patients with a wide range of body weights, including overweight and obese patients, with corresponding BMI values. The prophylactic population PK model by Bjorkman et al. was allometrically scaled to account for the wide ranges of body weight (17-124 kg) of the 50 included patients.[14] Nonetheless, the distribution of overweight and obese patients in this dataset is unclear. In addition in our study, a modified population PK model was developed which was able to describe the specific patients included in this study group.

Previously Graham et al. treated six obese hemophilia patients (BMI >30 kgm^{-2}) according to ideal body weight.[18] A significant reduction of infused concentrates and a good clinical outcome was observed. However, no information was available on FVIII trough levels 48 hours after infusion. In a study by Collins et al. in 143 severe hemophilia A patients treated prophylactically with a follow-up period of a minimum of 75 exposures, time spent with FVIII levels below trough levels were associated with an increased risk of bleeding.[19] In our study, we showed that dosing based on ideal body weight results in FVIII trough plasma concentrations below specified FVIII target ranges for a life threatening bleeding event and thus leads to a potential increased risk of severe bleeding. Earlier reports, have also observed poor correlations between IVR and FVIII trough levels.[20, 21] In our opinion, this inability to predict trough levels makes IVR-based dosing undoubtedly less useful in both prophylactic and "on demand" settings. Therefore, PK-guided dosing is preferred as it takes both targeted peak and trough levels into account when establishing necessary dosing and frequency of dosing. In addition, in daily practice interindividual differences in FVIII clearance may occur with significant consequences for trough FVIII plasma concentrations and dosing without an effect on IVR.[22]

In conclusion, we believe that PK-guided dosing for overweight and obese hemophilia A patients based on Bayesian analysis using an enriched FVIII population PK model is superior to IVR-based dosing as it adequately predicts both required peak and trough levels of FVIII. Although, other body size descriptors such as ideal body weight have been suggested to optimize IVR-based dosing, our simulations show that this approach does not guarantee adequate targeting of FVIII. Future studies are needed to validate current findings, which will lead to optimization of current treatment strategies for both overweight and obese patients.
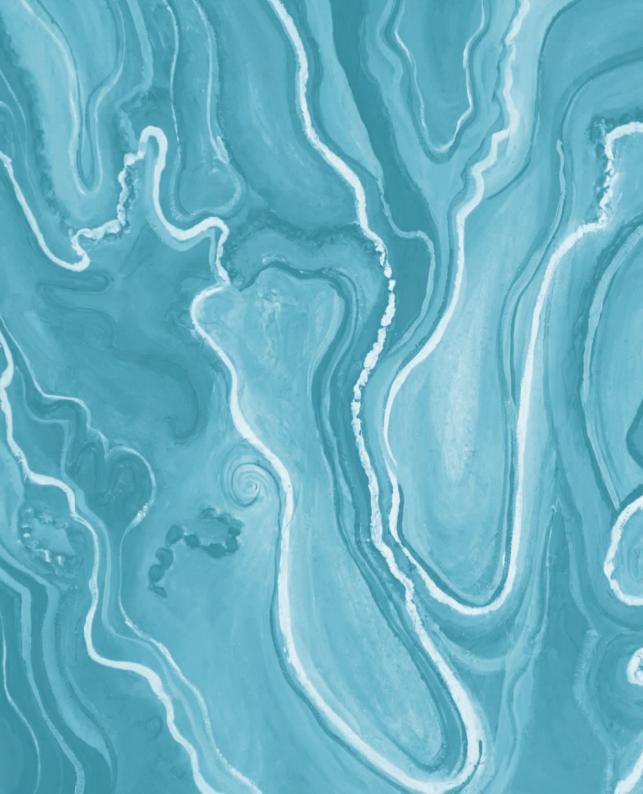
ACKNOWLEGDMENTS

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Chapter 9

Pharmacokinetic-guided dosing of factor VIII concentrate in a patient with hemophilia during renal transplantation

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SUMMARY

A 29 year old man with severe hemophilia A and end-stage renal disease underwent a renal transplantation. To prevent bleeding, patient was treated with replacement therapy using factor VIII (FVIII) concentrate, according to National guidelines. Bayesian analysis was performed by combining observed FVIII concentrations with a population pharmacokinetic (PK) model for patients with severe hemophilia A in a perioperative setting. Application of Bayesian analysis led to accurate prediction of observed concentrations after prescribing dosing advice. We believe PK-guided dosing of factor concentrates is a valuable step towards further individualization of treatment in patients with bleeding disorders. Especially in those patients requiring precise targeting of coagulation factor levels due to high risk of either bleeding or thrombosis, as illustrated by this patient undergoing a major surgical procedure.

BACKGROUND

Hemophilia A is an X-linked inherited deficiency of coagulation factor VIII (FVIII), characterized by bleeding in muscles and joints. Patients are classified according to residual coagulation factor concentrations e.g. severe (FVIII<0.01 IUmL^{-1}), moderate (FVIII:0.01-0.05 IUmL^{-1}) and mild disease (FVIII:0.06-0.40 IUmL^{-1}).[1] Replacement therapy with factor concentrates is prescribed both "on demand" in case of acute bleeding or for surgical and dental procedures or "prophylactically" to prevent spontaneous bleeding in patients with a severe bleeding phenotype.

Hemophilia A patients are currently dosed with FVIII concentrate according to body weight, clinical phenotype, residual FVIII levels, severity of bleed or surgical bleeding risk, and crude estimations of clearance.[1] In case of surgical procedures or bleeding, minimal FVIII target levels are maintained according to National guidelines to safeguard haemostasis.[2] FVIII clearance is influenced by various factors, such as age, body weight and von Willebrand factor (VWF). The latter prevents FVIII clearance by protecting it from proteolysis and cellular uptake in the circulation. The liver is primarily responsible for FVIII clearance by mechanisms of cellular clearance. Due to high molecular weight of FVIII, clearance by the kidney does not play a role.[3, 4]

Previously, we demonstrated that novel dosing methods are necessary to minimalize under- and overdosing in the perioperative period.[5] In this study, 45% of trough and steady state FVIII plasma concentrations within 24 hours after surgery were lower than specified target ranges, while 75% of these plasma concentrations were above target more than six days after hospitalization.[5] Moreover, we developed a perioperative population PK dosing model for (moderate) severe hemophilia A patients to optimize dosing (Table 1).[6] In this case report, we applied Bayesian analysis using this model in order to individualize perioperative dosing. Important as this patient required precise targeting of coagulation factor levels due to a high risk of both bleeding and thrombosis. Hereby, we show feasibility of individualized PK-guided iterative dosing.

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Table 1. Model equations describing the perioperative population PK model*

CL	$CL\ (\dfrac{mL}{h}) = 150 \times (\dfrac{Body\ weight}{68})^{0.75} \times (\dfrac{Age}{40})^{-0.17} \times 1.26^{Blood\ group} \\ \times 0.93^{Severity\ of\ surgical\ procedure}$
V1	$V1\ (mL) = 2810 \times (\dfrac{Body\ weight}{68}) \times (\dfrac{Age}{40})^{-0.09}$
Q	$Q\ (mL/h) = 160 \times (\dfrac{Body\ weight}{68})^{0.75}$
V2	$V2\ (mL) = 1900 \times (\dfrac{Body\ weight}{68})$

*According to Hazendonk et al. 2016[6] ; CL=clearance; V1=central volume of distribution; Q=intercompartmental clearance; V2=peripheral volume of distribution
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

CASE PRESENTATION

A 29 year old man with severe hemophilia A presented with end-stage renal disease due to a proliferative familial IgA nephropathy and severe symptoms of nephrotic syndrome. Medical history also included a period of acute renal failure due to post infectious glomerulonephritis, which was treated conservatively. Renal treatment consisted of peritoneal dialysis, and prednisolone. Prophylactic treatment for hemophilia A consisted of 2000 IU FVIII concentrate three times a week. Further patient characteristics are depicted in Table 2. Patient underwent a renal transplantation with perioperative iterative FVIII concentrate dosing guided by application of Bayesian analysis using individual FVIII plasma concentrations in combination with information from the perioperative population PK model.

Table 2. Patient characteristics and laboratory measurements

Age (years)	29	
Body weight (kilograms)	93	
Blood group	O	
Prophylactic treatment	2000 IU FVIII (Helixate®) 3 times/week	
Individual pharmacokinetic parameters*		
Clearance (mLkg^{-1})	180	
Central volume of distribution (mL)	3260	
Intercompartmental clearance (mLkg^{-1})	186	
Peripheral distribution volume (mL)	2750	
	Prior surgery	*After surgery*
GFR (mLmin^{-1})	<10	73
Creatinine (umolL^{-1})	1427	105
Urea (mmolL^{-1})	50	6.9

* Derived from perioperative population PK model (Hazendonk et al. 2016)[6]

INVESTIGATIONS

Renal function tests prior and after surgery are depicted in Table 2. Peak and trough FVIII plasma concentrations were measured daily by a one-stage clotting factor assay, using FVIII-deficient plasma (Siemens healthcare, Marburg, Germany) and reference plasma (Cryocheck, Precision Biologic, Kordia, Leiden, The Netherlands) on an automated co-agulation analyser (Sysmex CA1500, Siemens, Breda, The Netherlands). PK analysis was performed using nonlinear mixed-effects modelling (NONMEM (version 7.2.0), Globo-max LLC, Ellicott City, Maryland, USA). Individual PK parameter estimates were obtained from Bayesian analysis after performance of an individual FVIII PK-profile (Figure 1). Application of Bayesian analysis using measured FVIII plasma concentrations resulted in iterative dose-adjustments.
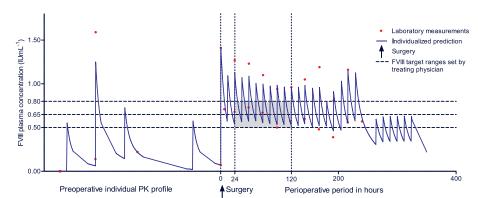
Figure 1. Individual pharmacokinetic profile and individual prediction of factor VIII plasma concentrations

An individual PK profile is constructed based upon measurement of three FVIII plasma concentrations according to the prophylactic population PK model by Björkman et al. In the perioperative setting, FVIII was targeted at >0.65 IUmL^{-1} in the first 24 hours following surgery followed by target trough FVIII plasma concentrations of >0.50 IUmL^{-1}. Application of Bayesian analysis using a perioperative population PK model resulted in iterative FVIII concentrate dose-adjustments.

TREATMENT

During the perioperative period, patient was treated with FVIII concentrate by bolus infusions, with specific FVIII trough target plasma concentrations >0.65 IUmL^{-1} during the first 24 hours and between 0.50 and 0.80 IUmL^{-1} during the next five days in accordance to protocol defined by the treating haematologist, who adapted standard treatment due to high risk of the intervention.[2] As shown in Figure 1, predicted trough FVIII plasma concentrations were in accordance with measured FVIII plasma concentrations. Moreover, trough FVIII plasma concentrations of >0.50 IUmL^{-1} were achieved during five consecutive days following surgery.

OUTCOME AND FOLLOW-UP

Perioperative hemostasis was evaluated as adequate by the surgical team and no post-surgical bleeding or thrombosis was observed. At twelve weeks post-surgical evaluation, renal graft was functioning well.

DISCUSSION

This is the first publication of a patient treated using PK-guided dosing during the total perioperative period based on a perioperative population PK model. We show that iterative adaptive dosing by Bayesian analysis is possible and feasible for major surgical interventions.

Renal transplant surgery is often complicated by adverse haematological events such as bleeding but also intravesical thrombosis, both with a risk of renal allograft rejection.[7] One earlier report described a renal transplantation in a mild hemophilia patient that was complicated by occurrence of an intravesicular bleed resulting in an allograft rejection.[8] In another case report, FVIII plasma concentrations were kept > 0.70 IUmL^{-1} for more than 2 weeks and afterwards >0.20 IUmL^{-1} with long-term successful transplantation of the allograft.[9] To prevent adverse events, maintenance of predefined trough levels is important. We have shown that it is possible to guide FVIII dosing by iterative application of Bayesian analysis using a recently developed perioperative population PK model in a major surgical procedure prone for complications such as bleeding and thrombosis.

Strikingly, actual peak and trough FVIII plasma concentrations after surgery were somewhat higher than predicted by the model. Most probably this under prediction is caused by high postsurgical VWF levels due to inflicted endothelial damage due to the intensity of the surgical procedure. VWF prolongs FVIII presence in the circulation, due to the decrease in clearance by protection from proteolysis, resulting in higher FVIII plasma concentrations.[4, 10, 11] In the ongoing prospective randomized controlled "OPTI-CLOT" trial (RCT), which is described in more detail elsewhere[12], we hope to gain more insight into the relationship between VWF levels and PK parameter estimates. It is expected that future incorporation of VWF into the population PK model will minimize discrepancies.

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A proposal for when and how often to measure VWF can then be provided, which will further improve individualized treatment.

Bayesian analysis is already routine practice for dosing of certain antibiotics, cyclosporine, and some chemotherapeutics. Therefore, we believe that implementation of this approach in the current routine practice of hemophilia will increase quality of care and help achieve individualization of treatment.

LEARNING POINTS

– Individualized treatment of perioperative hemophilia A patients is possible by application of a Bayesian approach using a recently developed FVIII population PK model as predefined target ranges were adequately maintained.
– Future individualized PK-guided dosing of factor concentrates may minimalize underdosing and overdosing, leading to improvement of quality of care.
– Especially in surgical procedures requiring strict maintenance of FVIII concentrations, PK-guided dosing may be of additional value.

PATIENT'S PERSPECTIVE

As a patient with hemophilia and comorbidity, I have often experienced anxiety with regard to hemostatic complications around the various surgical procedures I have undergone. Now that I have experienced the advantages and minimal disadvantages of PK-guided dosing, I realize that this methodology provides a real opportunity to improve suboptimal targeting of coagulation factor levels in the perioperative setting. My recent renal transplantation, which was associated with both a high risk of bleeding as well as thrombosis illustrates this nicely. Moreover, I realize that in general, minimization of overdosing will decrease thrombotic risk but also minimize health care costs by potential decrease of overall consumption of factor concentrates. Inversely, minimization of underdosing is important to decrease bleeding risk. To conclude, I gladly support this treatment innovation as it optimizes quality of care and leads to individualization of hemophilia treatment.

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PART IV
SUMMARY, GENERAL
DISCUSSION AND
CONCLUSION

Chapter 10

General discussion

Setting the stage for individualized therapy in hemophilia: What role can pharmacokinetics play?

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SUMMARY

Replacement therapy with clotting factor concentrates (CFC) is the mainstay of treatment in hemophilia. It's widespread application has led to a dramatic decrease in morbidity and mortality in patients, with concomitant improvement of quality of life. However, dosing is challenging and costs are high. This review discusses benefits and limitations of pharmacokinetic (PK)-guided dosing of replacement therapy as an alternative for current dosing regimens. Dosing of CFC is now primarily based on body weight and based on its in vivo recovery (IVR). Benefits of PK-guided dosing include individualization of treatment with better targeting, more flexible blood sampling, increased insight into association of coagulation factor levels and bleeding, and potential overall lowering of overall costs. Limitations include a slight burden for the patient, and availability of closely collaborating, experienced clinical pharmacologists.

HEMOPHILIA AND CURRENT TREATMENT

Background of the disease

Hemophilia A and B are X-linked inherited bleeding disorders characterized by deficiencies of factor VIII (FVIII) and factor IX (FIX), respectively. Prevalence is estimated at 1 in 5,000 male births for hemophilia A and 1 in 30,000 male births for hemophilia B.[1, 2] FVIII and FIX enhance formation of thrombin and consequently stabilize the hemostatic clot by increased fibrin formation. Disease severity is classified according to residual FVIII or FIX coagulation activity in plasma (FVIII:C or FIX:C).[3] Mild hemophilia patients have FVIII:C or FIX:C levels of 0.05-0.40 IUmL^{-1}, moderate patients FVIII:C or FIX:C levels of 0.01-0.05 IUmL^{-1} and severe patients FVIII:C or FIX:C levels of less than 0.01 IUmL^{-1}. Mild hemophilia is characterized by an increased risk of bleeding after trauma or surgery. Moreover, severe as well as moderate hemophilia patients suffer from spontaneous bleeding or bleeding after minimal trauma in muscles and/or joints, potentially resulting in disabling arthropathy.[4] Strikingly, bleeding phenotype differs between hemophilia patients with identical baseline FVIII:C or FIX:C levels and is probably influenced by inter-individual variation in patient characteristics such as age, body weight, modifying factors within the hemostatic system, behavioral factors and daily (sporting) activities and other yet unidentified factors.[5-10] In addition, it may be influenced by inter-individual variation of half-life of clotting factor concentrates (CFC) administered either prophylactically or on demand (Table 1).

Current treatment with replacement therapy

Replacement therapy with CFC can be given to prevent spontaneous or repetitive bleeding (prophylaxis), or "on demand" to treat acute bleeding and prevent bleeding at the time of dental or surgical procedures. Current CFCs are either of recombinant or plasma-derived origin. Prophylaxis is the mainstay of treatment in hemophilia. Its introduction has dramatically changed the lives of many hemophilia patients. Consequently, hemophilia has evolved from a crippling disease due to frequent bleeding in joints and muscles with a life expectancy of about 20 years due to often lethal severe bleeding, into a disease with a normal life expectancy, reduced prevalence of joint arthropathy and acceptable quality of life.[11, 12]

Table 1. Factors influencing bleeding phenotype in hemophilia patients

Patient characteristics	Hemostatic factors	Pharmacokinetics of treatment
Age	FVIII and FIX plasma levels	Clearance (Cl)
Body weight	FVIII and FIX gene mutation	Volume of distribution (Vd)
Other morphometric variables	Blood group	Half-life (T1/2)
Joint status	von Willebrand factor	In vivo recovery (IVR)
General (muscle) condition	Thrombin generation and fibrinolysis	
Daily (sporting) activities	Unidentified hemostatic factors	
Behavioral factors		
Adherence to treatment		
Miscellaneous		

Prophylaxis

Prophylaxis was introduced in 1965 by Ahlberg and is based on the observation that moderate hemophilia patients with FVIII:C or FIX:C levels above 0.01 IUmL^{-1} have far fewer joint bleeds and less subsequent arthropathy.[13] Therefore, it was reasoned that joint bleedings could be prevented in severe hemophilia by keeping FVIII:C and FIX:C levels above 0.01 IUmL^{-1}. To achieve this, CFCs must be regularly infused generally two to four times a week in hemophilia A and one to three times a week in hemophilia B.[14-17] Prophylactic treatment profoundly reduces frequency of bleeding and improves joint status as demonstrated by Manco Johnson et al. in a randomized controlled trial.[11] Various guidelines for prophylaxis are available of which Table 2 shows a selection of those most often applied. The efficacy of prophylaxis in preventing joint bleedings is largely dependent on maintaining minimal FVIII:C and FIX:C trough levels of 0.01 IUmL^{-1} in the patient. Moreover, time spent below trough levels is associated with number of bleeding events.[18] However, in standard clinical practice, trough levels are hardly measured and dose and frequency of prophylactic infusions are only adjusted when spontaneous or frequent bleeding occurs.

On demand treatment

When patients are treated "on demand" either for acute bleeding or in a dental and/or surgical setting, dosing of CFC is aimed to achieve FVIII:C and FIX levels above a certain threshold/ trough and below a certain maximum to avoid waste of CFC and high costs

Table 2. Prophylactic dosing regimens for hemophilia A and B

Prophylaxis	Hemophilia A		Hemophilia B	
	Dose (IUkg^{-1})	**Frequency dosing** (n/ week)	**Dose** (IUkg^{-1})	**Frequency dosing** (n/ week)
Utrecht protocol-*Dutch* (Low dose prophylactic regimen) [14]	15-30	three	15-30	two
Malmö protocol– *Nordic* (High dose prophylactic regimen) [17]	25-40	three	25-40	two
UKHCDO[16]	25-50	four	Not provided*	
WFH[15]	According to Utrecht or Malmö protocol		According to Utrecht or Malmö protocol	

*Recommendations for patients with hemophilia B are not provided given the paucity of published evidence.

without clinical effect according to various guidelines (Table 3).

More specifically, when acute bleeding occurs FVIII:C and FIX:C peak levels are generally considered particularly important, although they are rarely monitored. Targeted peak levels are dependent on both severity and location of bleeding. In Dutch guidelines[14], FVIII:C or FIX:C peak levels of 0.30 IUmL^{-1} for minor bleeds, 0.50 IUmL^{-1} for severe bleeds and 1.00 IUmL^{-1} for life threatening bleeds are targeted. In severe or life threatening bleeds, it is more important to take trough levels into account. These FVIII:C and FIX levels are sometimes monitored but often merely estimated, and maintained based on the opinions of the treating physician. In the perioperative setting, mainly trough levels are considered important although at initiation of surgery a specific peak FVIII:C and FIX:C range is targeted according to all guidelines. Overall, targeted perioperative FVIII:C and FIX:C trough levels depend on the invasiveness of the dental and/or surgical procedure and postoperative day, with e.g. Dutch guidelines prescribing FVIII:C or FIX trough levels of 0.80-1.00 IUmL^{-1} during the first 24 hours after surgery; 0.50-0.80 IUmL^{-1} 1 to 5 days (24-120 hours) after surgery; and 0.30-0.50 IUmL^{-1} >5 days after surgery (Table 3).

Table 3. Target ranges with peak and trough FVIII:C and FIX levels and duration of administration according to a selection of available guidelines

	Hemophilia A		Hemophilia B	
	Predefined target ranges (IUmL^{-1})	**Duration** (days)	**Predefined target ranges** (IUmL^{-1})	**Duration** (days)
Dutch[14]				
Major surgery				
Preoperative	*0.80-1.00*		0.80-1.00	
Postoperative	0.80-1.00	1	0.80-1.00	1
	0.50-0.80	2-5	0.50-0.80	2-5
	0.30-0.50	>6	0.30-0.50	>6
Minor surgery				
Preoperative	*0.80-1.00*		0.80-1.00	
Postoperative	>0.50	Depending on procedure	>0.50	Depending on procedure
Nordic[17]				
Major surgery				
Preoperative	*0.70-1.00*		*0.70-1.00*	
Postoperative	0.60-0.80	1-3	0.60-0.80	1-3
	0.40-0.60	4-6	0.40-0.60	4-6
	0.30-0.40	7-9	0.30-0.40	7-9
Minor surgery				
Preoperative	*>0.50*		*>0.50*	
Postoperative		1-5 depending on procedure		1-5 depending on procedure
WFH[15]	*No significant resource constraints*			
Major surgery				
Preoperative	*0.80-1.00*		*0.60-0.80*	
Postoperative	0.60-0.80	1 - 3	0.40-0.60	1 - 3
	0.40-0.60	4 - 6	0.30-0.50	4 - 6
	0.30-0.50	7 - 14	0.20-0.40	7 -14
Minor surgery				
Preoperative	*0.50-0.80*		*0.50-0.80*	
Postoperative	0.30-0.80	1 - 5	0.30-0.80	1 - 5

Table 3. Target ranges with peak and trough FVIII:C and FIX levels and duration of administration according to a selection of available guidelines (continued)

	Hemophilia A		Hemophilia B	
	Predefined target ranges (IUmL^{-1})	**Duration** (days)	**Predefined target ranges** (IUmL^{-1})	**Duration** (days)
WFH[15]	*Significant resource constraints*			
Major surgery				
Preoperative	*0.60-0.80*		*0.50-0.70*	
Postoperative	0.30-0.40	1 - 3	0.30-0.40	1 - 3
	0.20-0.30	4 - 6	0.20-0.30	4 - 6
	0.10-0.20	7 - 14	0.10-0.20	7 -14
Minor surgery				
Preoperative	*0.40-0.80*		*0.40-0.80*	
Postoperative	0.20-0.50	1 - 5	0.20-0.50	1 - 5

Peak FVIII:C and FIX levels are estimated based on average in vivo recovery (IVR) of FVIII or FIX concentrates and amounts of CFC (IU) infused per kilogram body weight. This IVR-based dosing originates from studies that show that each infused unit of CFC per kilogram results in a mean increase of 0.02 IUmL^{-1} for FVIII:C and 0.01 IUmL^{-1} for FIX.[9, 19] Application of this formula only provides a rough estimate of the maximum plasma concentration of FVIII:C and FIX after infusion. More explicitly, it does not take the pharmacokinetics (PK) of administered CFC of the individual patient into account, e.g., clearance, volume of distribution, and half-life. Application of these PK parameters results in a more precise estimate of peak FVIII:C and FIX but also enables calculation of FVIII:C or FIX levels and the formulation of recommendations on frequency and timing of dosing of FVIII and FIX concentrates.

When describing PK of the various CFC in hemophilia, differences are apparent between products. In both recombinant and plasma-derived FVIII concentrates, average half-life is estimated at 10.4 hours [95% CI 7.5-16.5] in adults and 9.4 hours [95%CI 7.4-13.1] in children.[20] Contrastingly, no relationship between age and terminal half-life is observed for FIX concentrates.[21] Differences in PK of current FVIII and FIX concentrates are significant, with a longer half-life of FIX in comparison to FVIII (18-34 hours and 11-16 hours, respectively).[22] Furthermore, FVIII clearance is lower than FIX clearance (2.4-3.4mL h^{-1} kg^{-1} versus 3.8-8.4 mL h^{-1} kg^{-1})[22], due to the binding of FVIII to its carrier protein VWF which

protects FVIII from proteolytic degradation.[23, 24] Although, FVIII has a lower clearance in comparison to FIX the longer half-life of FIX is explained by its much larger volume of distribution, as roughly t1/2 = 0.693*Volume of distribution (Vd)/ clearance (CL). This larger volume of distribution of FIX is due to FIX binding to the vascular endothelium and diffusion into interstitial fluid on account of its lower molecular weight when compared to FVIII (FIX: 57 kDa ; FVIII: 280 kDa).[25, 26]

Limitations of current treatment guidelines

Underlying the presently used dosing calculations is the assumption that all patients demonstrate similar PK of administered CFCs. However unfortunately, this is not the case. Bjorkman et al. were the first to report the significant inter-individual variations in PK after the administration of a standard bolus of FVIII or FIX concentrate in a large population. Significant differences were observed with regard to in vivo recovery (IVR), clearance and half-life[8, 20,27, 28] with FVIII half-life varying from 6-25 hours and FIX half-life from 25-56 hours between individuals. Collins et al. showed that the efficacy of prophylactic treatment is based on time spent above certain FVIII trough levels[29] and that therefore half-life and frequency of CFC dosing are more important than IVR of CFCs. Despite these findings, current treatment guidelines for replacement therapy are still based on IVR-based dosing regimens, which do not take the inter-individual variation of pharmacokinetics of CFCs into account.

Furthermore, as is observed in the general population, obesity also increasingly occurs in hemophilia patients.[30] This will result in in higher FVIII and FIX consumption if prophylactic and on demand treatment is persistently based on body weight and IVR-based dosing regimens. Importantly, increasing body weight is not linearly associated with increasing volume of distribution as assumed by IVR-based dosing regimens.[31] Therefore, these higher costs of treatment may not be necessary to safeguard hemostasis. Obviously, current global constraints of health care budgets, obligates hemophilia communities worldwide to generate dosing algorithms in hemophilia with optimal results for patients and minimal costs for society.

Moreover in the perioperative setting, we recently demonstrated that current dosing leads to significantly lower and higher FVIII and FIX levels than targeted in hemophilia A and B.[32, 33] In moderate and severe hemophilia A patients, a large proportion of trough and steady state FVIII:C levels were found to be below or above predefined target ranges.

Specifically, 45% of FVIII:C measurements were below the FVIII target range within first 24 hours after surgery and 75% above the target range during hospitalization more than six days after surgery.[32] Potentially, more optimal maintenance of perioperative target ranges could result in a reduction of 44% of CFC consumption, when ignoring logistical aspects of care.[32] In a recent retrospective study on perioperative management in moderate and severe hemophilia B patients, 60% of FIX measurements were below target and 59% FIX levels above target during hospitalization more than six days after surgery.[33] Although the terminology of under- and overdosing suggests putting the patient at risk which is not the case as perioperative complications were minimal, these data do underline the limitations of current dosing algorithms primarily based on body weight using IVR-based dosing. As well as potential cost-effectiveness of alternative algorithms.

PHARMACOKINETIC (PK)-GUIDED DOSING IN HEMOPHILIA

Principles of PK-guided dosing

To address interindividual differences in PK of CFC and to employ more effective dosing, PK-guided dosing is a potential strategy. PK-guided dose-calculations are based on individual PK parameters in relationship to the population PK model and obtained by Bayesian analysis using statistical software (NONMEM®). In a population PK model for CFC, relationships between dose and achieved FVIII:C or FIX:C levels are described by PK parameters of all individuals in the population under review. This makes it possible to describe both inter-individual and intra-individual variability within this population dataset. In general, an important condition for implementing PK-guided dosing, is that intra-individual variability is smaller than inter-individual variability. Identified covariates explaining variability can be used to further improve constructed models, while unknown factors are labeled as residual errors. The principal strength of PK-guided dosing is that a population PK model not only represents identified covariates influencing PK parameters, but also takes the unknown modifiers of PK into account as they are described by the population data included in the model.

Importantly, Bayesian adaptive dosing is only possible when population PK models are representative of the individual patient and her or his specific clinical setting. Construct-

ed models should therefore comprise a wide variation in patient-related (age, body weight, endogenous baseline FVIII/FIX, blood group) and circumstance-related factors (prophylaxis, on demand dosing during hemostatic challenges such as acute bleeding and surgery). For example, the recently published perioperative FVIII population PK model showed a significantly larger peripheral volume of distribution in comparison to the prophylactic PK model by Bjorkman et al. (1180 mL/68 kg versus 240 mL/68 kg).[8, 34] Further, to optimize current population models it is important to include often under-represented patient populations, such as children and overweight/obese patients since PK parameters in these populations may differ significantly.

Construction of individual PK profiles and population PK models

Extensive work performed by Bjorkman et al. has made PK-guided prophylactic dosing with limited blood sampling in hemophilia possible.[35] Prior to the construction of these population PK models, individual PK curves were constructed through extensive blood sampling (>10 samples), with an obligatory wash-out period, leaving the patient at potential risk of bleeding. Currently, individual PK profiles for FVIII and FIX can fortunately be constructed with limited blood sampling and without a wash out period (Table 4).[35-37] Using Bayesian analysis and a representative population PK model, individual PK estimates can be iteratively updated, providing prophylactic dosing advice and prediction of achieved FVIII:C and FIX:C levels.[38]

Perioperatively, several research groups have estimated preoperative loading doses of FVIII and FIX after constructing individual PK profiles.[39-43] However, until recently it was not possible to iteratively dose patients in the perioperative setting owing to the lack of population PK models for this specific setting. Construction of perioperative PK population models for both moderate and severe hemophilia A[34] and B, mild hemophilia A[44] and in the near future for von Willebrand disease[34] will eventually make this possible for several bleeding disorders.

The most important covariate in FVIII population PK models for hemophilia A patients, will most likely be von Willebrand factor (VWF). This is supported by findings that blood group O versus non-O is a significant covariate of clearance in the perioperative setting, with 26% higher clearance rates for patients with blood group O.[34] It is generally known that patients with blood group O have lower VWF levels due to influence of ABO antigens on the rate of synthesis or proteolysis of VWF.[45] However, this effect of blood group
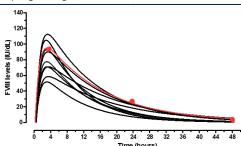
Table 4. Limited blood sampling strategies to construct individual PK curves.

	Bolus infusion (IUkg^{-1})	FVIII:C or FIX measurements
Factor VIII (FVIII) (Björkman et al.[35])	50	T=4, T=24, T=48 hours
Plasma derived Factor IX (FIX) (Brekkan et al.[36])	50	T=48, T=72 hours ór T=54, T=78 hours
Recombinant Factor IX (FIX) (Preijers et al.[37])	100	One sample post infusion, two samples between T=72 and T=80 hours.

O was not previously observed in a steady state prophylactic setting.[46] Most likely, this difference can be explained by an increase of VWF due to inflicted endothelial damage and its role in the acute phase reaction after surgery.[47]

Benefits of PK-guided treatment

As early as 1997, Carlsson et al. showed benefits of a PK-guided dosing approach for prophylaxis.[7] This small study was designed as a randomized cross-over study comparing PK-guided dosing of prophylaxis with standard prophylactic dosing in 14 individuals during a period of two times six months. Strikingly, a reduction of CFC administration of 30% was achieved. The number of reported bleedings was similar in both treatment arms.[7] Such a reduction can have a significant financial impact, since annual costs for replacement therapy in the Netherlands amount to more than 126 million euros.[48] Before drawing conclusions, however, it is important to prospectively evaluate these outcomes of PK-guided dosing in adequately designed and powered studies.[49] Currently, a randomized controlled trial comparing PK-guided perioperative treatment of CFC in moderate and severe hemophilia A patients is in place to analyze the amount of CFC

administered, time spent to achieve targeted FVIII levels, as well as staff investment and costs, all in accordance with the economic health principles established by Hakkaart-van Rooijen.[49, 50] This study may result in clear conclusions regarding the cost effectiveness of PK-guided dosing.

Another benefit of PK-guided dosing is that both prophylactic and "on demand" dosing will be based on actual FVIII:C and FIX:C trough and peak levels or FVIII and FIX levels predicted by population PK models, instead of current FVIII:C and FIX estimates based on IVR-based dosing. Furthermore, FVIII and FIX sampling can be made flexible and not necessarily fixed at certain time points before or after infusion, once models are in place. Moreover, PK-guidance will optimize dosing as knowledge will increase with regard to relationship between FVIII:C and FIX:C levels and bleeding in individual patients and patient groups. In addition, an increase in dosing will not only depend on actual bleeding and a reduction of dosing can be considered by the treating professional in consultation with patients and parents. Importantly, the dose and frequency of CFC of patients on prophylaxis should only be reduced if clinically justified and impact should be monitored with regard to bleeding events, bleeding pattern and joint status (Table 5).

Over time, more exact targeting of FVIII:C and FIX levels may also lead to reliably lowering of target levels of treatment. Especially in hemophilia B, studies and clinical experience suggest that lower target levels may be acceptable.[15, 51] In a recent retrospective study on perioperative management in moderate and severe hemophilia B patients, 60% of FIX measurements were below target, without clinical relevant bleeding and independent of the severity of surgical procedures.[33] Srivastava et al. showed that lower trough FVIII:C (0.20-0.40 IUmL^{-1}) and FIX:C (0.15-0.30 IUmL^{-1}) levels 0-72 hours after surgery were not accompanied by bleeding complications since only one patient experienced bleeding due to a lack of surgical hemostasis.[51] Furthermore, International WFH guidelines for perioperative treatment in hemophilia A and B patients recommend FIX levels 0.20 IUmL^{-1} lower than FVIII:C levels (Table 3).[15] In countries with significant financial constraints, even lower FIX target ranges are suggested.[15] Interestingly, various European guidelines do not differ regarding perioperative target ranges for hemophilia A and B[14, 17, 52] as reported in a survey by the European Therapy Standardization Board in 2009.[53]

PK-guided dosing will also facilitate individualization of dosing according to individual lifestyle and activities, therefore achieving true personalization of treatment. When

Table 5. Benefits and limitations of PK-guided dosing based on population PK models as alternative for body weight and IVR-based dosing regimens

Advantages	Conditions and remarks
1. Better targeting of FVIII:C and FIX levels with minimal burden to patients.	Although limited blood sampling decreases frequency of blood sampling, two/three samples for individual PK profile are still obligatory. Population PK models should however be representative of population and specific setting.
2. More flexible blood sampling	Once PK-guided dosing is in place.
3. Insight into association of FVIII:C and FIX trough and peak levels and bleeding Future possibilities to construct both PK and pharmacodynamics (PD) models and to further understand pathophysiology of hemostasis	Further development of global hemostatic assays measuring hemostatic potential also essential.
4. Possibility to potentially lower FVIII:C and FIX target values, due to more reliable targeting	Intensive collaboration between experienced clinical pharmacologist and (pediatric) hematologist necessary. Realization of risks and intensive monitoring of clinical impact of lowering of FVIII and FIX levels obligatory.
5. Facilitation of actual personalization of treatment according to lifestyle	Continuous adaptation of dosing regimen according to lifestyle also necessary. Individual PK profiles must be potentially repeated every 3-4 years. Adherence must be discussed.
6. Potential reduction of overall treatment costs	Prospective studies to evaluate actual impact on costs are obligatory.
7. Further enrichment of population PK models	Intensive collaboration between experienced clinical pharmacologist and (pediatric) hematologist necessary.

targeting weekly FVIII:C and FIX:C levels, personal activities and preferences should be taken into account, as bleeding risk is closely related to these factors.[54-56] Moreover, non-adherence should be discussed as implementation of minimal dosing schemes may lead to an increased risk of bleeding.[57-59] Patients and families should be aware of time points when factor concentrate levels are low or high and consider additional dosing when bleeding risk is significant.

All benefits of PK-guided dosing are also applicable with regard to upcoming enhanced half-life (EHL) products. Moreover, costs of treatment will directly depend on the dose and frequency of treatment and therefore on individual PK and population PK param-

eters. Furthermore, the ongoing discussion of the association of trough levels and the role of peak levels with regard to bleeding will be made more transparent. This is especially relevant in EHL products as higher troughs will be possible and treatment peaks will be less frequent.[60]

Limitations of PK-guided treatment

Important limitations with regard to PK-guided dosing include the requirement of close collaboration with a clinical pharmacologist with expertise in PK modeling. Furthermore, time investments by patients, parents and medical professionals may be substantial as individual PK profiles must be performed regularly (every three to four years depending on patient characteristics) and perioperative PK-guided iterative dosing requires daily dosing recommendations. Solutions to overcome these limitations are the availability of web portal-based consultancies for PK-guided dosing advice, as established by Iorio[61], for instance, and as developed by a pharmaceutical company for the prophylactic setting.[62] Both initiatives to implement a closer collaboration and to educate both professionals and patients are valuable for future patient care. Transparency and reliability of the data used to construct underlying population models are of course of crucial importance in such settings.

FUTURE ROLE FOR PK-GUIDED DOSING OF FACTOR CONCENTRATES IN HEMOPHILIA CARE AND RESEARCH PERSPECTIVE

Replacement therapy has led to the high standard of hemophilia care in high-income countries. However, recent studies show that treatment is suboptimal; although bleeding is rare, both under- and overdosing of CFC occur. We believe that PK-guided dosing as alternative to body weight and IVR-based dosing, will play an important role in further individualization of therapy. We have summarized the anticipated improvements in Table 5.

Future research should include studies prospectively validating constructed population PK models but also combining PK with pharmacodynamic data (e.g. bleeding events, global hemostatic test results) and simulations to objectify minimal FVIII:C and FIX levels required for adequate hemostasis in the individual patient and in populations. These

data may subsequently support studies aiming at lower target levels in specific bleeding disorders.

CONCLUSION

We believe that PK-guided dosing deserves attention as a means of ensuring the individualization of treatment in hemophilia since benefits are significant and limitations can be overcome. The burden for patients and parents appears to be minimal. Accordingly, we call on patients, medical professionals, clinical pharmacologists, hemostatic laboratories and pharmaceutical companies to join hands in applying this approach for all CFCs, in hemophilia and other bleeding disorders requiring CFC replacement therapy.

PRACTICE POINTS

– Replacement therapy with clotting factor concentrates (CFC) is the mainstay of treatment in hemophilia.
– However, dosing is challenging and costs are high.
– Current dosing is based on body weight and in vivo recovery (IVR) of CFC.
– PK-guided dosing will enable individualization of treatment with better targeting of coagulation factor levels.

RESEARCH AGENDA

– Prospective studies are warranted validating constructed population PK models
– Future studies combining PK with pharmacodynamic data (e.g. bleeding events, global hemostatic test results)
– Simulation analyses to objectify minimal FVIII:C and FIX:C levels required for adequate hemostasis in individual patients and specific patient populations.

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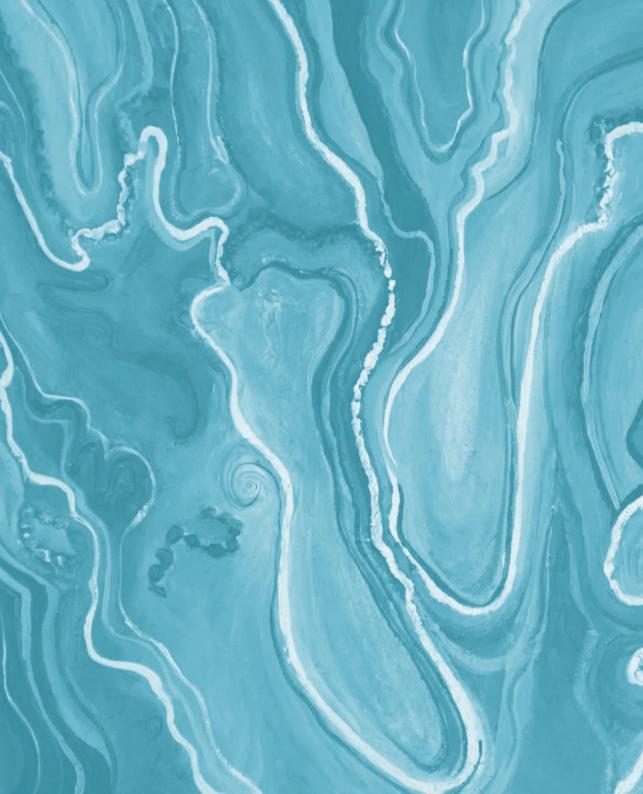
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Chapter 11

Summary

Samenvatting

SUMMARY

All studies described in this thesis are part of the "OPTI-CLOT" research program on patient tailOred PharmacokineTIc (PK)-guided dosing of CLOTting factor concentrate in bleeding disorders. These are (inter)national multicenter studies which aim to implement PK-guided dosing of clotting factor replacement therapy by initiation of studies to prove the implications of PK-guided dosing, to construct perioperative and prophylactic population PK models and to evaluate the cost-effectiveness of a PK-guided approach.

This thesis focuses on the evaluation of current dosing strategies and the feasibility of alternative, more individualized dosing based on PK-guidance using Bayesian analysis.

In **chapter 1,** a short introduction to this thesis is presented which includes an overview of current treatment of inherited bleeding disorders and introduces the terminology used to describe pharmacokinetic (PK) principles. As replacement therapy with factor concentrates is administered intravenously, especially volume of distribution and clearance are important factors when determining the dosage of factor concentrate necessary to achieve a certain coagulation factor level. Moreover, mainly volume of distribution is of importance in case of bolus infusion therapy and the administration of a loading dose while clearance of the factor concentrate is most relevant when continuous infusion is the mode of administration of factor concentrate.

In **part I,** the current management of patients with an inherited bleeding disorder undergoing a surgical procedure is evaluated with the aim to identify the extent and predictors of levels under target range and above target range as prescribed by National guidelines.

In **chapter 2,** perioperative treatment of hemophilia A patients was evaluated with special attention to the extent and predictors of factor VIII (FVIII) values under and below target values as set by National guidelines. We demonstrated that targeting of factor VIII (FVIII) values is challenging in the periperative setting in a study which included 119 hemophilia A patients undergoing 198 elective minor or major surgical procedures. Remarkably, in the first 24 hours after surgery, 45% of achieved trough and steady state FVIII levels were under predefined target ranges. Depending on postoperative

day, 33-75% of FVIII levels were above predefined target ranges. Strikingly, a potential reduction of FVIII consumption of 44% would have been attained if FVIII levels had been maintained within target ranges. Blood group O and major surgery were predictive of underdosing (OR=6.3; 95%CI [2.7-14.9];OR=3.3; 95%CI [1.4-7.9]). Also, blood group O patients had more bleeding complications in comparison to patients with blood group non-O (OR=2.02 95%CI[1.00-4.09]). Patients with blood group non-O were at higher risk of overdosing (OR=1.5 95%CI[1.1-1.9]). Most probably, this is explained by higher VWF levels and therefore higher FVIII levels, as VWF protects FVIII against proteolytic degradation in the circulation. Additionally, patients treated with bolus infusions were at higher risk of excessive overdosing (OR=1.8 95%CI[1.3-2.4]). It was concluded that refinement of dosing strategies based on individual patient characteristics such as blood group and mode of infusion can potentially lead to improved quality of care and cost-effectiveness. The perioperative treatment of hemophilia B patients is evaluated in **chapter 3**. In this retrospective international multicenter study, a total of 118 patients were included that underwent 255 surgical procedures. The aim of the study was to investigate the perioperative management and to assess predictors of low and high FIX levels. Patients were included from a total of ten Hemophilia Treatment Centers situated in the Netherlands and United Kingdom. Sixty percent of factor IX (FIX) levels ≤ 24 hours after surgery were under target level with a median deviation of 0.22 IUmL^{-1} [IQR 0.12-0.36]; while 59% of FIX levels were above target level >six days after surgery with a median deviation of 0.19 IUmL^{-1} [IQR 0.10-0.39]. However, in only three procedures (1.2%), clinically relevant bleeding complications occurred, defined as procedures requiring a second surgical intervention or necessity of a red blood cell transfusion. These events were not associated with lowFIX levels. This study shows that targeting of prescribed FIX levels in the perioperative setting is complex and results are suboptimal, but bleeding is minimal. Therefore, this may indicate that current target ranges may be debatable. Moreover, that PK-guided dosing may not only make it possible to target FIX ranges more optimally, but also to reliably target lower FIX ranges to minimalize bleeding risk.

In **chapter 4,** the perioperative management of patients with von Willebrand disease (VWD) treated with von Willebrand factor (VWF)/ FVIII concentrate was evaluated to investigate whether current strategies not based on PK are sufficient to reach the target levels of coagulation factors perioperatively. Achieved VWF activity (VWF:Act) and FVIII:C activity (FVIII) levels during FVIII-based treatment regimens were compared to pre-

defined VWF:Act and FVIII target levels stated in National guidelines. In total, 103 VWD patients undergoing 148 surgical procedures were included: 54 type 1 (73 surgeries), 43 type 2 (67 surgeries) and 6 type 3 (8 surgeries). Overall during treatment, VWF:Act and FVIII levels were measured, and were defined as high when plasma levels were ≥ 0.20 $IUmL^{-1}$ above predefined target levels. In type 1 VWD patients, respectively 65% and 91% of trough VWF:Act and FVIII levels were classified as high. In type 2 VWD and type 3 respectively, 53% and 57% of trough VWF:Act and 72% and 73% of trough FVIII levels were classified as high. In addition, as expected accumulation of FVIII levels was observed after perioperative FVIII-based replacement therapy in VWD patients. Prevalence of FVIII and VWF:Act levels >0.20 $IUmL^{-1}$ lower than target levels was rare. When analyzing predictors of high and low levels, in type 1 VWD, during the total postoperative period, only blood group O was predictive of high VWF:Act levels (VWF:Act levels ≥0.20 $IUmL^{-1}$ above target) (OR 2.9; 95%CI [1.3-6.6]). Most probably this is explained by lower endogenous baseline VWF:Act and FVIII:C levels resulting in administration of higher dosages of VWF/FVIII concentrates. No other predictors were found for low and high VWF:Act and FVIII levels in both type 1 and type 2 VWD patients. It was concluded, that more efficient therapy as well as further individualization is possible in VWD patients requiring replacement therapy. PK-guided dosing may be a potential strategy to optimize and individualize dosing in VWD. The complexity of the disease with great variation in VWD types, mutations and endothelial activation, e.g. production, secretion, and clearance of VWF however makes this a challenging prospect.

In **part II,** we used the retrospectively collected data of the observational studies described in part I to construct population PK models using nonlinear mixed-effects modeling.

In **chapter 5,** we describe the construction of a perioperative population PK model for patients with hemophilia A which depicts the perioperative PK of various currently used FVIII concentrates in order to optimize dosing based on this PK model. Population PK parameters were estimated in 119 patients of which 75 were adults (median age: 48 years, median weight: 80 kg) and 44 were children (median age: 4.3 years, median weight: 18.5 kg) undergoing respectively 140 and 58 surgical procedures. PK profiles were best described by a two-compartment model. Typical values for clearance, inter-compartmental 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. Inter-patient variability in clearance and central volume was 37% and 27%. Clearance decreased with increasing age (p<0.01) and increased in case of 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). In comparison to the population PK model constructed for the prophylactic setting, a large peripheral volume was observed. We hypothesized, that this may be explained by the perioperative increase of VWF which protects FVIII from elimination, thereby reducing clearance of FVIII. Prospective studies are however needed to evaluate this relationship in the perioperative setting. Moreover, this will be investigated in the randomized controlled "OPTI-CLOT" trial, described in **chapter 7**. The development of the described model in **chapter 5** will allow individualization of perioperative FVIII dosing in severe and moderate severe hemophilia A patients by Bayesian adaptive dosing.

In **chapter 6,** we also constructed such a perioperative population PK model for severe and moderate severe hemophilia B patients with the aim to describe FIX concentrations and interpatient variability in the perioperative period, during FIX replacement therapy, ultimately leading to more individualized therapy. A total of 118 hemophilia B patients were included (median age 40 years, median body weight 79 kilogram) who underwent a total of 255 surgical procedures. In contrast to the model constructed for FVIII concentrate, FIX:C versus time profiles were now adequately described using a three-compartment model. Average clearance (CL), inter-compartmental clearance (Q2, Q3), distribution volume of the central compartment (V1) and peripheral compartments (V2, V3), plus inter-patient variability (%) were: CL: 251 mLh^{-1}70kg^{-1} (13%), V1: 4950 mL70kg^{-1} (13%), Q2: 91.3 mLh^{-1}70kg^{-1} (99%), V2: 7900 mL70kg^{-1} (57%), Q3: 831 mLh^{-1}70kg^{-1}, V3: 1600 mL70kg^{-1} for a 32 year old patient. The estimated population PK parameters were different from those reported for prophylactic treatment, suggesting a less rapid first phase disposition to the interstitial fluids during the perioperative period. A tentative explanation for this finding is that endogenous consumption and complexation of FIX with FVIII during hemostatic challenge causes a lower distribution towards the interstitial fluids. Therefore, a dedicated population PK model is needed when PK-guided dosing is performed during surgery. With increasing age, CL and V1 increased 1.2% and 1.9% per year, respectively, until the age of 32 years (p<0.001, p<0.01). Strikingly, the final model showed that CL and V1 differed between countries. CL and V1 were 20.1% and 28.3% higher when a patient was treated in the Netherlands. Further investigations

should focus on preferences of factor concentrate brands between countries, which may explain this variation. Furthermore, the use of tranexamic acid decreased V1 by 9.8%, thus leading to a lower V1. This suggests that tranexamic acid leads to higher FIX:C directly after dosing of tranexamic acid. However, to date this pharmacodynamic effect has never been described and should be further investigated before drawing conclusions.

In **part III,** the feasibility and validation of PK-guided dosing of factor concentrates in patients with bleeding disorders is investigated. In **chapter 7,** the design of the "OPTI-CLOT trial is described. The "OPTI-CLOT" trial is an open-label, prospective, multicenter randomized controlled superiority trial (RCT), which compares standard dosing procedure with iterative Bayesian PK-guided dosing, aiming to detect a 25% difference in perioperative FVIII concentrate consumption. Patients are stratified according to mode of administration of FVIII (continuous or bolus infusion) and severity of the surgical procedure. At least sixty hemophilia A patients $\geq$ 12 years of age, with FVIII levels $\leq$ 0.05 IUml^{-1} will be included, requiring FVIII replacement therapy for an elective, minor or major surgical procedure. In this RCT, the perioperative population PK model, discussed in **chapter 5**, will be prospectively validated. In addition, concomitantly during the RCT participating Hemophilia Treatment centers will gain experience with PK-guided dosing, facilitating future implementation of this intervention.

Because some previous studies showed that PK parameters may be different in children compared to adults and in obese versus normal weight individuals we analyzed in **chapter 8,** alternative dosing strategies based on body size descriptors in overweight and obese hemophilia A patients and compared them to individualized treatment based on PK guidance. Current replacement therapy in hemophilia is based on residual FVIII levels, body weight in kilograms, and influenced by clinical phenotype, crude clearance estimations and severity of (risk of) bleeding. Historically, guidelines for dosing of hemophilia A are based on an in vivo recovery (IVR) of 2.0 which equals an increase of 2.0 IUdL^{-1} per unit of infused FVIII concentrate per kilogram. Obese patients have significantly higher IVR values, potentially leading to overdosing of factor concentrate. Therefore, alternative dosing strategies using ideal body weight or lean body weight have been proposed by several groups. We discuss the benefits and limitations of alternative dosing strategies using body size descriptors in the obese hemophilia patient. In
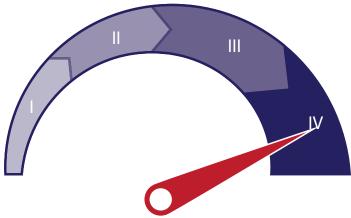
the study, 22 severe and moderate severe hemophilia A patients were included (baseline FVIII <0.05 IUml^{-1}) and categorized according to body mass index (BMI), normal: <25 kgm^{-2} (n=5) overweight: 25-30 kgm^{-2} (n=12) and obese: >30 kgm^{-2} (n=5). All patients received ± 50 IUkg^{-1} FVIII, with FVIII sampling after 4, 24 and 48 hours. Population PK models were applied to calculate FVIII plasma concentration over time. The population PK model by Bjorkman et al. did not correctly predict FVIII levels in the overweight/ obese. A modified model was constructed, describing PK parameters and FVIII levels adequately in this overweight and obese patient group. Median IVR was significantly higher in overweight (2.65) and obese (3.00) patients when compared to those with a normal BMI (2.17) (p<0.05). IVR was independent of BMI when ideal body weight was applied. Nevertheless, for all body size descriptors IVR-based dosing (IVR of 2.0) resulted in FVIII trough levels below set target levels for bleeding events. It was concluded that, in contrast to what is generally hypothesized, alternative body size descriptors are not able to substitute PK-guided dosing. We conclude that when PK-guided dosing of factor VIII concentrate is performed, the population PK model should be representative of the specific patient population, in this case e.g.obese/overweight patients.

In **chapter 9** it is illustrated how an individual PK profile and a perioperative population PK model can be utilized to individualize treatment in a single patient undergoing a renal transplantation. During the perioperative period, we were able to maintain pre-defined target ranges and to reliably predict FVIII dosing requirements by a Bayesian analysis approach using the constructed perioperative FVIII population PK model from **chapter 5**. This case report of a complex patient shows the role this innovation can play, especially in patients requiring precise targeting of coagulation factor levels due to a high risk of either bleeding or thrombosis during a major surgical procedure.

In **chapter 10**, the benefits and limitations of PK-guided dosing are discussed. Benefits of PK-guided dosing include individualization of treatment with better targeting, more flexible blood sampling, increased insight into association of coagulation factor levels and bleeding, and potential lowering of overall costs. Limitations include a slight burden for the patient due to somewhat more blood sampling, and the necessity of closely collaborating, experienced clinical pharmacologists.

Overall, the studies performed and included in this thesis show that laboriously collected retrospective data can lead to construction of high quality population PK

Figure 1. Different steps towards individualized PK-guided dosing of clotting factor concentrates ("OPTI-CLOT" studies)

I	Data collection regarding current management
II	Construction of population PK models
III	External validation and implementation of PK guided dosing
IV	Individualized treatment

Different steps towards individualized PK-guided dosing of factor concentrates include data collection of replacement therapy followed by the construction of population PK models. These should be externally validated and implemented in clinical practice leading to more individualized treatment.

models (Figure 1). The internal validation performed shows a good performance of the developed population PK models. Prospective studies are needed to further externally validate these population PK models and to further improve the constructed population PK models.

SAMENVATTING

De studies beschreven in dit proefschrift maken allen onderdeel uit van de "OPTI-CLOT" onderzoekslijn die nastreeft patiënten met een stollingsstoornis geïndividualiseerder te behandelen met stollingsfactorconcentraten door implementatie van het farma-cokinetisch (PK) gestuurd doseren van stollingsfactorconcentraten. De "OPTI-CLOT" onderzoeksgroep bestaat uit hemofiliebehandelaren werkzaam in alle Nederlandse Hemofiliebehandelcentra als ook behandelcentra in Groot Brittannië.

De studies beschreven in dit proefschrift evalueren de huidige behandeling met stol-lingsfactorconcentraten in de verschillende stollingsstoornissen en de haalbaarheid van alternatieve, meer geïndividualiseerde behandeling op basis van farmacokinetisch gestuurd doseren aan de hand van Bayesiaanse analyse.

In **hoofdstuk 1** wordt een korte inleiding van dit proefschrift gegeven met een gedetail-leerde beschrijving van de huidige behandeling met stollingsfactorconcentraten van patiënten met een stollingsstoornis. Dit hoofdstuk beschrijft de terminologie om farma-cokinetiek (PK) te beschrijven. Omdat stollingsfactorconcentraten intraveneus worden toegediend zijn verdelingsvolume en klaring belangrijke factoren die mede de dosering bepalen. Bij bolus infusietherapie is met name het verdelingsvolume van belang, terwijl bij continue toediening van stollingsfactorconcentraten klaring de belangrijkste deter-minant is.

In **deel I** wordt de huidige behandeling geëvalueerd van patiënten met een erfelijke stollingsstoornis die een chirurgische ingreep ondergaan met het doel de prevalentie en voorspellers van plasma spiegels van stollingsfactoren onder en boven de streefwaarde te identificeren zoals beschreven door de Nationale richtlijn.
In **hoofdstuk 2** werd de behandeling van hemofilie A patiënten ten tijde van een chirurgische ingreep in de perioperatieve periode geëvalueerd. Er werden predictoren geïdentificeerd van onder- en overbehandeling ten aanzien van streefwaarde zoals vastgesteld door de Nationale richtlijn. In de studie waarbij 119 hemofilie A patiënten 198 electieve kleine of grote chirurgische ingrepen ondergingen, toonden we aan dat het bereiken van FVIII streefwaarden moeilijk is. Opmerkelijk was dat in de eerste 24 uur

na de operatie, 45% van de dal of 'steady state' FVIII waarden die bereikt waren onder de streefwaarde waren. Afhankelijk van de hoeveelheid dagen na operatie, waren 33-75% van de FVIII spiegels boven de streefwaarde. Er werd berekend dat een reductie van 44% van FVIII concentraat mogelijk zou zijn geweest indien er zodanig was gedoseerd dat FVIII spiegels binnen de streefwaarden waren geweest. Bloedgroep O en een grotere operatie waren predictoren voor lagere bereikte FVIII spiegels (OR = 6.3; 95% CI [2.7-14.9]; OR = 3.3; 95% CI [1.4-7.9]). Daarnaast hadden patiënten met bloedgroep O ook meer bloedingscomplicaties in vergelijking met patiënten met bloedgroep non-O (OR = 2.02 95% CI [1.00-4.09]). Bij patiënten met bloedgroep non-O werden ook vaker FVIII waardes boven streefwaarde gevonden (OR = 1.5 95% CI [1.1-1.9]). Een verklaring voor deze bevinding is dat bloedgroep non-O patiënten hogere spiegels van VWF hebben en daarbij een hogere spiegel FVIII in het plasma, doordat VWF de proteolytische afbraak van FVIII voorkomt door binding aan FVIII. Er werd tevens vastgesteld dat patiënten die behandeld werden met bolus infusie therapie een grotere kans hadden op excessief hogere FVIII waardes (OR = 1.8 95% CI [1.3-2.4]). Geconcludeerd werd dat verfijning van doseerstrategieën gebaseerd op individuele patiënt kenmerken zoals bloedgroep en wijze van infusie mogelijk kan leiden tot een betere kwaliteit van zorg en kosteneffectiviteit van de behandeling.

De perioperatieve behandeling van hemofilie B patiënten werd geëvalueerd in **hoofdstuk 3**. In deze retrospectieve, internationale, multicenter studie werden 118 patiënten die 255 chirurgische ingrepen ondergingen geïncludeerd. Het doel van de studie was de behandeling te evalueren en predictoren van lage en hoge factor IX (FIX) spiegels te identificeren. Data werd verzameld in totaal tien hemofiliebehandelcentra in Nederland en het Verenigd Koninkrijk. Zestig procent van de FIX spiegels binnen 24 uur na de operatie waren onder de streefwaarde met een mediane afwijking van 0.22 IUmL^{-1}[IQR 0.12-0.36]; terwijl 59% van de FIX spiegels boven de streefwaarde waren meer dan zes dagen na de operatie met een gemiddelde afwijking van 0.19 IUmL^{-1} [IQR 0.10-0.39]. In slechts drie chirurgische ingrepen (1.2%) waren er klinisch relevante bloedingscomplicaties opgetreden, gedefinieerd als ingrepen die een tweede chirurgische ingreep of een bloedtransfusie behoeften. Deze gebeurtenissen waren niet geassocieerd met lage FIX spiegels. Deze studie toont aan dat behandeling met behalen van FIX streefwaarden complex is en FIX spiegels in de huidige therapie suboptimaal zijn, maar met een minimaal bloedingsrisico. Dit kan erop wijzen dat de huidige streefwaarden discutabel

zijn. Farmacokinetisch gestuurd doseren kan mogelijk gebruikt worden om lagere FIX streefwaarde te identificeren in combinatie met een minimaal risico op bloedingen.

In **hoofdstuk 4** werd de perioperatieve behandeling met van Willebrand factor (VWF)/ factor VIII (FVIII) concentraten van patiënten met de ziekte van von Willebrand (VWD) geëvalueerd. Dit met als doel om te onderzoeken of de huidige doseerstrategieën adequaat zijn om de voorgestelde streefwaarden te bereiken. De bereikte VWF-activiteit (VWF:Act) en FVIII:C-activiteit (FVIII) spiegels werden vergeleken met de VWF:Act en FVIII streefwaarden zoals beschreven in de Nationale richtlijn. In totaal werden 103 VWD patiënten die 148 chirurgische ingrepen ondergingen geïncludeerd: 54 type 1 (73 operaties), 43 type 2 (67 operaties) en 6 type 3 (8 operaties). VWF:Act en FVIII spiegels werden postoperatief meerdere keren gemeten. Spiegels > 0.20 IUmL^{-1} boven de vermelde streefwaarden werden gedefinieerd als hoog. In type 1 VWD patiënten, waren respectievelijk 65% en 91% van alle dalspiegels van VWF:Act en FVIII hoog. In type 2 VWD en type 3 VWD waren respectievelijk 53% en 57% van de dalspiegels van VWF:Act en 72% en 73% van de dalspiegels van FVIII te hoog. Zoals verwacht werd er een accumulatie van FVIII dalspiegels geobserveerd door behandeling gebaseerd op FVIII spiegels. Prevalentie van FVIII en VWF:Act spiegels > 0.20 IUmL^{-1} onder de streefwaarde was zeldzaam. Bij het analyseren van predictoren van spiegels > 0.20 IUmL^{-1} boven en onder de streefwaarde werd alleen bloedgroep O als predictor voor hoge spiegels gevonden in type 1 VWD patiënten (OR 2.9; 95 % CI [1.3-6.6]). Waarschijnlijk is dit te verklaren door lagere endogene spiegels van VWF:Act en FVIII resulterend in het toedienen van hogere doseringen van stollingsfactorconcentraten. Geen andere predictoren werden gevonden voor lage en hoge VWF:Act en FVIII spiegels in type 1 en type 2 VWD patiënten. Geconcludeerd werd dat een efficiëntere behandeling en verdere individualisering van behandeling mogelijk is in VWD patiënten. Farmacokinetisch gestuurd doseren kan een potentiele strategie zijn. Echter, de complexiteit van VWD met een grote variatie in VWD type, mutaties en endotheel activatie, b.v. in verschillen in productie, secretie en klaring van VWF maakt dit een uitdaging.

In **deel II** werden op basis van de retrospectief verzamelde gegevens van de observationele studies in deel I populatie farmacokinetische (PK) modellen geconstrueerd met behulp van non-linear mixed-effects modelling (NONMEM) software.

In **hoofdstuk 5** beschrijven we de constructie van een perioperatief FVIII populatie PK model voor patiënten met hemofilie A. Dit model kan gebruikt worden in de perioperatieve periode om de behandeling te individualiseren en daarmee te optimaliseren. Populatie PK parameters werden beschreven van 119 patiënten; 75 volwassenen (gemiddelde leeftijd: 48 jaar, mediaan gewicht: 80 kg) en 44 kinderen (gemiddelde leeftijd: 4.3 jaar, mediaan gewicht: 18.5 kg) die respectievelijk 140 en 58 chirurgische ingrepen ondergingen. FVIII concentratie-tijd curven werden het best beschreven door een twee-compartimenten model. Populatie waarden voor klaring, intercompartimentele klaring, centraal en perifere verdelingsvolume waren 0.15 L/uur/68 kg, 0.16 L/uur/68 kg, 2.81 L/68 kg en 1.90 L/68 kg. Interpatiënt variabiliteit in klaring en het centrale verdelingsvolume waren 37% en 27%. Klaring neemt af met toenemende leeftijd (p <0,01) en is groter van patiënten met bloedgroep O (26%, p <0,01). Daarnaast werd een kleine afname van de klaring waargenomen als een grote chirurgische ingreep werd uitgevoerd (7%, p <0,01). In vergelijking met het bestaande populatie PK model van Björkman et al. voor de profylactische behandeling, werd een groter perifeer verdelingsvolume waargenomen. Gehypothetiseerd werd dat de toename van VWF postoperatief zorgt voor een verminderde klaring van FVIII. Prospectieve studies zijn echter nodig om deze relatie in de perioperatieve setting te evalueren. Dit zal verder worden onderzocht in de "OPTI-CLOT" trial, beschreven in **hoofdstuk 7**. De ontwikkeling van het model beschreven in **hoofdstuk 5** zal individualisering van de perioperatieve FVIII dosering bij ernstige en matig ernstige hemofilie A patiënten mogelijk maken door middel van doseren aan de hand van Bayesiaanse analyse.

In **hoofdstuk 6** wordt de constructie van een perioperatief populatie PK model voor ernstige en matig-ernstige hemofilie B patiënten beschreven. Het doel was om gemeten FIX spiegels en de variabiliteit tussen patiënten in de perioperatieve periode te beschrijven tijdens de behandeling met stollingsfactorconcentraat. Er werden in totaal 118 hemofilie B patiënten geïncludeerd (mediane leeftijd 40 jaar, mediaan gewicht 79 kilogram) die gezamenlijk 255 chirurgische ingrepen ondergingen. In tegenstelling tot het model voor FVIII, werden FIX spiegels versus tijd curven het beste beschreven door een drie compartimenten model. Hierbij werden de volgende PK parameters beschreven: Klaring (CL), inter-compartimentale klaring (Q2, Q3), distributievolume van het centrale compartiment (V1) en perifere compartimenten (V2, V3), plus inter-patiënt variabiliteit (%) met de volgende populatiegemiddelden: CL: 251 mLh^{-1}70kg^{-1}

(13%), V1: 4950 mL70kg^{-1} (13%), Q2: 91.3 mLh^{-1}70kg^{-1} (99%), V2: 7900 mL70kg^{-1} (57%), Q3: 831 mLh^{-1}70kg^{-1}, V3: 1600 mL70kg^{-1} voor een 32 jaar oude patiënt. Deze populatie PK parameters zijn verschillend ten opzichte van de waarden beschreven op basis van het profylaxe populatie PK model met een minder snelle eerste fase distributie naar het interstitium in de perioperatieve periode. Een mogelijke verklaring is endogene consumptie tijdens de perioperatieve periode en het vormen van FIX/FVIII complex met als gevolg een verminderde distributie naar het interstitium. Om deze reden is een specifiek populatie PK model nodig voor de perioperatieve periode. Bij toename van de leeftijd nemen CL en V1 toe met respectievelijk 1,2% en 1,9% per jaar tot een leeftijd van 32 jaar (p<0.001, p<0.01). Opvallend genoeg bleken CL en V1 verschillend tussen Nederland en het Verenigd Koninkrijk. Verder onderzoek is nodig om een verklaring voor deze associatie te vinden. Dit verschil zou kunnen zijn veroorzaakt door voorkeur voor bepaalde stollingsfactorconcentraten en het geven van comedicatie. Opvallenderwijs, bleek tranexaminezuur geassocieerd te zijn met een afname van V1 (9.8%). Dit suggereert dat tranexaminezuur leidt tot hogere FIX:C direct na de toediening van tranexaminezuur. Dit farmacodynamisch effect is niet eerder beschreven en moet verder onderzocht worden voordat hier conclusies aan verbonden kunnen worden.

In **Deel III** werd de haalbaarheid en validatie van het PK gestuurd doseren van stollingsfactoren in patiënten met stollingsstoornissen in kaart gebracht.

In **hoofdstuk 7** wordt de opzet van de "OPTI-CLOT" trial beschreven. Dit is een open-label, prospectieve, multicenter, gerandomiseerde trial (RCT) die een vergelijking maakt tussen de standaard manier van doseren en een iteratief Bayesiaans PK-gestuurd doseren met als doel het aantonen van een reductie van 25% in FVIII consumptie als ook het sneller behalen van de specifieke streefwaardes. Patiënten worden verdeeld over beide behandelarmen op basis van de manier van toedienen van FVIII (continu of bolus) en de ernst van de chirurgische ingreep. Er zullen minimaal zestig hemofilie A patiënten met baseline FVIII spiegels ≤ 0,05 IUmL^{-1}, ≥12 jaar, geïncludeerd worden die een electieve, kleine of grote chirurgische ingreep moeten ondergaan. In deze RCT, wordt het perioperatieve populatie PK model, zoals beschreven in **hoofdstuk 5**, prospectief gevalideerd. Tegelijkertijd zullen participerende Hemofiliebehandelcentra ervaring opdoen met PK-gestuurd doseren waardoor latere implementatie van deze behandelstrategie gemakkelijker maakt.

Eerdere studies hebben aangetoond dat PK parameters van kinderen en obese patiënten verschillen van volwassenen met een normaal gewicht. In **hoofdstuk 8** zijn alternatieve doseerstrategieën op basis van verschillende definities die lichaamsgrootte beschrijven "body size descriptors" vergeleken met een geïndividualiseerde PK gestuurde behandeling in hemofilie A patiënten met overgewicht of obesitas. De huidige behandeling van hemofilie patiënten is gebaseerd op baseline FVIII spiegels, lichaamsgewicht per kilogram, klinisch fenotype, inschatting van klaring en grootte/kans op een bloeding. Van oudsher zijn de richtlijnen voor de dosering gebaseerd op in een vivo recovery (IVR) van 2.0, wat overeenkomt met een toename van 2.0 $IUdL^{-1}$ per IU FVIII per kilogram lichaamsgewicht. Obese patiënten hebben significant hogere IVR waarden wat potentieel kan leiden tot overdosering. Om deze reden hebben diverse onderzoeksgroepen voorgesteld om alternatieve doseerstrategieën te gebruiken op basis van ideaal lichaamsgewicht of lean body weight. De voordelen en beperkingen van alternatieve doseerstrategieën bij obese hemofilie A patiënten werden onderzocht. In de studie werden 22 ernstige en matig-ernstige hemofilie A patiënten geïncludeerd (baseline FVIII <0.05 $IUmL^{-1}$) en gecategoriseerd op basis van body mass index (BMI), normaal: <25 kgm^{-2} (n=5) overgewicht: 25-30 kgm^{-2} (n=12) en obesitas: >30 kgm^{-2} (n=5). Alle patiënten kregen ± 50 $IUkg^{-1}$ FVIII toegediend, waarna FVIII werd gemeten op 4, 24 en 48 uur. Op basis van populatie PK modellen werden individuele FVIII versus tijd curven geconstrueerd. Het populatie PK model van Björkman et al. voorspelde niet de correcte FVIII spiegels bij patiënten met overgewicht en/of obesitas. Er werd een aangepast populatie PK model geconstrueerd welke PK parameters en FVIII spiegels correct beschreven van deze patiëntengroep. De mediane IVR was significant hoger van patiënten met overgewicht (2.65) en obesitas (3.00) ten opzichte van patiënten met een normale BMI (2.17) ($p<0,05$). IVR was onafhankelijk van BMI bij gebruik van ideaal lichaamsgewicht. Desondanks gold voor alle body size descriptors dat IVR gebaseerd doseren (IVR van 2.0) resulteerde in FVIII dalspiegels onder de gewenste streefwaarden voor behandeling van bloedingen. In tegenstelling tot de algemene hypothese, concluderen wij dat alternatieve body size descriptors niet als surrogaat gebruikt kunnen worden dan wel PK gestuurd doseren kunnen vervangen. Om PK gestuurd te kunnen doseren dient het populatie PK model representatief te zijn voor de specifieke patiëntenpopulatie; in dit geval dus patiënten met overgewicht en obesitas.

In **hoofdstuk 9** wordt geïllustreerd hoe aan de hand van een individueel PK profiel en een perioperatief populatie PK model de behandeling geïndividualiseerd kan worden in een hemofilie A patiënt die een niertransplantatie ondergaat. Gedurende de perioperatieve periode, was het mogelijk door toepassing van het ontwikkelde populatie PK model binnen de vooraf vastgestelde streefwaarden te blijven. Er kon een betrouwbare voorspelling gedaan worden van de benodigde FVIII doseringen met behulp van een Bayesiaanse analyse, gebruikmakend van het geconstrueerde perioperatieve FVIII populatie PK model uit **hoofdstuk 5**. Deze casus toont aan welke rol deze innovatie kan spelen, zeker bij patiënten waarbij het van groot belang is dat de stollingsfactorwaarden dicht bij de streefwaarden liggen, omdat zij een hoge kans op bloedingen of trombose hebben.
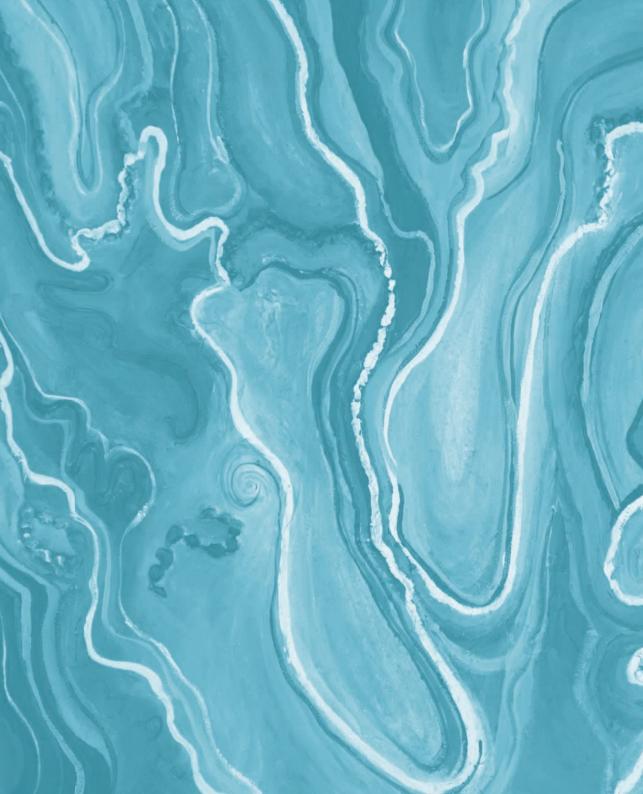
Figuur 1. Verschillende stappen op weg naar geïndividualiseerde behandeling ("OPTI-CLOT" studies)

I	Data verzamelen ten aanzien van de huidige behandeling
II	Constructie van populatie PK modellen
III	Externe validatie en implementatie van PK gestuurd doseren
IV	Geïndividualiseerde behandeling

Verschillende stappen in de richting van geïndividualiseerde behandeling van stollingsfactorconcentraten zijn onder meer het verzamelen van gegevens van behandeling gevolgd door de constructie van populatie PK modellen. Externe validatie en implementatie van PK gestuurd doseren zijn nodig om te leiden tot geïndividualiseerde behandeling.

In **hoofdstuk 10**, worden de voordelen en beperkingen van PK gestuurd doseren bediscussieerd. De voordelen van PK gestuurd doseren zijn individualisatie van behandeling met meer mogelijkheden om streefwaarden na te streven, flexibele bloedafnames, verhoogd inzicht in het verband tussen stollingsfactorspiegels en bloedingen, en potentieel een verlaging van de kosten van behandeling. Beperkingen zijn een kleine extra last voor de patiënt omdat er vaker bloed afgenomen dient te worden, en de noodzaak van een nauwe samenwerking met een ervaren klinisch farmacoloog.

Over het geheel genomen geldt dat de studies uit dit proefschrift aantonen dat het verzamelen van retrospectieve data kan leiden tot kwalitatief hoogstaande populatie PK modellen (Figuur 1). Interne validatie van het ontwikkelde populatie PK model laat zien dat deze goede resultaten oplevert. Er zijn prospectieve studies nodig om de modellen extern te valideren en verder te verbeteren.

Appendices

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Hazendonk HCAM, Rijneveld AW, van Osch-Gevers L, Pijnenburg MWH, van den Toorn LM, Koopman LP, Cnossen MH. Nitric Oxide Depletion in Sickle Cell Disease: Fact or Fiction? *Blood E-letter 2010September 29.*

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Preijers T, **Hazendonk HCAM**, Liesner R, Chowdary P, Driessens MHE, Hart D, Keeling D, Laros-van Gorkom BAP, van der Meer FJM, Meijer K, Fijnvandraat K, Leebeek FWG, Collins PW, Cnossen MH*, Mathôt RAA* for the "OPTI-CLOT" study group; *both are last authors. A population pharmacokinetic model for perioperative dosing of factor IX in hemophilia B patients. *Manuscript in preparation*.

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Erasmus University Medical Center – Sophia Children's Hospital, Rotterdam
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F.W.G. Leebeek
Academic Medical Center, Amsterdam
K. Fijnvandraat, R.A.A. Mathôt

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E.W de Bekker-Grob, H.C.A.M. Hazendonk, J.M. Heijdra, M.J.H.A. Kruip, J. Lock, I. van Moort, S. Polinder, E.W. Steijerberg, I. van Vliet, S.N. de Wildt, C.M. Zwaan

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R. Liesner

Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London
P. Chowdary

Department of Haematology, The Royal London Hospital Barts Health NHS Trust, London
D. Hart

Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals, Churchill Hospital, Oxford
D. Keeling

LIST OF ABBREVIATIONS

ABO	ABO blood group
ABW	Adjusted Body Weight
BMI	Body Mass Index
BU	Bethesda Units
BW	Body Weight
CI	Confidence Interval
CL	Clearance
FIX	Factor IX
FOCE	First-Order Conditional Estimation
FVIII	Factor VIII
IBW	Ideal Body Weight
IIV	Inter-Individual Variability; variability between patients
IOV	Inter-Occasion Variabilitiy; variability within patients
IQR	Interquartile Range
ISTH	International Society of Thrombosis and Hemostasis
IU	International Units
IVR	In Vivo Recovery
LBM	Lean Body Mass
MEC	Medical Ethical Committee
NONMEM	NON-linear Mixed-Effects Modelling software
OFV	Objective Function Value
OPTI-CLOT	Patient tail**O**red **P**harmacokine**TI**c-guided dosing of **CLOT**ting factor concentrate in clotting disorders
OR	Odds Ratio
PD	Pharmacodynamic
PK	Pharmacokinetics
PK	parameters Pharmacokinetic parameters (e.g. CL, V1, Q, V2)
Q	Intercompartmental clearance
RBCT	Red Blood Cell Transfusion
V1	Volume of distribution of the central compartment
V2	Volume of distribution of the peripheral compartment

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Vd	Volume of Distribution
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
VWF:Act	Von Willebrand Factor Activity
VWF:Ag	Von Willebrand Factor Antigen

DANKWOORD

Al lerende leren wij. Samen steeds een stapje verder. Wat een enorme eer om de afgelopen jaren met zoveel mensen samen te kunnen werken. Ik wil iedereen die bijgedragen heeft aan dit spannende avontuur hartelijk bedanken.

Allereerst alle patiënten die met onze studies hebben meegedaan. Zonder jullie enthousiasme en het open staan voor wetenschappelijk onderzoek zou het niet mogelijk zijn om nieuwe stappen en verbeteringen in de zorg te maken.

Ik wil graag mijn promotoren bedanken, prof. dr. F.W.G. Leebeek en prof. dr. R.A.A. Mathôt.
Beste prof. dr. F.W.G. Leebeek, beste Frank, dank voor jouw waardevolle begeleiding, kritische blik, je steun en vertrouwen tijdens het onderzoek. Ik bewonder je gedrevenheid en passie voor de kliniek en wetenschap.
Beste prof. dr. R.A.A. Mathôt, beste Ron, hartelijk dank voor jouw enthousiasme en de mogelijkheid om mij het modelleren met NONMEM te leren. Nooit gedacht dat ik nog eens in een soort van oud zwart DOS-schermpje zou werken. Maar jij liet me zien hoe je daar prachtige dingen uit tevoorschijn kan toveren. Er valt nog heel veel meer te leren, maar de mogelijkheden en de klinische toepassingen van het modelleren zie ik inmiddels overal terug.

Beste dr. M.H. Cnossen, lieve Marjon, in het tweedejaars keuzeonderwijs heb ik je leren kennen als een bevlogen arts en een enthousiaste onderzoeker. Keer op keer kruisten onze paden. Ik vind het een eer dat ik één van jouw promovendi mag zijn. Ik heb bewondering voor jouw passie en enthousiasme voor patiënten en onderzoek. Je bent een inspiratie voor mij. Dank voor het vertrouwen dat je me gegeven hebt om nieuwe avonturen aan te gaan en 'out of the box' te denken. Met jou kon ik altijd even sparren, vrij associëren en discussiëren en daarbij niet alleen denken in problemen, maar juist in oplossingen. Als we niet linksaf kunnen, gaan we toch rechtsaf? Een wijze levensles.

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Dank aan prof. dr. T. van Gelder, prof. dr. C.M. Zwaan, prof. dr. R.E.G. Schutgens, prof. dr. K. Fijnvandraat, prof. dr. P.W. Collins en prof. dr. M. de Hoog voor het plaatsnemen in mijn promotiecommissie.

Met heel veel plezier heb ik samen met alle leden van de OPTI-CLOT werkgroep en de verschillende OPTI-CLOTters in alle deelnemende centra aan mooie studies mogen werken. Zonder de hulp en steun van (research)verpleegkundigen, secretaressen, laboratoriummedewerkers, datamanagers en vele anderen zou dit boekje niet bestaan. Dank voor jullie enthousiasme en inzet!

Prof. dr. T. van Gelder en prof. dr. S.N. de Wildt, beste Teun en lieve Saskia, ik heb jullie leren kennen als bevlogen en enthousiaste klinisch-farmacologen. Met veel geduld en passie maken jullie eenieder enthousiast voor het vakgebied farmacologie. Dank voor jullie begeleiding en de leuke besprekingen en het oplossen van de casuïstiek. Het niet-ziekmakende farmacologie-virus heeft ook mij bereikt!

Prof. dr. K. Fijnvandraat, lieve Karin, dank voor jouw kritische blik op mijn manuscripten en onze telefonische overleggen en daarmee de leuke discussies. Jij weet altijd verder te denken en mij te stimuleren om me verder te verdiepen in de pathofysiologie. Hier heb ik veel van geleerd. Ik heb een enorme bewondering voor jouw gedrevenheid in het doen van onderzoek.

Dear prof. dr. P.W. Collins and dr. R. Liesner, dear Peter and dear Ri, thank you very much for your effort and help in the OPTI-CLOT goes UK study. Dear Peter, you are a very inspiring clinician and researcher. You make time for everyone and I enjoyed our conversations and discussions very much.
Dear Ri, thank you for the opportunity to stay at the Great Ormond Street Hospital. It was wonderful to be a part of your team. I hope to come back in the future. Thank you both for your trust, knowledge and efforts.
Dear Anja, Mary, Nicola, Jamie, Nicola, Alpha, Kate, Keath, Julia, Melanie, Jemma, David and Paul, thank you for making me feel welcome at the Great Ormond Street Hospital. I was the strange girl from Holland, who didn't drink milk in her very light tea. I very much

enjoyed my stay. Without your help I would not have accomplished what I have done now.

I would also like to thank the people in all participating Hemophilia Treatment Centers of the United Kingdom for their participation in the OPTI-CLOT goes UK study, especially dr. Dan Hart, dr. Pratima Chowdary and dr. David Keeling.

Discussies leiden tot nieuwe inzichten en geven soms een verrassende nieuwe invalshoek voor het doen van onderzoek. Bij deze wil ik dan ook alle mensen bedanken van diverse werkgroepen en de daarbij behorende werkbesprekingen, namelijk werkgroep hematologie, werkgroep (kinder)farmacologie en de NONMEM-werkgroep.

Maaike van den Akker, beste Maaike, dank voor het tot leven brengen van onze eigen stripheld. Dank ook aan de NVHP, de Nederlandse Vereniging van Hemofilie-Patiënten. Er kwamen al snel via Facebook vele ideeën binnen voor de naam. Het is Felix Factor geworden. In vier delen hebben wij de PK-avonturen uiteen kunnen zetten. En wie weet, welke rol Felix Factor in de toekomst nog meer zal gaan spelen.

Het secretariaat van de hematologie, kindergeneeskunde en farmacologie wil ik graag bedanken voor alle hulp en ondersteuning. Ontzettend knap hoe jullie alles managen, jullie zijn het middelpunt en het hart van de afdeling.

Lieve collega's van de (kinder)hematologie, dank voor jullie gezelligheid, kletspraatjes, hulp, zowel klein als groot.

Mijn speciale dank gaat uit naar mijn directe collega's en kamergenoten: Lieve Michelle, jij was altijd onze fotograaf en wist alle leuke momenten vast te leggen. Jouw vrolijkheid en relativeringsvermogen zijn een voorbeeld voor mij. Dank voor de gezellige tijd. Janske, samen hebben we veel data verzameld voor de studies van de OPTI-CLOT. Wat een drukke tijd! Dank voor de samenwerking. Lieve Iris, de OPTI-CLOT trial managen, dat is geen makkelijke taak, maar jou gaat het gemakkelijk af. Echt super knap! Jouw laboratoriumachtergrond maakt het discussiëren over de ins en outs van de stolling en de rol in PK-PD modellen nog leuker. Ik hoop dat we nog vaak samen kunnen discussiëren. Lieve Hilde, jouw begeleiden als keuze-onderzoekstudent was ontzettend leuk. Wat heb

jij in korte tijd bergen verzet! Beste Tim, wat kun jij ongelooflijk snel modelleren, petje af! Succes met het maken van alle PK-modellen. Lieve Jossi, je bent enorm gedreven, jou is niet snel iets te veel. Samen sparren over statistiek of regressievergelijkingen. Ook jouw promotie komt al snel dichterbij. Heel veel succes met de laatste loodjes. Lieve Caroline, mijn halve naamgenoot, met ine of ien? Het werd nog moeilijker toen wij op onze kamer het Caroline/Carolien eiland werden. Hoe leuk was het dat jij in London een concert gaf en ik jou daar mocht ontmoeten. Joyce, Shiraaz, Shirley, Jessica en Lisette ook bedankt voor alle gezelligheid. Ja Johan, bij jou aangekomen, last but not least. Jij bent een vrolijke noot, maar ook een serieus gesprek ga je niet uit de weg. Ik stel voor dat we de gordijnen discussie laten voor wat het is…

Lieve Eva, Corien, Alice, Janneke, Hilde en Sophie, dank voor jullie interesse en dat ik ook met vragen bij jullie terecht kon. Het NVTH congres zou zonder jullie nooit zo leuk zijn geweest. Tiramisu maken met 40 liter slagroom en hoeveel liter drank? Ik weet het niet meer. Wat een gezellige tijd!

Vanaf september 2016 een nieuwe uitdaging als arts-assistent kindergeneeskunde in het Elisabeth-TweeSteden Ziekenhuis in Tilburg. Lieve collega's, dank voor de gezelligheid en onze samenwerking in de kliniek. In het bijzonder wil ik graag dr. Charlie Obihara en drs. Carien Smeets bedanken, als opleider en mentor kan ik altijd op jullie steun rekenen en kan ik bij jullie terecht. Ik geniet volop in de kliniek!

Beste Antoinette, na mijn eerste schilderavonturen op de kunstacademie in London was het super fijn om onder jouw begeleiding verder te gaan met schilderen. Dank voor de gezellige tijd en tips tijdens de verschillende schilderlessen. Ik ben enorm trots op mijn schilderij dat op de voorkant van mijn boekje staat. Voor menigeen zal het niets betekenen, maar voor mij betekent het de verschillende wegen die wij afleggen in ons leven, mooie avonturen! Mijn promotieonderzoek is er daar één van.

Lieve vrienden/vriendinnen (Yvonne & Bouke, Carina & Maarten, Dianne & Ruud, Stephanie & Alexander, Kim & Erwin, Lisette, Bart, Bart & Erica, Bram & Emmy, Ronny & Wendy, Suzanne & Pieter, Karin & Ferdi, Cynthia & Marc, Niels & Maartje), er is altijd weinig tijd

om af te spreken met alle drukke agenda's, maar we hebben het altijd weer gezellig. Dank voor jullie steun en alle gezellige etentjes en uitjes.

Lieve Carina en Yvonne, wat fijn dat jullie mijn paranimfen willen zijn. Lieve Carina, dank voor jouw steun en dat ik bij je terecht kan. Samen discussiëren, een heerlijk tijdverdrijf. De gezellige etentjes, met een lekkere kop thee en 'wat lekkers' zijn altijd te snel voorbij. Het betekende erg veel voor mij/ons dat jij op onze bruiloft in de kerk wilde zingen. Lieve Yvonne, op dag één zorgde jij dat ik me meteen thuis voelde. Jouw openheid en rust zorgen ervoor dat iedereen zichzelf kan zijn. Ik kan altijd bij je terecht, samen lachen, samen huilen. Een woord is vaak niet eens nodig om elkaar te begrijpen. Een gedeelde passie is schilderen, wie had dat kunnen denken? Jullie betekenen veel voor mij.

Lieve familie, dank voor jullie interesse in mij en de gezelligheid tijdens de verjaardagen, etentjes en borrels. Op naar nog vele mooie momenten die we met elkaar mogen delen!

Lieve opa & oma, we mogen altijd bij jullie aankloppen. Oma, van u heb ik leren schrijven. U liet mij niet alleen zien dat letters woorden vormen, woorden zinnen vormen, maar ook dat zinnen een verhaal worden. U bent een echte inspiratie voor mij.

Lieve opa Willem & oma Sina, dank voor jullie liefde voor ons.

Lieve Tein, wat een inspiratie en bron van energie ben jij. Samen gezellig fietsen voor de boodschappen en de trucjes voor het snijden van een paprika; ik voel me al bijna een professionele kok!

Lieve Jolanda, Piet-Hein, Hidde en Mats; heerlijk om samen met jullie het leven te vieren en te genieten van mooie momenten.

Lieve Paul en Nadya, ik heb bewondering voor jullie reislust en nu ook jullie nieuwe avontuur met de zoektocht naar een mooi (vakantie)huis in het buitenland. Wij komen graag klussen!

Lieve schoonouders, wat fijn dat jullie mij een plekje hebben gegeven in jullie gezin. Een promotietraject is voor jullie niet nieuw. Dank dat ik met al mijn verhalen en vragen terecht kan. Fijn dat wij altijd op jullie mogen en kunnen terugvallen.

Lieve Nicole & Marjolein, lieve zusjes, we zijn de 'haasjes' en daar zijn we trots op! Nicole, jij straalt als je het over je werk hebt. Jij bent zorgzaam en gaat voor je patiënt. Als patiënt zou ik geen andere verpleegkundige aan mijn zijde willen hebben. Marjolein, jij bent mijn kleine zusje. Jij bent super goed in je werk als mondhygiëniste, weet ik als ervaringsdeskundige. En wat was het leuk dat jouw artikel zo snel was geaccepteerd. Ik ben trots op jullie! Dank dat jullie er altijd voor mij zijn.

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Lieve Sjors, jij bent er altijd voor mij. Aan mijn zijde sta jij. Jij stimuleert mij om mijn dromen waar te maken. Niet alleen leren of doen, maar ook het leven beleven is jouw motto. Samen staan wij sterk!

Lieve groet, Carolien

ABOUT THE AUTHOR

Carolien Hazendonk was born on the 23th of October 1987 in Utrecht, the Netherlands. After graduating from secondary school at the Heerenlanden College in Leerdam, she went to the Erasmus University Medical Center Rotterdam to study medicine. During her study, she took part in various small research projects at the Department of Pediatric Hematology under supervision of dr. M.H. Cnossen. In October 2012, she graduated with honors.

In November 2012, she started with her PhD project which is part of the "OPTI-CLOT" study program initiated by the Department of Pediatric Hematology of the Erasmus University Medical Center Rotterdam under supervision of dr. M.H. Cnossen (pediatric hematologist and principal investigator "OPTI-CLOT"), prof. dr. F.W.G. Leebeek (hematologist) and prof. dr. R.A.A. Mathot (clinical pharmacologist and hospital pharmacist; Academic Medical Center Amsterdam).

During her PhD study period, she worked in the United Kingdom at the Great Ormond Street Hospital for seven months with co-investigators from various clinics under supervision of dr. R. Liesner (pediatric hematologist; Great Ormond Street Hospital London) and prof. dr. P.W. Collins (hematologist; Cardiff). In 2015, she received a Young Investigator Award and Poster Award from the International Society of Thrombosis and Haemostasis; and the Jean Stibbe Award for best oral presentation at the congress of the Dutch Society of Thrombosis and Hemostasis (NVTH). In September 2016, she started as a pediatric resident not in training at the Elisabeth-TweeSteden Hospital in Tilburg under supervision of dr. C.C. Obihara.

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PHD PORTFOLIO

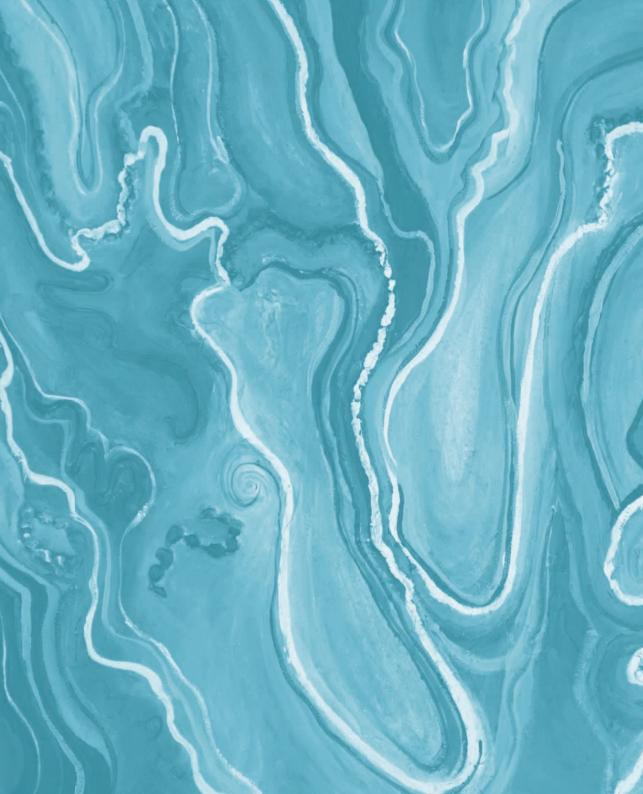| Name PhD student: H.C.A.M. Hazendonk	PhD period: November 2012 to August 2016
Erasmus MC Department: Pediatric Hematology	Promotors: prof.dr. F.W.G. Leebeek, prof.dr. R.A.A. Mathôt
Research School: COEUR	Copromotor: dr. M.H. Cnossen

1. PhD training	Year	Workload (ECTS)
General academic skills		
Biomedical English Writing and Communication	2013	4.0
Systematic Literature Retrieval (medical library)	2013	0.5
BROK (Basiscursus Regelgeving Klinisch Onderzoek) Erasmus MC	2013	1.0
Research Integrity	2014	0.3
Symposium Implementatie en Kwaliteit	2013	0.3
ZonMw Doelmatigheidsonderzoek	2013	0.1
Research skills		
Principles of Research in Medicine (NIHES)	2014	0.7
Introduction to Data-analysis (NIHES)	2014	0.7
Regression Analysis (NIHES)	2014	1.4
NIH – Principles of Clinical Pharmacology, course of webinars	2014	2.0
NIH – Pediatric Clinical Pharmacology webinars	2014	1.0
In-depth courses (e.g. Research school, Medical Training)		
2x NVTH annual AIO course on hemostasis and thrombosis	2013-2014	2.0
COEUR Symposium Personalized Medicine	2015	0.1
NONMEM journal club	2013-2016	2.0
Oral presentations		
Dutch Society of Pediatrics	2013	0.5
Von Creveld symposium (invited speaker)	2014	0.5
Dutch Hematology Congress	2015	0.5
International Society on Thrombosis and Haemostasis Congress	2015	0.5
NVTH symposium	2015	0.5
FIGON Dutch medicines day	2015	0.5
Sophia Research day	2016	0.5
COEUR PhD day	2016	0.5

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1. PhD training	**Year**	**Workload (ECTS)**
Poster presentations		
International Society on Thrombosis and Haemostasis Congress	2013, 2015	0.4
Bari International Conference	2014	0.2
Dutch Society of Pediatrics	2014	0.2
Sophia Research day	2014	0.2
European Association of Hemophilia and Allied Disorders Congress	2015	0.2
European Congress on Thrombosis and Haemostasis	2016	0.2
National Conferences		
Nationaal Trombo-Embolie Symposium	2013	0.3
Annual meeting of the Dutch Society of Pediatrics	2013, 2014	0.6
Dutch Hematology Congress	2013, 2015	0.6
NVTH symposium	2013-2015	1.4
Von Creveld Symposium	2014	0.3
AMSTOL Symposium	2014, 2016	0.6
FIGON Dutch Medicine Days	2015	0.6
NVT Pediatric drug development	2016	0.3
International Conferences		
3x European Association of Hemophilia and Allies Disorders Congress	2013-2015	2.7
2x International Society on Thrombosis and Haemostasis Congress	2013,2015	3.6
Bari International Conference	2014	0.9
Seminars and workshops		
Young Investigators day TULIPS	2013-2015	0.9
Sophia research day	2013,2014, 2016	0.9
COEUR PhD day, Rotterdam	2013, 2014, 2016	0.9
Lareb - introduction day and adverse events day	2014	0.3
Masterclass Timothy Springer	2014	0.3
Masterclass David Lillicrap	2016	0.3
Didactic skills		
Teach the Teacher course	2013	0.5

1. PhD training	Year	Workload (ECTS)
2. Teaching activities		
Lecturing		
Tutor first year medical students	2013	1.5
Teaching polypharmacy medical students	2014-2015	0.2
Supervising Master's theses		
Supervising final year medical student (1x 27 weeks)	2015	1.0
Hematology PhD training		
Work discussions and literature discussions	2012-2016	8.0
Other		
Pediatric Pharmacology Research Meetings	2013-2015	1.0
Clinical Pharmacology and Pharmacogenetics meetings	2014-2016	1.0
COEUR PhD committee and organizing COEUR PhD day	2013-2015	2.0
Total		**52.2**

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Felix Factor en zijn PK-avonturen

FELIX FACTOR EN ZIJN PK-AVONTUREN

Tot nu toe bepalen artsen op basis van lichaamsgewicht hoeveel stollingsfactoren iemand met hemofilie nodig heeft, maar niet ieder lichaam reageert hetzelfde op de medicijnen. Dat noem je 'farmacokinetiek', in het Engels 'pharmacokinetics'. OPTI-CLOT onderzoekt of je mensen met hemofilie patiëntgerichter kunt behandelen door te kijken naar farmacokinetische modellen.
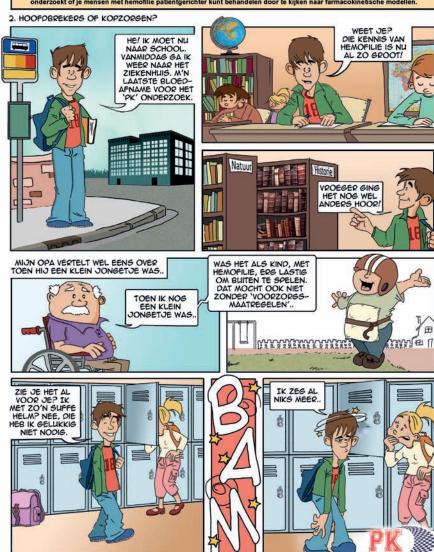
2. HOOFDBREKERS OF KOPZORGEN?

PK OPTICLOT
© Maaike van den Akker

FELIX FACTOR EN ZIJN PK-AVONTUREN

Tot nu toe bepalen artsen op basis van lichaamsgewicht hoeveel stollingsfactoren iemand met hemofilie nodig heeft, maar niet ieder lichaam reageert hetzelfde op de medicijnen. Dat noem je 'farmacokinetiek', in het Engels 'pharmacokinetics'. OPTI-CLOT onderzoekt of je mensen met hemofilie patiëntgerichter kunt behandelen door te kijken naar farmacokinetische modellen.

4. LOST AND FOUND!

EÉN MOMENTJE HOOR.. IK MOET DIT FF OPSLAAN.

NIEUWE INFORMATIE GEVONDEN VOOR MIJN OPSTEL OVER HEMOFILIE..

ECHT VET! MOET JE ES HOREN..

ZE HEBBEN EEN OUDE EGYPTISCHE PAPYRUSROL GEVONDEN WAAROP HEMOFILIE WORDT GENOEMD.

IN DE 2E EEUW WAS HET AL BEKEND DAT DE ZIEKTE ERFELIJK IS. DAT IS TE VINDEN IN DE JOODSE TALMUD!

EN ER IS EEN MIDDELEEUWS HANDBOEK GEVONDEN VAN EEN MOORSE ARTS.

OOK DAARIN WORDT HEMOFILIE BESCHREVEN.

HÉ, EIGENLIJK ZOU IEMAND MOETEN VASTLEGGEN WAT WE INMIDDELS WETEN OVER DE ZIEKTE.

LEUK ALS DE MENSEN IN DE TOEKOMST HET TERUGVINDEN!

2013..START VAN HET PK-ONDERZOEK ....

BLIEP BLIEP

ZEG, HEEFT IEMAND MISSCHIEN MIJN IPAD GEZIEN ??

PK
OPTICLOT
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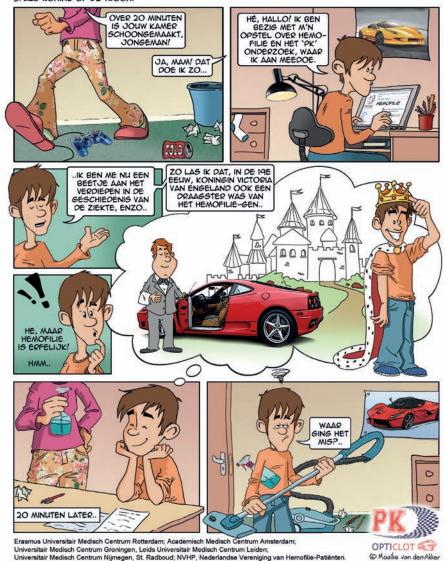
Erasmus Universitair Medisch Centrum Rotterdam; Academisch Medisch Centrum Amsterdam;
Universitair Medisch Centrum Groningen, Leids Universitair Medisch Centrum Leiden;
Universitair Medisch Centrum Nijmegen, St. Radboud; NVHP, Nederlandse Vereniging van Hemofilie-Patiënten.