Population pharmacokinetics of the von Willebrand factor–factor VIII interaction in patients with von Willebrand disease


1Hospital Pharmacy–Clinical Pharmacology, Amsterdam University Medical Center (UMC), University of Amsterdam, Amsterdam, The Netherlands; 2Department of Pediatrics, Erasmus MC–Sophia Children’s Hospital, University Medical Center Rotterdam, The Netherlands; 3Pediatric Hematology, Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; 4Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; 5Division of Thrombosis and Hemostasis, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands; 6Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands; and 7Department of Hematology, Erasmus MC, University Medical Center Rotterdam, The Netherlands

Key Points

- The developed population PK model could adequately describe the interaction between VWF and FVIII in perioperative patients with VWD.
- Presence of VWF decreases FVIII clearance, clarifying FVIII accumulation over time as observed after multiple VWF/FVIII concentrate doses.

Recent studies have reported that patients with von Willebrand disease treated perioperatively with a von Willebrand factor (VWF)/factor VIII (FVIII) concentrate with a ratio of 2.4:1 (Humate P/Haemate P) often present with VWF and/or FVIII levels outside of prespecified target levels necessary to prevent bleeding. Pharmacokinetic (PK)-guided dosing may resolve this problem. As clinical guidelines increasingly recommend aiming for certain target levels of both VWF and FVIII, application of an integrated population PK model describing both VWF activity (VWF:Act) and FVIII levels may improve dosing and quality of care. In total, 695 VWF:Act and 894 FVIII level measurements from 118 patients (174 surgeries) who were treated perioperatively with the VWF/FVIII concentrate were used to develop this population PK model using nonlinear mixed-effects modeling. VWF:Act and FVIII levels were analyzed simultaneously using a turnover model. The protective effect of VWF:Act on FVIII clearance was described with an inhibitory maximum effect function. An average perioperative VWF:Act level of 1.23 IU/mL decreased FVIII clearance from 460 mL/h to 264 mL/h, and increased FVIII half-life from 6.6 to 11.4 hours. Clearly, in the presence of VWF, FVIII clearance decreased with a concomitant increase of FVIII half-life, clarifying the higher FVIII levels observed after repetitive dosing with this concentrate. VWF:Act and FVIII levels during perioperative treatment were described adequately by this newly developed integrated population PK model. Clinical application of this model may facilitate more accurate targeting of VWF:Act and FVIII levels during perioperative treatment with this specific VWF/FVIII concentrate (Humate P/Haemate P).

Introduction

von Willebrand disease (VWD) is an autosomally inherited bleeding disorder, with an estimated prevalence between 0.6 and 1.3%. Patients with VWD suffer from bleeding caused by von Willebrand factor (VWF) deficiency or dysfunction, leading to defects in the primary hemostasis as VWF promotes platelet adhesion and aggregation. VWF also plays a role in the secondary hemostasis as it acts as chaperone protein for factor VIII (FVIII), protecting it from degradation and clearance in the circulation. Therefore, patients with VWD often also present with reduced FVIII levels. VWD is categorized into 3...
Treatment of VWD is usually on demand and focuses on normalization of VWF and FVIII levels in critical situations such as surgery, child delivery, acute bleeding, and/or trauma. A therapeutic increase of VWF and FVIII levels can be achieved by administration of desmopressin, which stimulates the endogenous release of VWF and subsequently increases circulating FVIII, or by IV infusion of a VWF-containing concentrate when desmopressin is contraindicated or desmopressin response is insufficient.

Most plasma-derived VWF-containing concentrates also contain FVIII, as acute situations necessitate readily available FVIII for adequate hemostasis. However, during prolonged treatment with these concentrates, FVIII accumulates as FVIII production and secretion are not affected in VWD, thereby inducing a hypothetical risk of thrombosis. Factor concentrates with varying VWF activity (VWF:Act)/FVIII ratios are available, and several studies have indicated that repeated dosing with VWF/FVIII concentrates with a ratio of > 1 results in less FVIII accumulation if VWF concentrate dosing is based only on VWF levels.

A commonly used plasma-derived VWF/FVIII concentrate is Humate P or Haemate P (CSL Behring, Marburg, Germany), which has a VWF:Act/FVIII ratio of 2.4:1. Nonetheless, also with this specific concentrate, FVIII accumulation is observed after perioperative treatment.

Hazendonk et al have reported that, respectively, 65% and 91% of trough VWF:Act and FVIII levels in patients with type 1 VWD treated with Humate P during surgery were ≥0.20 IU/mL higher than predetermined target levels as prescribed in clinical guidelines. This results in higher treatment costs than necessary and an increased risk of adverse events. On the other hand, this study also observed 7 VWF:Act levels and FVIII levels of 5 patients below the prespecified target levels during the first 36 hours after surgery, thereby increasing bleeding risk. The wide variability in achieved levels is due to the large interindividual variability (IVV) in the pharmacokinetics (PK) of both exogenous and endogenous VWF and FVIII. A possible solution for this large variability in achieved VWF and FVIII levels is PK-guided dosing, which uses maximum a posteriori Bayesian estimation to determine individual PK parameters that can be used to calculate an adequate dose to achieve a target level. The application of this approach for perioperative dosing with this VWF/FVIII concentrate has been examined in 2 earlier studies.

Contrastingly, in the study by Di Paolo et al, the in vivo recovery of the individual PK profile performed before surgery did not match the in vivo recovery observed in the perioperative period, indicating that PK-guided dosing is less beneficial. However, data in this study were analyzed using a standard 2-compartment model without taking prior population knowledge or the influence of covariates into account. Development of a population PK model, which is based on data from a population and describes the typical PK parameters with corresponding IVV and intraindividual variability, could possibly improve the PK-guided dosing approach for patients with VWD treated with this VWF/FVIII concentrate perioperatively.

We have recently developed a population PK model describing FVIII PK after VWF/FVIII concentrate (ratio 2.4:1) administration, enabling perioperative PK-guided dosing based on FVIII target levels. However, as several clinical guidelines advise target levels for both VWF and FVIII to ensure adequate hemostasis, application of an integrated population PK model to predict VWF:Act as well as FVIII levels may allow for more accurate perioperative dosing and therefore improve quality of care. In addition, this model may also give insight into the mechanisms of FVIII accumulation observed in these patients. Therefore, the aim of our study was to develop the first population PK model for perioperative VWF/FVIII concentrate (ratio 2.4:1) dosing that describes the interaction between VWF and FVIII in patients with VWD.

Methods

Data collection

We used data from a retrospective multicenter study to develop this integrated population PK model. The data set included patients with VWD who underwent surgery in 1 of 5 academic hemophilia treatment centers in The Netherlands between 2000 and 2018. All patients received multiple perioperative doses of a plasma-derived VWF-containing concentrate with a VWF/FVIII ratio of 2.4:1 (Humate P or Haemate P) and were included in the data set if at least 2 perioperative VWF:Act and FVIII level measurements were available. Patients were excluded if other hemostatic disorders were present or if desmopressin was concomitantly used. Dose adjustments were generally based on FVIII levels, as FVIII results were usually more rapidly available. All FVIII levels were measured by a 1-stage assay, whereas different centers performed different VWF:Act assays: 4 centers used a VWF ristocetin cofactor (VWF:RCO) assay, whereas 1 center used different assays over time (VWF:RCo assay from 2000 to 2005; monoclonal antibody [VWF antibody (VWF:Ab)] assay from 2005 to 2012), and a VWF glycoprotein 1b binding (VWF:GP1bM) assay from 2012 onward. More specifications of these assays are detailed in supplemental Methods. Additional information, such as patient characteristics and surgical characteristics, were collected from electronic patient files. All data were collected following Good Clinical Practice and Dutch regulations. Informed consent was not obtained, as anonymized, retrospective data were used as reported in an earlier publication.

Population PK modeling

A population PK model describing VWF:Act and FVIII PK after VWF/FVIII concentrate administration was constructed using nonlinear mixed-effect modeling software (NONMEM version 7.4.2; ICON Development Solution). A population PK model considers data from a whole population simultaneously instead of analyzing patients separately. Herewith, enabling simultaneous analyses of patients where PK differences are expected, such as with patients with different types of VWD. This technique can handle sparse data with random sampling times, as was the case in our retrospective clinical data set.

We used turnover models to describe the change of endogenous and exogenous VWF:Act and FVIII levels over time. This method enables handling of endogenous baseline concentrations in PK modeling, as it is able to correct for analytic assay variability of the measured endogenous baseline level; this cannot be done with the frequently used baseline subtraction method. First, separate PK models for VWF:Act and FVIII were developed. These models were then combined and the interaction between VWF:Act and FVIII was added. An inhibitory maximal effect ($I_{\text{max}}$) function relating
VWF:Act levels and FVIII clearance was incorporated to describe the inhibitory effect of the VWF:Act levels on FVIII elimination.

During model development, the number of compartments, inclusion of IIV, interoccasion variability, and residual error structure were evaluated. The incorporation of a separate residual error for VWF levels measured by VWF:RCo and VWF levels measured by other assays (VWF:GP1bM or VWF:Ab) was tested to correct for the use of different analysis methods. As both children and adults were included in the data set and a wide range of weights was present, allometric scaling to body weight was applied.

**Covariate analysis**

Patient characteristics or surgical characteristics may potentially explain part of the IIV observed in PK parameters. To identify these characteristics, a covariate analysis was performed using forward inclusion and backward elimination. The following patient characteristics were tested: age, sex, VWD type as diagnosed by the local center, blood group, and physical status as determined by the American Society of Anesthesiologists (ASA) classification. The influence of liver and kidney parameters was evaluated by the following covariates: alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, albumin, creatinine, and urea levels. Surgical characteristics included duration and severity of the procedure. Administration of comedication such as tranexamic acid, nonsteroidal anti-inflammatory drugs, or heparin was evaluated in the covariate analysis. First, covariates were included univariately to statistically select potential covariates. Thereafter, we performed a forward inclusion and backward elimination procedure. Finally, inclusion of interoccasion variability was evaluated and the final population PK model was constructed. More in-depth details of the modeling process can be found in supplemental Methods.

**Model evaluation**

To evaluate the adequacy of the population PK models to predict the VWF:Act and FVIII levels, goodness-of-fit plots were inspected. The final model was internally validated using a visual predictive check (VPD). One thousand data sets were simulated with the final model and the simulated levels were compared with the observed levels. Additionally, a bootstrap was performed to test the robustness of the model. During the bootstrap analysis, 1000 new data sets were randomly created from the original data set and the model was re-estimated using the newly created data sets.

**Results**

The data set consisted of 118 patients with different types of VWD, aged 1 to 82 years, who underwent 174 surgeries (Table 1). Eight children (<18 years) were included, with a median age of 14 years (range, 1-17 years) and median height of 154 cm (range, 94-194 cm). Patients received a median of 5 doses of the VWF/FVIII concentrate per perioperative period, and a total of 695 VWF:Act and 894 FVIII levels were available. None of the FVIII levels were below the quantification limit (<0.01 IU/mL), but 3 VWF:Act levels were below the quantification limit of 0.20 IU/mL. These VWF:Act levels were excluded from analysis as the percentage of samples below the quantification limit was only 0.4%. A median of 4 VWF:Act levels and 5 FVIII levels were collected per perioperative period. These samples were taken between 171 hours before the start of surgery and 524 hours after surgery; but 96% of the samples were collected within 168 hours after surgery. After the first perioperative VWF:FVIII concentrate dose, the median FVIII level was 1.30 IU/mL (range 0.41-3.64 IU/mL), which accumulated to a median FVIII level of 1.80 IU/mL (range 0.59-4.21 IU/mL) on day 5. The VPC, which is explained later in “Results,” also illustrates the (prediction-corrected) observed VWF:Act and FVIII levels over time (Figure 1).

**Population PK model**

Time profiles of both VWF:Act and FVIII were described using turnover models. In these models, the change in endogenous VWF and FVIII levels over time was described with a zero-order production rate, \( k_{in} \), and a first order elimination rate, \( k_{out} \). Upon
administration of the factor concentrate, VWF and FVIII were injected in the respective central compartments. The interaction between VWF and FVIII was described by an inhibitory effect of VWF:Act on FVIII clearance. An $I_{\text{max}}$ relation was chosen to describe this relationship, following equation 1: 

$$\text{inhibition} = 1 - \left( \frac{I_{\text{max}} \times C_{\text{VWF}}}{IC_{\text{50}} + C_{\text{VWF}}} \right)$$

in which $C_{\text{VWF}}$ represents the VWF level, $I_{\text{max}}$ the maximal inhibitory effect on FVIII clearance, and $IC_{\text{50}}$ the VWF level at which 50% FVIII clearance inhibition was established. A visual representation of the model can be found in Figure 2.

In 77 surgeries, the VWF:Act level before the first VWF/FVIII concentrate infusion (preadministration level) was higher (0.26 IU/mL [range, 0.01-3.74]) than the historical baseline (lowest level ever measured; 0.15 IU/mL [range, 0.00-0.58]). The preadministration FVIII level (0.68 IU/mL [range, 0.01-3.11]) was also higher than the historical baseline level (0.41 IU/mL [range, 0.01-0.97]) in 98 surgeries. In the turnover models, the preadministration VWF:Act and FVIII levels were considered as baseline values instead of the historical baseline levels, assuming that the increase in endogenous VWF:Act and FVIII levels was permanent and levels would return to the preadministration level after the perioperative period.

The structural model consisted of 1-compartment turnover models for both VWF:Act and FVIII (Figure 2). Typical values for VWF (1) preadministration baseline, (2) clearance, and (3) volume of distribution with corresponding IIV values (percentage) were (1) 0.42 IU/mL (126.4%), (2) 262 mL/h (55.3%), and (3) 4990 mL (25.2%) for a patient of 70 kg (Table 2). Using the integrated turnover model, typical values for FVIII (1) preadministration baseline, (2) clearance, and (3) volume of distribution were (1) 0.77 IU/mL (32.2%), (2) 460 mL/h (81.5%), and (3) 4350 mL. These values reflect the theoretical situation in which VWF is absent. VWF inhibited FVIII clearance with an $IC_{\text{50}}$ value of 1.65 IU/mL. An average perioperative VWF:Act level of 1.23 IU/mL decreased FVIII clearance from 460 mL/h to 264 mL/h and increased FVIII elimination half-life from 6.6 hours to 11.4 hours.

**Covariate analysis**

During univariate selection, the following associations were statistically significant ($P < .05$): surgery duration on VWF clearance; sex on VWF volume of distribution; VWD type; ASA score and age on VWF baseline; VWD type on FVIII clearance; and ASA score, age, and blood group 0 on baseline FVIII. After forward inclusion and backward elimination, only duration of surgery on VWF clearance, VWD type and ASA score on VWF preadministration baseline, and VWD type on FVIII clearance were retained in the model ($P < .01$). Increase in surgery duration was associated with a decrease of VWF clearance. Specifically, when the duration of surgery increased from 45 to 110 minutes (interquartile range), VWF clearance decreased from 284 to 219 mL/h. The VWF preadministration baseline of VWD type 2 and type 3 patients was 61.0% and 81.8% lower than the VWF baseline of type 1 patients. For patients with an ASA score of III or IV, a 53% higher VWF:Act preadministration baseline was observed than for patients with ASA score 0 or I.
All patients had at least ASA score II, as VWD is a mild systemic disease and only completely healthy patients classify as ASA I. Patients with VWD type 2 and type 3 had a 56.4 and 65.7% lower FVIII clearance, respectively, compared with type 1.

Model evaluation

The goodness-of-fit plots of the final model demonstrate that the model describes VWF:Act and FVIII levels adequately (Figure 3). The VPC shows similar adequate model performance (Figure 1). Finally, the estimates and 95% confidence intervals of the bootstrap confirm robustness of the model (Table 2).

Clinical application of the novel population PK model

To demonstrate the clinical application of the newly developed model, a 33-year-old man (69 kg) with type 3 VWD who underwent ankle surgery while being treated with the VWF/FVIII concentrate (ratio 2.4:1) was fitted with the newly developed integrated VWF/FVIII model retrospectively. The patient was not included in the original data set and informed consent of the patient was obtained. An initial dose of 50 IU/kg, followed by doses of 25 IU/kg every 12 hours, following clinical guidelines pursuing prespecified VWF and FVIII target levels, were administrated to the patient. Figure 4A confirms that the measured FVIII and VWF levels of this patient were adequately
described by the newly developed integrated VWF/FVIII population PK model, including the observed accumulating FVIII levels. Only the initial preadministration FVIII level was estimated higher than observed, probably caused by the fact that only a few type 3 patients with a low endogenous FVIII baseline were included in the model. Interestingly, during the first 36 hours after the start of surgery, the VWF target level of >0.80 IU/mL, as prespecified in the clinical guidelines to prevent bleeding, was not achieved after administration of the dosing scheme as described herein, although no bleeding or adverse events occurred.20

Thereafter, the individual dosing scheme that would have been necessary to reach the prespecified VWF and FVIII target levels was calculated. This advised dosing scheme was composed based on individual PK parameters retrieved from the available preoperative PK profile in which VWF and FVIII levels were measured before and at 3 time points after infusion of 25 IU/kg of the VWF/FVIII concentrate. When dosing was based on the individual PK parameters (PK-guided dosing), higher doses would have been necessary for this unique patient to reach the specified target levels (Figure 4B).

Discussion

A novel population PK model was successfully developed that describes VWF:Act and FVIII levels simultaneously, illustrating their physiological interaction, after perioperative dosing with a VWF/FVIII concentrate (ratio 2.4:1) in patients with VWD. In literature, the protective effect of VWF on FVIII metabolism and clearance has not yet been quantified in a population PK model. Moreover, the model demonstrates that the presence of VWF increased the half-life of FVIII, thereby clarifying FVIII accumulation as is generally observed after perioperative treatment with this VWF/FVIII concentrate.

In this integrated population PK model, the observed VWF:Act and FVIII levels over time were both described by 1-compartment turnover models. The interaction between both coagulation proteins was captured by an \( I_{\text{max}} \) relation function connecting VWF:Act to FVIII clearance. The PK parameters obtained in this integrated population PK model are consistent with the values described in literature. The developed population PK model predicts a FVIII half-life of 11.4 hours in the presence of 1.23 IU/mL VWF:Act, which is similar to the average FVIII half-life of 12 hours as described in literature.26,27 In patients with type 3 and type 2N VWD, the FVIII half-life without VWF presence or VWF binding can be assessed.
Generally, an FVIII half-life of 2 to 3 hours is observed in these patients, which approaches the FVIII half-life of 6.6 hours without VWF presence as observed in the present model. In literature, the VWF half-life is found to be between 12 and 15 hours. Similarly, Lethagen et al have described the VWF half-life to be 15.6 hours in a VWD population receiving this VWF/FVIII concentrate preoperatively. This is almost equivalent to the 13.9 hours we observed in our analyses. In our previously published population PK model, which only describes FVIII levels after perioperative treatment with this specific concentrate, we reported a FVIII volume of distribution of 3.28 L/70 kg and clearance of 0.038 L/70 kg per hour. This is almost equivalent to the 13.9 hours we observed in our analyses. In our previously published population PK model, which only describes FVIII levels after perioperative treatment with this specific concentrate, we reported a FVIII volume of distribution of 3.28 L/70 kg and clearance of 0.038 L/70 kg per hour. With these PK parameters, a typical patient of 70 kg will have a FVIII half-life of 60 hours, which does not comply with the FVIII half-life of 12 hours as described in literature. As this newly developed population PK model presents PK parameters that approach values reported in literature, we assume to have captured the PK of FVIII after perioperative treatment with this VWF/FVIII concentrate more realistically.

During covariate analysis, several patient characteristics and surgical characteristics were identified that were able to explain parts of the IIV in the PK parameters. The observed negative association between surgery duration and VWF clearance may indicate that more VWF is produced and/or released when a surgical intervention takes longer to perform. Higher VWF baseline was associated with more comorbidities as defined by an ASA classification of III or IV. Atiq et al also observed the association between more comorbidities and increased VWF levels in patients with VWD. This report indicated that this association was most likely explained by increasing age, especially in patients with type 1 VWD. In our study, type of VWD was found to be associated with the baseline of VWF, which is consistent with the classification system of VWD types. The high relative standard error value of the association between type 3 patients and the VWF baseline is probably caused by the small number of type 3 patients in this data set. We decided to maintain this covariate in the final model, as it properly displays the clinical difference between the types of patients with VWD. Finally, an association between FVIII clearance and VWD type was observed, indicating that type 2 and type 3 patients show decreased FVIII clearance. This observation feels contradictory, as...
binding of VWF to FVIII is dysfunctional in patients with type 2N and endogenous VWF is normally not present in type 3 patients, causing enhanced FVIII clearance. However, exogenous FVIII and VWF may have different PK properties than endogenous FVIII and VWF, that is, the exogenous VWF administered in type 2N patients has no dysfunctional binding to FVIII and the presence of exogenous VWF possibly lowers the enhanced FVIII clearance seen in type 3 patients not treated with factor concentrates.

During model development, we chose to model the preadministration VWF and FVIII levels as endogenous baseline levels instead of the often lower historical (lowest ever measured) baseline level. The observed differences between the historical baseline and preadministration VWF and FVIII levels may be caused by multiple factors, such as preoperative stress, inflammation, increasing age, comorbidities, or analytical variation. If this difference is only a temporary increase caused by, for example, preoperative stress, factor levels will return to the historical baseline in the postoperative period. However, if increasing age or comorbidity is the underlying reason, levels will approach the preadministration level postoperatively as this reflects the current endogenous baseline. In the analysis, we assumed that the baseline difference is permanent, and caused by, for example, increasing age, as the FVIII level dropped below the preadministration level in only 1 surgical procedure, and the VWF:Act level dropped below the preadministration level in 3 procedures. These differences were small (<0.10 IU/mL). An endogenous baseline increase caused by increasing age is especially expected in type 1 patients with an VWF:Act baseline ≥0.10 IU/mL. For type 1 patients with a baseline <0.10 IU/mL as well as type 2 and type 3 patients, the endogenous baseline is expected to remain similar over time. In our data set, type 1 patients contributed most to the baseline differences (58%), but, surprisingly, other types of patients also showed an endogenous baseline increase compared with the historical baseline.

A limitation of this study is that type 2B (n = 9), type 2M (n = 11), type 2N (n = 3), and type 3 (n = 6) patients were underrepresented. Although goodness-of-fit plots show adequate prediction of the separate disease types (supplemental Figures 1-3) and VWF:Act and FVIII levels of the clinical case (type 3 VWD) were adequately described, application of the population PK model in these types of patients may be less accurate. Another limitation is that we were unable to distinguish endogenous from exogenous coagulation factors in the population PK model. Endogenous and exogenous FVIII and VWF may have different PK and, as a result, the model may be improved by estimation of separate PK parameters for both endogenous and exogenous coagulation factors. Unfortunately, it is not yet possible to measure these coagulation factors separately and it was necessary to model the change in the cumulative sum of the endogenous and exogenous VWF:Act and FVIII levels over time. A third limitation is the high relative standard error (>30%) obtained for FVIII clearance in the final model, indicating that there is some uncertainty around the estimated value. Possibly, this can be solved by adding data with more level measurements per subject or by implementing a better sampling scheme. Finally, the population PK model was only based on data from patients receiving 1 particular VWF/FVIII concentrate. A study by Kessler et al showed bioequivalent VWF PK properties for 2 commonly used VWF/FVIII concentrates, but PK of FVIII after administration of the concentrates is different. Therefore, we recommend only using the model for patients receiving this specific concentrate. For VWF/FVIII concentrates with other ratios or multimer compositions, other population PK models will have to be developed.

Clinical applicability of our newly developed model was demonstrated by the clinical case described in this manuscript. For this unique type 3 patient, higher VWF/FVIII concentrate doses would have been necessary to reach the prespecified targets, although, for the majority of patients, lower doses are expected to reach the targets (supplemental Figure 4). Undoubtedly, this single case does not confirm external validity of the model and external validation in a larger cohort is recommended. This case only demonstrates the clinical implications of PK-guided dosing using an interaction model. As clinical guidelines increasingly recommend monitoring and targeting both VWF and FVIII levels, this population PK model is beneficial over the previously developed population PK model based only on FVIII levels. Despite the fact that this population PK model will support the targeting of sufficient VWF and FVIII levels, it is important to realize that the VWF:FVIII ratio of this concentrate is fixed and that both coagulation factors have different PK properties. Therefore, it remains challenging to achieve FVIII and VWF levels within similar ranges, and sometimes it may be unavoidable to accept higher FVIII (or possibly FVIII) levels when dosing repetitively. Future prospective studies that examine the feasibility and reliability of PK-guided dosing with VWF/FVIII concentrates in patients with perioperative VWD will further verify the validity of this PK-guided dosing approach and its clinical impact.

Conclusion

This novel integrated population PK model adequately describes VWF:Act and FVIII levels after perioperative dosing with a VWF/FVIII concentrate (ratio 2.4:1; Humate P/Haemate P). In this model, presence of VWF decreases FVIII clearance and increases FVIII half-life, thereby approaching a more physiological situation and explaining FVIII accumulation observed in this specific situation. Application of this model may facilitate PK-guided perioperative dosing with this specific concentrate based on both FVIII and VWF:Act targets, thereby potentially improving quality and cost-effectiveness of care.

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Authorship

Contribution: L.H.B., N.C.B.d.J., and R.A.A.M. analyzed the data by developing the population PK model; L.H.B. wrote the manuscript; J.M.H. and H.C.A.M.H. collected the clinical data; patient inclusion was monitored by H.C.A.M.H., K.F., K.M., J.C.J.E., B.A.P.L.-v.G., F.W.G.L., and M.H.C.; R.A.A.M. and M.H.C. supervised the study; F.W.G.L. gave critical guidance; and all authors contributed substantially to the critical revision of the manuscript and approved the final draft.

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