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ORIGINAL ARTICLE

Von Willebrand disease

Quantification of the relationship between desmopressin concentration and Von Willebrand factor in Von Willebrand disease type 1: A pharmacodynamic study

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Abstract

Introduction: Desmopressin can be used to prevent bleeding in von Willebrand disease (VWD), but the relationship between desmopressin and von Willebrand factor activity (VWF:Act) has yet to be quantified.

Aim: To quantify the relationship between desmopressin dose, its plasma concentration and the VWF:Act response in type 1 VWD patients.

Methods: Forty-seven VWD patients (median age 25 years, IQR: 19–37; median body weight 71 kg, IQR: 59–86) received an IV desmopressin dose of .3 mcg/kg. In total, 177 blood samples were available for analysis. We developed an integrated population pharmacokinetic-pharmacodynamic (PK-PD) model using nonlinear mixed effect modelling. Subsequently, we performed Monte Carlo simulations to investigate the efficacy of the current dosing regimen.

Results: A one-compartment PK model best described the time profile of the desmopressin concentrations. In the PD turnover model, the relationship between desmopressin plasma concentration and release of VWF:Act from the vascular endothelium was best described with an Emax model. Typically, VWF:Act increased 452% with an EC50 of .174 ng/ml. Simulations demonstrated that after .3 mcg/kg desmopressin intravenously, >90% patients with a VWF:Act baseline of ≥.20 IU/mL attain a VWF:Act >.5 IU/ml up to ≥4 h after administration. A capped dose of 30 mcg was sufficient in patients weighing over 100 kg.

Conclusion: The relationship between desmopressin and VWF:Act was quantified in a PK-PD model. The simulations provide evidence that recently published international guidelines advising an intravenous desmopressin dose of .3 mcg/kg with a capped dose of 30 mcg > 100 kg gives a sufficient desmopressin response.

KEYWORDS
desmopressin, PK-PD desmopressin, turn-over model, Von Willebrand disease, Von Willebrand factor

1 | INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder and is caused by a deficiency or qualitative defect of von Willebrand factor (VWF).[1] VWF is a plasma glycoprotein which plays a crucial role in primary haemostasis by promoting platelet adhesion to the subendothelium at sites of vascular injury and by initiating platelet aggregation. Subsequently, it also plays a role in secondary haemostasis by protecting factor VIII (FVIII) from proteolysis in the circulation, safeguarding thrombin and fibrin generation.[2] VWD is classified into three main types based on a partial or complete quantitative defect of VWF (type 1 and 3) or a qualitative defect in VWF (Type 2).[2] Type 1 consists of patients with VWF lower than .30 IU/ml or between .30 and .50 IU/ml, with abnormal bleeding.[3] Type 2 is further divided into the subtypes 2A, 2B, 2M and 2N. Risk of bleeding as well as treatment choice depends on VWD type, although inter-individual variation in bleeding tendency and response to treatment is notably large in VWD.

Desmopressin (1-deamino-8-d-arginine vasopressin) is a synthetic analogue of the antidiuretic hormone l-arginine vasopressin.[4] Desmopressin binds to V2 receptors and thereby induces the release of endogenous VWF from vascular endothelial cells.[5,6] Desmopressin can be used to prevent bleeding during surgical procedures in most type 1 VWD patients and in some patients with type 2A, 2M, and 2N VWD.[7] The most recent advice is to always perform a desmopressin test in VWD patients with baseline VWF activity <.30 IU/ml, in order to quantify the VWF response.[3] The use of desmopressin is contraindicated in type 2B VWD as it may induce thrombocytopenia. Desmopressin is not effective in type 3 VWD.

Recently, published international guidelines recommend an intravenous desmopressin dose of .3 mcg/kg, with a capped dose of 20–30 mcg.[3,8] This recommendation is, however, solely based on empirical evidence. It is unclear if the variability in pharmacokinetics (PK) of desmopressin contributes to the consecutive observed variability in VWF response, or pharmacodynamic (PD) effect. Furthermore, proposed capping of dosing, that is applying a fixed dose independent of body weight when .3 mcg/kg exceeds 20–30 mcg, has never been substantiated by pharmacological evidence. Population PK-PD modelling can be used to establish this concentration-effect relationship.[9,10] We developed a population PK-PD model to evaluate and quantify the concentration-effect relation of desmopressin on the VWF activity (VWF:Act) response in type 1 VWD. The aim of this study was to investigate if current treatment guidelines-including capped dosing- can be substantiated with this novel PK-PD model.

2 | PATIENTS AND METHODS

2.1 | Patients

VWD patients (historical lowest VWF antigen (VWF:Ag) and/or VWF:Act < .50 IU/ml) with abnormal bleeding and/or a family history of VWD were included if a desmopressin test was performed at the Erasmus MC or Erasmus MC – Sophia Children's Hospital Rotterdam, the Netherlands, between 1st April 2011 and 1st July 2014. The study was not subject to the Medical Research Involving Human Subjects Act (WMO) and was approved by the Medical Ethics Committee of the Erasmus University Medical Centre Rotterdam. All patients provided written informed consent.

2.2 | Blood sampling

Residual stored plasma samples from a prospective single-centre cohort study, investigating desmopressin side effects, were obtained.[11] All patients signed informed consent before data and samples were collected.

2.3 | Desmopressin test protocol

In all patients, desmopressin was administered intravenously in a dose of .3 μg/kg dissolved in 30 or 50 ml of NaCl .9% in children and adults respectively and infused in 30 min. In children, blood was sampled prior to (T0) desmopressin infusion, and at 1 (T1), 2 (T2), 4 (T4) and 6 (T6) hours after infusion. In adults, blood was sampled at T0, T1, T3, T6 and T24.

2.4 | Laboratory measurements

Venous whole blood was collected in 0.105 M sodium citrate tubes and centrifuged twice at 2.200 × g for 10 min at room temperature and stored at −80°C. Coagulation factor measurements were performed within a few days after sample collection. VWF:Ag was measured by ELISA and VWF:Act was measured by GpIbα binding assay (HemosIL™ von Willebrand Factor Activity; Instrumentation Laboratory BV, Breda, the Netherlands). FVIII activity (FVIII:C) was measured by one-stage clotting assay. Desmopressin plasma concentrations were assessed in the Amsterdam UMC using LC-MS/MS in positive ionisation mode on a Shimadzu LC-30 (Nishinokyo-Kuwabaracho, Japan) UPLC system coupled to an ABSciex (Framingham, MA, USA) API5500Q LC-MS.[12] The method was validated over a range of .0200–4.00 ng/ml. The accuracy ranged from 89.2% to 111.8% across the validated range, with intra-day and inter-day imprecision below 17.6% and 13.8%, respectively.

2.5 | Software

Nonlinear mixed-effects modelling software (NONMEM 7.3 ICON Development Solutions, Hanover, MD, USA) and Pirana (version 2.9.4), R (version 3.6.1) and PsN version (version 4.6.0) were used for the PK-PD analysis.

2.6 | Pharmacokinetic modeling

We performed a sequential PK-PD analysis. During PK model development, both one- and two-compartment models were evaluated. A priori allometric scaling of PK parameters by body weight was included in the structural PK model. Inter-individual variability (IIV) was estimated

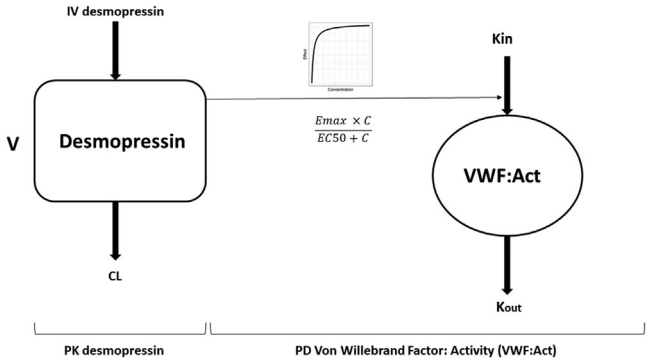

FIGURE 1 A schematic representation of the PK-PD model relating desmopressin concentration to VWF:Act. V represents the volume of distribution, CL represents the clearance, C the plasma concentration of desmopressin, Emax the maximum effect, EC50 the concentration at half maximal effect, K*in*, the zero-order constant for release of VWF:Act by the endothelium and K*out* the first-order rate constant for loss of VWF:Act, IV = intravenous

for each population PK model parameter. Various residual error models were evaluated. Next, associations between specific covariates and PK parameters were tested in order to explain the IIV in these parameters, by using a stepwise approach. The following covariates were evaluated: age, sex, height, baseline FVIII, baseline VWF:Act, baseline VWF:Ag and blood group (O, non-O). The supplement contains more details about the development of the PK model.

2.7 | Pharmacodynamic modeling

We used individual post-hoc PK parameter estimates as input for the PD model. In literature, the maximum effect of desmopressin occurs approximately 1 h after the end of intravenous administration.[13] We modelled the time lag using a turn-over model (Figure 1).[14] The turn-over model consists of a zero-order rate constant describing the constant release of VWF from the vascular endothelium (K*in*) and a first-order rate constant for loss of VWF (K*out*) from plasma. The baseline VWF:Act (BASE) of each patient is determined by the equilibrium of K*in* and K*out* and was fixed at the VWF:Act level as determined before the desmopressin administration.

In the PD analysis, the relationship between the increase in VWF release (K*in*) and desmopressin plasma concentration was quantified by a linear function, Emax function and sigmoidal Emax function. IIV was estimated for the PD parameters, and various residual error models were evaluated. The covariates as mentioned under the PK analysis were tested for correlation with the PD parameters.

The supplement contains more details on the development of the PD model.

2.8 | Pharmacokinetic-pharmacodynamic model evaluation

Model selection criteria were based on the change in the objective function value (OFV), goodness-of-fit (GOF) plots, precision of parameter estimates, decreases in IIV and residual variability, condition number, shrinkage and a successful convergence step, with at least three significant digits in parameter estimates.[16]

Visual predictive checks (VPCs) with 1000 simulated data sets were used to assess the predictive performance of the model. The 5th, 50th, and 95th percentiles of the predictions from the simulations and observations from the original dataset were derived and plotted against time. A non-parametric bootstrap was performed to assess parameter precision and to calculate confidence intervals (CI) for both the population PK and PD parameters. The 5th and 95th percentiles of the bootstrap parameter distribution constitute the 90% CI.

2.9 | Monte Carlo simulations

Using the final population PK and PD models, Monte Carlo simulations were performed for 1000 patients (females and males) with body weights of 50, 70, 100 and 130 kg to investigate if recently published international desmopressin guidelines[3] can be substantiated by the constructed PK-PD model. Moreover, we investigated whether dosing can be simplified by capping of desmopressin dosing when .3 mcg/kg dosing exceeds the 20–30 mcg cap in patients >100 kg.

All virtual patients had a baseline VWF:Act of .20 IU/ml. VWF:Act time profiles were simulated and desmopressin doses of 5, 10, 15, 21, 25, 30, 35 and 39 mcg were administered in all patients. A patient was considered a responder if VWF:Act levels were greater than .50 IU/mL at 4 h after desmopressin administration. For each body weight and dose, the percentage of responders was calculated. Treatment was considered effective > when > 90% of the simulated patients of each body weight were responders.

3 | RESULTS

3.1 | Patients

The study population consisted of 47 patients, 15 males and 32 females with type 1 VWD. The median age was 25 years and body weight was 71 kg. Further characteristics are summarised in Table 1.

3.2 | Pharmacokinetic analysis

A total of 177 desmopressin plasma concentrations were available. A one-compartment model adequately described the PK of desmopressin. IIV could be estimated for clearance (CL) and volume of distribution (V), which resulted in a significant ($p < .05$) decrease in OFV. The residual variability was described by a combined (proportional + additive) error model.

During covariate model selection, inclusion of the following covariates significantly improved the fit of the PK model to the data ($p < .05$): sex on CL and sex, baseline FVIII, baseline VWF:Ag and baseline VWF:Act on V. The association between sex and V produced the largest improvement in model fit ($p < .001$): V was 22% higher in females

TABLE 1 Patient characteristics

	N = 47 Number or median (interquartile range)
Sex (female)	32
Age, years	25 (19–37)
Body weight, kg	71 (59–86)
Height, cm	167 (160–177)
Historical lowest VWF:Act, IU/ml	.46 (.34–.51)
Historical lowest VWF:Ag, IU/ml	.43 (.35–.49)
Baseline (T0) VWF:Act, IU/ml	.48 (.41–.60)
Baseline (T0) FVIII, IU/ml	.59 (.51–.71)
Baseline (T0) VWF:Ag, IU/ml	.45 (.39–.59)
Blood group (n)[a]	
Non O	13
O	32
Bleeding score (ISTH-BAT) at diagnosis	
Blood group non O	5 (2–6)
Blood group O	4 (1–6)

Abbreviations: VWD, Von Willebrand disease; VWF, Von Willebrand factor; FVIII, factor VIII.
[a]Blood group data were unknown in two patients.

TABLE 2 Desmopressin population pharmacokinetic parameters

Parameter	Final model values (RSE%) (Shrinkage %)	Bootstrap Median value (95% CI)
CL (L/h/70 kg)	9.43 (5)	9.48 (8.48–10.3)
V (L/70 kg)	25.9 (11)	26.1 (21.1–32.5)
(%) Increase V in females	22.0 (10)	20.6 (4.11–49.2)
Inter-individual variability		
CL (CV%)	31.7 (16) [4]	30.7 (21.3–41.7)
V (CV%)	36.3 (18) [11]	35.0 (20.4–46.7)
Covariance CL~V	.0705	.0683 (.0128–.0131)
Residual variability		
Proportional error (CV%)	1.22 (12)	1.18 (.869–2.00)
Additive error (ng/ml)	.146 (13)	.145 (.0890–.184)

Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; RSE, relative standard error; V, central volume of distribution.
CV was calculated as: CV = sqrt(exp(variance)−1) x 100%; RSE was calculated as: RSE = 100 × standard error/parameter estimate.

TABLE 3 Population pharmacodynamic parameters

Parameter	Final parameterValues (RSE%)(Shrinkage %)	Bootstrap median (95% CI) of parameter value
Kout (h^{-1})	5.66 (4)	5.66 (4.71–6.81)
EC50 (ng/ml)	.174 (26)	.178 (.107–.277)
Emax	4.52 (10)	4.54 (3.80–5.55)
Inter-individual variability		
Emax (CV%)	29.1 (10) (11)	28.8 (22.2–34.1)
Residual variability		
Additive error (IU/ml)	.238 (11)	.235 (.183–.282)

Kout = first-order rate constant for loss of VWF:Act; Emax = maximum effect; EC50 = drug concentration which produces 50% of the maximal effect; CV, coefficient of variation; RSE = relative standard error; CI = confidence interval; CV was calculated as: CV = sqrt(exp(variance)-1) x 100%; RSE was calculated as: RSE = 100 × standard error/parameter estimate.

compared to males. After inclusion of sex in the model, the remaining significant covariates were added one-by-one. However, no improvement of the model was observed ($p > .05$).

The goodness-of-fit plots showed sufficient agreement between predicted and observed desmopressin concentrations (Figure S1). The VPC of the final model is presented in Figure S2. Overall, the 2.5th, 50th and 97.5th percentiles of observed concentrations were mostly within the predicted 95% confidence interval (CI) of the predicted percentiles. The median values of the parameter estimations of the bootstraps were approximately equal to the final model's respective values (Table 2).

3.3 | Pharmacodynamic analysis

A total of 177 VWF:Act levels were available. The time profile of VWF:Act was described using the turn-over model shown in Figure 1. In the modelling procedure BASE (baseline VWF:Act) was fixed to individual baseline VWF:Act values (Table 1). The performance of several PD functions describing the relationship between VWF release and desmopressin concentration was tested (i.e. a linear function, Emax function, and sigmoid Emax function): The relationship between the VWF release and desmopressin concentration was best described with an Emax function (supplement Equation (10)). We attempted to estimate the value of BASE, but this did not result in successful convergence of the model. Implementation of IIV on Emax significantly improved the model ($p < .001$). Residual variability was best described by an additive error model. No significant relationship was found between covariates and PD parameters. Baseline VWF release (*Kin*) was typically increased by 452% with an EC50 of .174 ng/ml (Table 3). The IIV of Emax was modest with a value of 29.1%. In the concentration-effect curve, the EC90 was reached at a desmopressin concentration of .314 ng/ml. Figure 2 displays the time profile of the desmopressin plasma concentration, PD effect and VWF:Act for a typical patient of 70 kg receiving .3 mcg/kg desmopressin.

Goodness-of-fit plots showed good agreement between predicted and observed VWF:Act concentrations (Figure S1). The VPC plots in Figure S2 show that the observed VWF:Act values are well-centred around the predicted median of the PD model. The bootstrap median

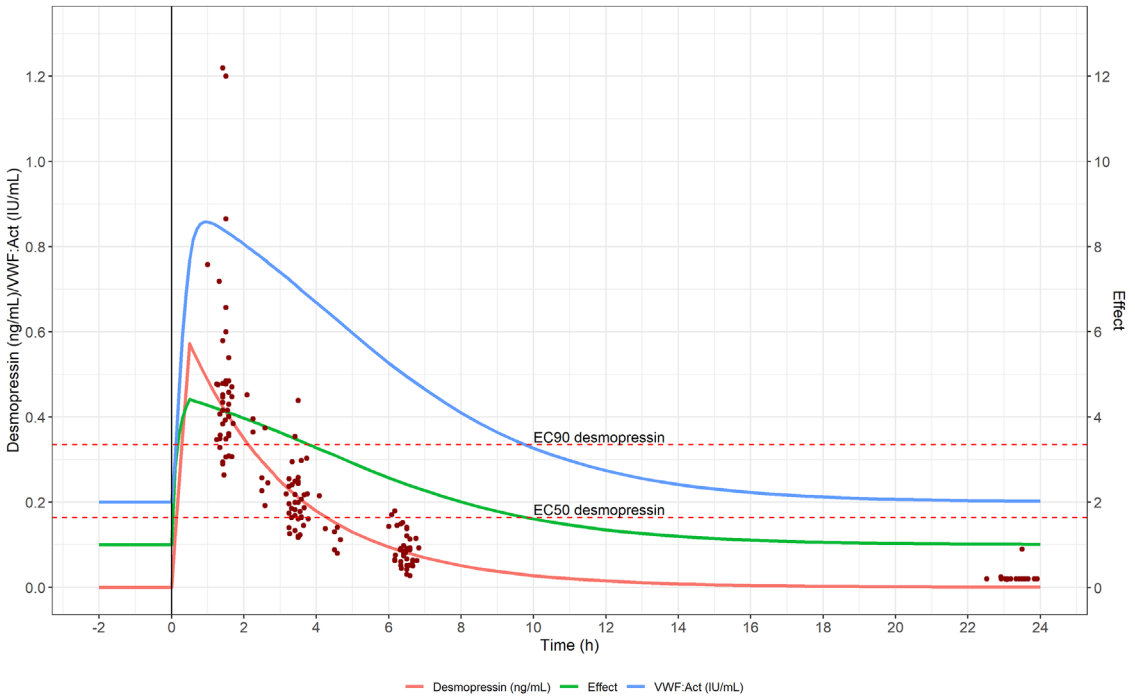

FIGURE 2 Time profiles of desmopressin plasma concentration, the PD effect and VWF:Act for a typical patient weighing 70 kg with a VWF:Act baseline of .20 IU/ml. The red line represents the typical plasma desmopressin concentration, the red dots represent the observed concentration in all individual patients. The green line depicts the effect of desmopressin starting at unity (no effect) with a maximum value of 5.8. The blue line depicts the VWF:Act response on the basis of the turnover model

and confidence intervals are comparable to the parameter estimates (Table 3).

3.4 | Monte Carlo simulations

The simulated dosage regimens targeting VWF:Act levels above .50 IU/ml at 4 h after desmopressin administration are shown in Figure 3. Figure 3 displays the percentage responders against various dosage regimens for patients with a body weight of 50, 70, 100 and 130 kg. For patients weighing 50 kg, a dose of 15 mcg was necessary to attain a sufficient response in 92% of patients. For patients weighing 70 kg, a dose of 21 mcg was necessary to attain a sufficient response in 93% of patients. Patients with a body weight of 100 kg needed a dose of 25 mcg to attain a sufficient response in 92% of patients. Finally, Patients with a body weight of 130 kg needed a dose of 30 mcg to attain a sufficient response in 91% of patients.

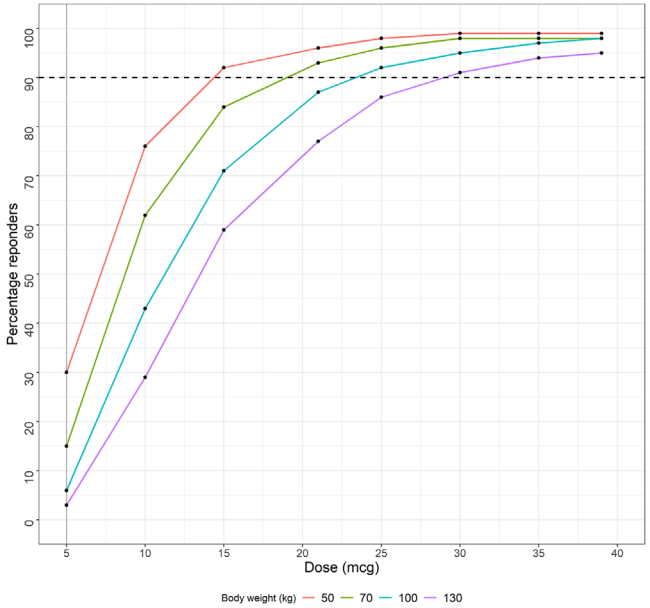

FIGURE 3 Percentage of VWF:Act responders 4 h (T4) after desmopressin administration. Desmopressin dosages (5, 10, 15, 21, 25, 30, 35, 39 mcg) given to virtual patients with various body weights (50, 70, 100 or 130 kg). Responders demonstrated VWF:Act greater than .50 IU/ml at 4 h after desmopressin administration. The *y*-axis denotes the percentage of virtual patients that demonstrated a response. The dashed horizontal black line denotes the 90% responders threshold

4 | DISCUSSION

An innovative and novel turn-over PK-PD model was developed characterising the relationship between desmopressin dose, desmopressin plasma concentration and VWF:Act response. We demonstrate that a maximum increase in VWF:Act can be established by capped dosing with a fixed dose when body weight exceeds a certain maximum.

By performing simulations based on the developed PK-PD model, we confirm the feasibility and efficacy of the recently published guidelines for treatment of VWD with desmopressin of the ASH ISTH NHF WFH 2021.[3]

Our simulations demonstrate that an adequate response is reached when patients weighing 50–100 kg receive a dose of .3 mcg/kg desmopressin intravenously. Although administration of 25 mcg resulted in an adequate response in patients weighing 100 kg, this dose may be insufficient for patients over 100 kg (Figure 3). For practical considerations we therefore suggest a capped dose of 30 mcg desmopressin in all patients above 100 kg and .3 mcg/kg for all patients below 100 kg, to ensure an adequate VWF:Act response.

In our PK model describing desmopressin concentrations, the volume of distribution (V) was 22% higher in females compared to males. V was 25.9 L/70 kg in males which may reflect limited distribution of desmopressin to other tissues other than plasma, which could be explained by the higher body fat percentage in females compared to males.[15] Due to a higher V, females exhibited lower peak concentrations than males. When we stratified our simulations for sex, a slightly higher peak in desmopressin concentration in males was observed in comparison to females [data not shown]. However, this has no implications for the attained VWF:Act levels, as VWF:Act levels at T1 and T4 were similar in both males and females. The median peak desmopressin concentration for females is .52 ng/ml and for males .63 ng/ml, which is more than adequate to produce the maximum effect, as the EC50 is .174 ng/ml. Therefore, dose adjustments based on sex are not necessary. In addition, simulations were performed for patients with a VWF:Act baseline of .20 IU/ml. Patients with either a higher or lower baseline will attain higher and lower VWF:Act values after receiving .3 mcg/kg. Nevertheless, in our study population, only four patients had a baseline lower than .20 IU/ml. In usual clinical practice, patients with a VWF:Act baseline lower than .30 IU/mL always undergo a desmopressin test to check their responsiveness. If a patient fails to achieve an adequate VWF:Act response, a VWF-containing factor concentrate should be administered to achieve sufficient VWF:Act levels.[16]

Based on Figure 2, desmopressin is eliminated from the body after approximately 14 h in a typical patient of 70 kg. Still, in most patients, it is advised to administer a subsequent desmopressin dose only after 24 h due to potential side effects, such as fluid retention due to its antidiuretic effects.[17]

It is well known that patients with blood group O have lower VWF:Act levels.[18] During population PK-PD model development, we tested blood group O and non-O as a covariate. In our PD model, K*out* reflects the CL of VWF:Act. We investigated if the K*out* differs between blood group O and non-O, but this did not improve the model. Therefore, we did not include blood group O as a covariate in our models.

Argenti et al. explored the relationship between desmopressin concentrations and VWF:Act in healthy volunteers.[6] In this study, the temporary delay in VWF response was described by a hypothetical effect compartment model. A value of .237 ng/ml was reported for EC50 and 367% for Emax, which is comparable to the values observed for VWD patients in our study. Furthermore, this study reported a value of 2.16 h^{-1} for rate constant K*e0*, which corresponds to a half-life of ca. 20 minutes and a delay of ca. 80 min before desmopressin changes in plasma are completely reflected in VWF:Act. This also corresponds with the results of our simulations.

A strength of this study is that we have included patients from a real-life population, including a wide range of ages. We included patients in our study if they had abnormal bleeding symptoms and either a historical lowest VWF:Ag or VWF:Act below .50 IU/ml. In some patients, there was a difference between historical lowest VWF:Act and VWF:Act at T0. A few patients were diagnosed with VWD 10–30 years before the desmopressin test. In these patients, the higher VWF:Act at T0 could be explained by an age-related increase of VWF.[19] We however also observed differences in some patients who underwent a desmopressin test shortly after diagnosis. It is well known that VWF may also increase due to stress[1] and a desmopressin test can be a stressful event for some patients, especially children.

We acknowledge some limitations of our study. Our analysis was limited to only type 1 VWD. Therefore, the concentration-effect relationship could not be established for other types of VWD. Also, we did not observe extremely fast clearance as observed in type 1 Vicenza in any of the patients. Furthermore, our dataset contained only six patients with a body weight over 100 kg. Therefore, simulations may be less precise in this category of patients. V of desmopressin was 25.9 L/70 kg and we assumed that desmopressin has a limited distribution to the other tissues. This is important for obese patients, since they have more adipose tissue compared to non-obese patients. The total body weight in obese patients is mainly increased because of the adipose tissue, but lean body weight would increase much less.[20] Based on this, we assumed that 30 mcg would be adequate for more severely obese patients based the finding for the 130 kg patients.

In conclusion, our novel turn-over PK-PD model successfully characterised the relationship between desmopressin dose, desmopressin plasma concentration and VWF:Act response. Simulations confirm that current international desmopressin dosing guidelines in which an intravenous dose of .3 mcg/kg and a capped dose of 30 mcg desmopressin is recommended are effective for the treatment of VWD patients. The developed PK-PD model can be applied to further investigate the relationship between specific patient characteristics and VWF response, thereby potentially eliminating the necessity of desmopressin testing in the near future.

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Principal investigator: Dr. M.H. Cnossen. Project manager: Dr. S.H. Reitsma.

Beneficiaries of the SYMPHONY consortium: Erasmus MC and Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, project leadership and coordination; Sanquin Diagnostics; Sanquin Research; Amsterdam University Medical Centers; University Medical Center Groningen; University Medical Center Utrecht; Leiden University Medical Center; Radboud University Medical Center; Netherlands Society of Hemophilia Patients (NVHP); Netherlands Society for Thrombosis and Hemostasis (NVTH); Bayer B.V., CSL Behring B.V., Swedish Orphan Biovitrum (Belgium) BVBA/SPRL.

This paper is written on behalf of the international multicentre "OPTI-CLOT" (patient tailOred PharmacokineTIc-guided dosing of CLOTting factor concentrates in bleeding disorders) and "To WiN" studies that aim to implement a PK-guided approach for the treatment of bleeding disorders using population PK models for desmopressin, factor concentrates and other alternative drugs. "OPTI-CLOT" and "To WiN" study group.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

M.E. Cloesmeijer, N.C.B. de Jager and R.A.A. Mathôt performed the analyses and developed the population pharmacokinetic-pharmacodynamic model. J.M. Heijdra collected the clinical data and provided clinical input. M.E. Cloesmeijer and J.M. Heijdra wrote the manuscript, with assistance of R.A.A. Mathôt and M.H. Cnossen while F.W.G. Leebeek and M.H.J.A. Kruip gave critical guidance. All authors contributed substantially to the critical revision of the manuscript and approved the final draft.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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