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Full Length Article

A comparison of methods for prediction of pharmacokinetics across factor concentrate switching in hemophilia patients

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ABSTRACT

Introduction: This study proposes a method to predict individual pharmacokinetics of a future product by using the individual pharmacokinetic profile on the current product and the PopPK models of the current and future product.

Methods: Individual dense data was collected from two PK crossover studies, one enrolling 29 patients switching from Advate to Eloctate and one enrolling 15 patients switching from Advate to Novoeight. Three methods were designed to predict the second product's individual PK parameters (CL, V1, Q, and V2). Method 1 used the second product's typical population value of PK parameters from its PopPK model. Method 2 used the second product's calculated PK parameters based on individual covariates and its PopPK model. Method 3 used method 2, along with the predicted η-values of CL and V1 from the first product and its PopPK model. Each method was used to assess PK prediction during switching from Advate to Novoeight, Novoeight to Advate, and Advate to Eloctate.

Results: The three methods produced different outcomes. The mean absolute relative errors for half-life were lowest for method 3 for each study (11.6%, 13.1%, 13.6%). The regression line between predicted and observed half-life for method 3 was closest to the line of identity for each study (0.84, 0.67, 0.66).

Conclusion: Taking into account individual PK from a previous clotting factor product was shown to provide better means of estimating individual PK for a new product. This may improve regimen design across switches and reduce the time to tailor optimal dose of FVIII products.

1. Introduction

Hemophilia A is a genetic disorder caused by a deficiency in clotting factor VIII (FVIII) production. People with untreated hemophilia have significantly lower life expectancy [1] and may develop hemophilic arthropathy, which impairs mobility and quality of life [2]. The severity of hemophilia is dependent on the endogenous levels of FVIII activity (severe defined as < 1 IU/dL or < 1%, moderate as 1–5%, and mild as equal or > 5%) [2]. Historically, FVIII infusions were administered to treat an acute bleed (on-demand), but this treatment modality was found to be suboptimal when compared to prophylactic treatment in terms of reducing the number of bleeds and minimizing joint damage. [3] People with severe hemophilia A are now often treated with prophylactic factor concentrate infusions in order to decrease the risk of joint deterioration and bleeds [2,4].

When initiating hemophilia A prophylaxis, FVIII concentrates are generally used at 20–40 international units per kg of body weight (e.g. 20–40 IU/kg), but this one-size-fits-all dosing method fails to account for the large inter-individual pharmacokinetic (PK) variability observed within the hemophilia population [5]. In order to optimize treatment, individual PK-tailored dosing may be a more effective method for ensuring that factor concentrate activities are maintained above target levels [6]. Back in 2001, the International Society of Thrombosis and Hemostasis (ISTH) recommendations for PK studies of factor concentrates did not allow for adequate uptake of individual PK profiling as part of routine clinical practice [7,8]. Building on the innovative application to hemophilia [6] of population pharmacokinetics (PopPK) with subsequent Bayesian estimation (leveraging prior knowledge available from a patient population and thus requires only a few blood samples from a single patient to derive individual PK), [9,10] the ISTH

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issued new guidelines [11] in 2017, which suggests using only a few blood samples from a single patient to derive individual PK.

The main focus of PopPK modelling is to quantify and describe the variability of a drug's PK in a population [12]. Variability can be explained by incorporating covariates such as demographic (age, sex, body weight, race), genetic (blood group or other phenotypes), or physiological (medical conditions, pregnancy) characteristics into our model [12]. Although covariates may explain a large portion of the observed between subject variability (BSV), there is still a remaining amount of unexplained variability [13]. This residual variability accounts for the difference between an individual's PK parameter value, such as clearance (CL), and the average value in the population after accounting for the covariates, and is typically represented by using an eta-value (η) [14]. When inputting the specific values of the covariates for the patient, estimation of η can be performed using Bayesian methods, leading to stable PK parameter estimates in limited sampling cases [11].

The use of PopPK models and Bayesian forecasting provides the optimal way to estimate individual PK profiles in order to design appropriate treatment regimens for people with hemophilia treated with factor concentrates [15]. Since the practical adoption of PopPK is beyond the technical capacity of most individual clinicians, the Web Accessible Population Pharmacokinetic Service – Hemophilia (www.wapps-hemo.org; WAPPS-Hemo) has been implemented as an online platform to facilitate hemophilia treatment optimization using individual PK profiling. Clinicians input patient characteristics and 2 to 3 post-infusion factor VIII/IX plasma levels, receive an expert-reviewed individual PK estimate report, use a simple clinical calculator module to tailor a treatment regimen, and have the option to activate a mobile app (myWAPPS) for the patient to provide him with real-time estimated factor activity levels.

As it is rare for people with hemophilia to use the same FVIII product throughout their life, [16] clinicians acquire new individual PK and re-design a dosing regimen for their patients when they switch factor concentrates. Factor concentrate switches may be prompted by the availability of new, improved concentrates [17] by termination of national contracts resulting in a discontinuation of drug coverage, hypersensitivity to their current drug formulation, or adverse drug reactions [18]. Hemophilia A patients will likely switch between FVIII concentrates at some point or at multiple points in their life, but current recommendations do not formally take into account what was learned on a current concentrate when switching to a new one [15]. Clinically, a patient switching from one concentrate to a new one is either maintained on the same dose and frequency, or is prescribed the average dose and frequency indicated in the drug label or package insert. Indeed, patients may be switching from a regimen tailored on individually documented PK parameters to one based on average PK parameters.

The lack of PK-tailored guidance when switching from one product to another may result in a period of time where treatment may increase the risk of inappropriate dosing, leading to either an increased risk of bleeds or waste of expensive factor concentrate. While the PopPK models in WAPPS-Hemo can determine individual PK for each factor concentrate, extrapolating PK from one product to another has not yet been explored. Knowledge of an individual's PK on one brand and how their PK parameters differ from the population (e.g. by using their η-values) may be useful knowledge that can be applied to predict their PK for the switched brand. We hypothesize that the knowledge of η-values of the current factor concentrate will help predict PK of a new factor concentrate.

2. Materials and methods

2.1. Study population

2.1.1. Patient switching between two different standard half-life FVIII concentrates

Pharmacokinetic data from people with severe hemophilia A (n = 15, mean age = 23.3 years) with a baseline FVIII activity level of < 0.01 IU/mL was obtained from an open-label, sequential dosing study (NCT00837356) by Novo Nordisk [19]. The study aimed to compare PK properties of two serum-free FVIII products, octocog alfa (Advate; Baxter, Deerfield, IL) and turoctocog alfa (Novoeight; Novo-Nordisk, Copenhagen, Denmark). Subjects received a single intravenous dose of 50 IU/kg of Advate followed 4 days later by a single intravenous dose of 50 IU/kg of Novoeight. Blood samples were taken prior to and 0.25, 0.5, 1, 4, 8, 12, 24, and 48 h after dose administration (average number of samples = 8) [19]. Factor activity levels of < 0.0125 IU/mL were considered to be below the limit of quantification (BLQ).

2.1.2. Patient switching from standard to extended half-life FVIII concentrates

Pharmacokinetic data from people with hemophilia A was obtained from a phase III study (NCT01181128) by Bioverativ Therapeutics Inc. [20]. This study was an open-labeled, multicenter, partially randomized study of recombinant FVIII Fc fusion protein (rFVIIIFc), Eloctate (Bioverativ, Waltham, MA) enrolling 165 male patients aged ≥12 years with severe hemophilia A [20]. A subgroup of these patients (n = 29, mean age = 31 years) had sequential PK evaluations using Advate for comparison. An injection of Advate 50 IU/kg was administered and samples were taken over 72 h (average number of samples = 8). After a washout period, an injection of Eloctate 50 IU/kg was administered, and samples were taken over 120 h (average number of samples = 7). Factor activity levels of < 0.005 IU/mL were considered to be BLQ [20].

2.2. PK Analysis

Three concentrate-specific (Advate, Novoeight, Eloctate) PopPK models were used as prior information in the Bayesian estimation of this study. The PopPK models were developed for WAPPS-Hemo and the details are published elsewhere [21,22]. All three PK models were two-compartment models including clearance (CL), intercompartmental clearance (Q), central volume (V1), and peripheral volume (V2), with BSV on CL and V1. With respect to covariates, CL, V1, and V2 are a function of fat-free mass (FFM) [23] and CL is a function of age [24]. The three PopPK models were built on dense PK data from pivotal studies, including the data used in this study (Table S1).

Ultimately, Bayesian forecasting is estimating BSV terms within their distributions as assumed in the PopPK models. As an illustration of using a PopPK modelling approach [24], a patient i with known FFM (FFM_i) and age (Age_i), and who is infused with Advate, will have a Bayesian estimate for CL (CL_i) of:

$$CL_i\,[L/h] = CL_{pop} \times \left(\frac{FFM_i}{median\ FFM}\right)^{\theta_{FFM}} \times \left(1 + \theta_{AGE} \times \frac{\max(0 Age_i - median\ Age)}{median\ Age}\right) \times e^{\eta_i}$$

where CL_{pop} is the typical clearance value for the population, θ_{FFM} is the effect of fat-free mass on CL, θ_{AGE} is the effect of age on CL, η_i is the estimated deviation of CL of patient i from a typical individual with same FFM and age. For each BSV term of each PopPK model, the distributions of η were assumed normal with a standard deviation σ (e.g. CL and V1 were assumed to be log normally distributed).

To ensure that the estimated PK parameters did not bring any bias in the predictions of the trial, the Bayesian method was compared to a

Table 1
Three methods and the information gathered from PopPK models of the two products to estimate PK of the second product.

	PopPK model of first product	PopPK model of second product
Method 1	–	$\begin{Bmatrix} CL = CL_{pop} \\ V1 = V1_{pop} \\ Q = Q_{pop} \\ V2 = V2_{pop} \end{Bmatrix}$
Method 2	–	$\begin{Bmatrix} CL = CL_{pop} \times f_{CL}(FFM, AGE) \\ V1 = V1_{pop} \times f_{V1}(FFM) \\ Q = Q_{pop} \\ V2 = V2_{pop} \times f_{V2}(FFM) \end{Bmatrix}$
Method 3	η_{CL} and η_{V1} calculated from first product	$\begin{Bmatrix} CL = CL_{pop} \times f_{CL}(FFM, AGE) \times e^{\eta_{CL}} \\ V1 = V1_{pop} \times f_{V1}(FFM) \times e^{\eta_{V1}} \\ Q = Q_{pop} \\ V2 = V2_{pop} \times f_{V2}(FFM) \end{Bmatrix}$

Age is in years, fat-free mass (FFM) is in kg. CL, clearance; CLpop, population clearance; Q, intercompartmental clearance; Q_{pop}, population intercompartmental clearance; V1, central volume; $V1_{pop}$, population central volume; V2, peripheral volume; $V2_{pop}$, population peripheral volume; η_{CL}, Unaccounted between-subject variability on clearance; η_{V1}, Unaccounted between-subject variability on central volume.

non-compartmental analysis (NCA). The NCA was performed using the MATLAB® *sbionca* function. The regression was performed following the recommendation from the Pharmaceuticals Users Software Exchange [25] with a minimum of 4 points per individual. Individuals who did not meet the requirements from the recommendation were excluded from the comparison with Bayesian forecast.

2.3. Experimental design

Three methods were used to assess PK prediction accuracy during switching from a first product (Advate or Novoeight) to a second product (Novoeight or Eloctate when the first product was Advate, Advate when the first product was Novoeight). Table 1 presents the three methods used to predict the individual PK parameters (CL, V1, Q, and V2) on the second product.

- Method 1 used the typical population value of CL, V1, Q, and V2 of the second product from its PopPK model. This method assumes that all individuals have the same PK parameters.
- Method 2 used the calculated values of CL, V1, Q, and V2 for the second product based on the individual with a given set of covariates and the PopPK model of the second product. This method assumes that all individuals with identical fat-free mass and age will have the same PK parameters.
- Method 3 used the values of CL, V1, Q, and V2 for the second product based on an individual with a given set of covariates and the PopPK model of the second product, along with the predicted η-values of CL and V1 from the first product and its PopPK model. This method takes into account what had happened on the first product in addition to Method 2.

Method 3 assumes that percentiles of deviation are equivalent between PopPK models. Using the first product PopPK model, Bayesian forecasting was performed for each individual in the trial to obtain the individual η-values for CL and V1 (η_1). Corresponding individual η-values for the second product (η_2) were calculated from η-values of the first product (η_1) assuming that the percentiles of deviation were equivalent between the two PopPK models. Operationally, η_2 was obtained by multiplying η_1 by the ratio between the standard deviations of the BSV of the PK parameters of the first (σ_1) and second (σ_2) products as shown:

$$\eta_2 = \eta_1 \times \frac{\sigma_2}{\sigma_1}$$

An example of the scaling algorithm is provided in Fig. 1. The individual predicted η-value for CL and V1 of the second product was then used in addition to individual covariates to estimate individual values of CL and V1. Once all PK parameters were predicted for an individual, the predicted values of half-life, time-to-0.05, −0.02, −0.01 IU/mL and plasma factor activity at 24 h, 48 h, and 72 h were derived using the PK parameters and dose administered.

2.4. Comparison of the different methods

To determine the most accurate method for predicting PK of the second product, absolute relative errors were calculated for each individual with regards to CL, V1, half-life, time-to-0.05, −0.02, −0.01 IU/mL and plasma factor activity at 24 h, 48 h, and 72 h. Absolute relative errors were calculated using the following equation:

$$Absolute\ relative\ error_{PK} = \left| \frac{PK_{pred} - PK_{est}}{PK_{est}} \right|$$

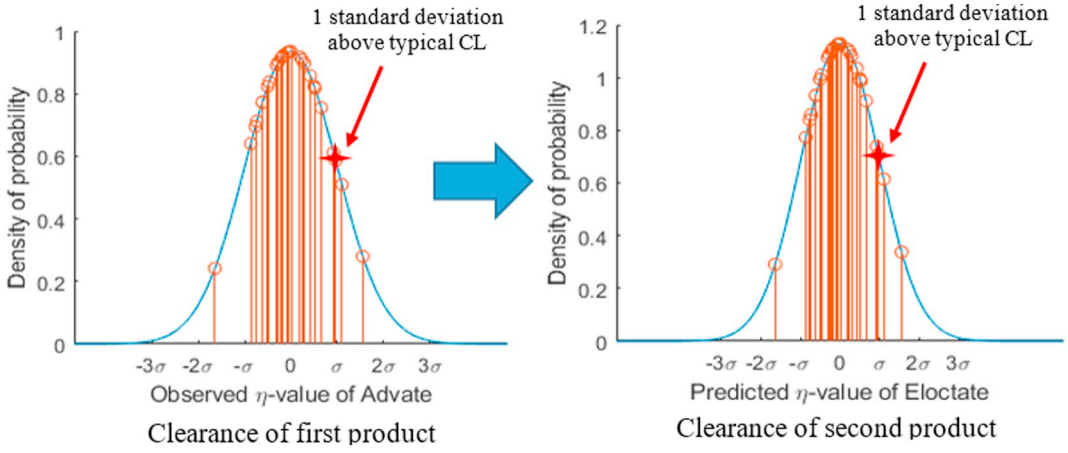

Fig. 1. Converting eta-values of e.g. Advate CL to Eloctate CL. Converting η-values of e.g. Advate CL to Eloctate CL. The observed eta-(η-) values of Advate CL have a mean of 0 and a standard deviation of σ_{ADV}. The distribution is divided by $\sigma_{ADV}$to obtain an η-distribution with a mean of 0 and standard deviation of 1. The normalized η-distribution of Advate is assumed to be equivalent to the predicted η-distribution of Eloctate. Lastly, the η-values used to predict Eloctate PK parameters are multiplied by the standard deviation of σ_{ELO} to obtain the predicted η-values of Eloctate. η, individual deviation of a PK parameter from the population; σ_{ADV}, standard deviation of Advate η-values; σ_{ELO}, standard deviation of Eloctate η-values.

where PK_{pred} is the individual parameter prediction obtained using one of the three methods and PK_{est} is the actual PK value estimated with Bayesian forecasting using the second product PopPK model, individual covariates, and measured factor activity levels from the clinical studies. The method with the lowest mean and range of the absolute relative errors was considered to be the most accurate method. In addition, individual CL, V1, half-life, time-to-0.05, −0.02, −0.01 IU/mL and plasma factor activity at 24 h, 48 h, and 72 h were estimated with each of the three methods (PK_{pred}) and were regressed against the observed values (PK_{est}). Any regression line (PK_{pred} vs. PK_{est}) with a 95% CI that included the line of identity (slope of 1) indicated that the method was considered to be able to accurately predict the estimated PK.

2.5. Software

Bayesian forecasting and PK predictions were performed using non-linear mixed effects modelling as implemented in NONMEM (version 7.3, ICON, Hanover, MD) [26]. Graphics for model evaluation and statistical analysis were created using MATLAB® (version 2017b, The MathWorks, Natick, MA).

3. Results

3.1. NCA versus Bayesian method

The typical NCA and Bayesian half-life estimates are found in Table S2. NCA was flagged as unreliable for 1 instance (Advate from the Advate to Eloctate dataset) according to the relevant guidelines [25]. The remaining instances showed an average difference in half-life estimates for NCA as compared to the Bayesian method of 0.37 h (Advate), 0.23 h (Eloctate), 0.42 h (Advate), and 0.70 h (Novoeight) (Fig. 2).

3.2. Comparative performance of the three prediction methods

The mean and range of absolute relative errors were lowest for method 3 across all studies and all PK outcomes (Table 2). The regression lines for each of the PK outcomes using method 1 and method 2 were significantly different from the line of identity, while only some were different using method 3 (Table 3). The slope for method 3 was closer to the line of identity than the other two methods for all PK outcomes (examples shown in Fig. 3-5).

Individual predicted half-lives are reported in Table S3. Method 3 produced predicted half-lives closest to the observed half-life 66.7%, 66.7%, and 48.3% of the time for Advate to Novoeight, Novoeight to Advate, and Advate to Eloctate respectively.

4. Discussion

We have established that the use of information from the PK profile on a current factor VIII concentrate can be used to predict the individual PK profile on a future concentrate, reducing the relative error in predicting half-life by 16.0%, 20.2%, and 5.2% (Advate to Novoeight, Novoeight to Advate, and Advate to Eloctate respectively) as compared to method 2 for estimating half-life on the new concentrate. Adoption of method 3 in clinical practice can reduce the likelihood of improperly dosing patients when switching among different factor concentrates.

Currently, hemophilia switching guidelines suggest initiating EHL FVIII products at the same dose as standard half-life (SHL) FVIII products, reducing the frequency from three to two times weekly [11,15]. This course of action, however, assumes all patients to have a similar

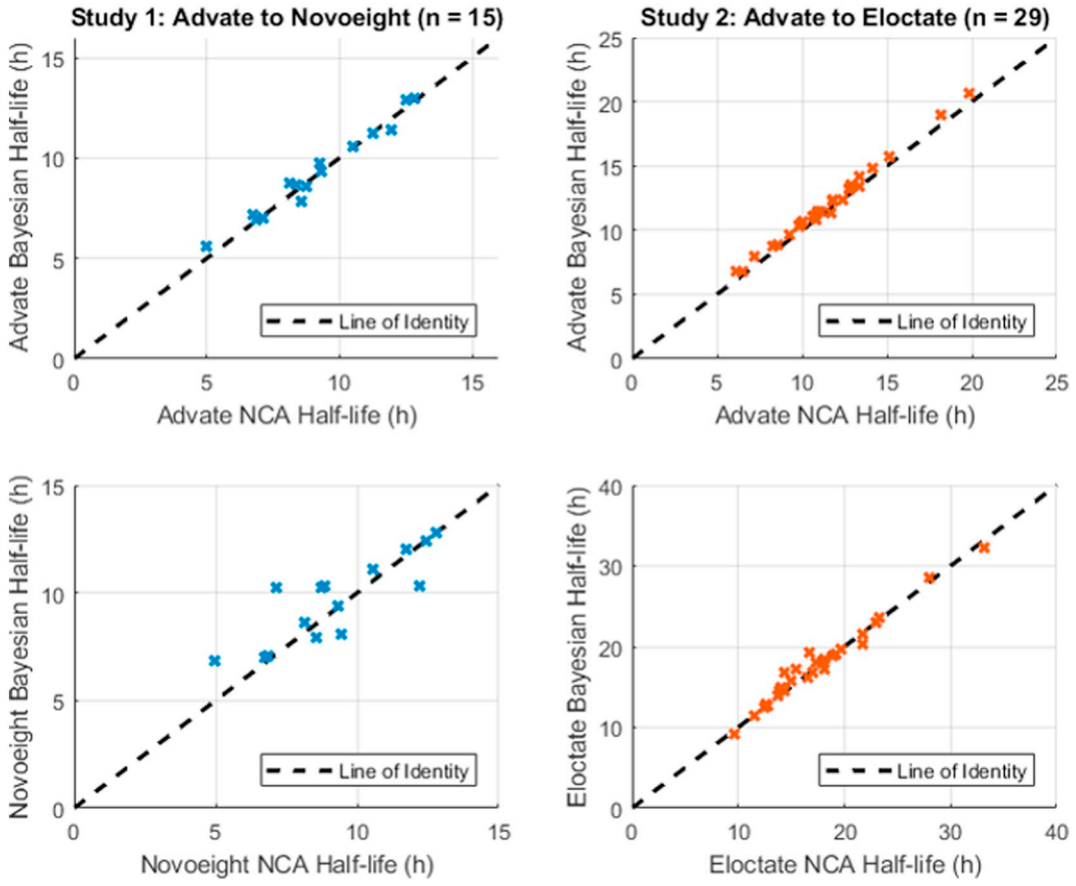

Fig. 2. NCA vs. Bayesian half-life predictions.

Table 2
Mean absolute relative errors of subjects' predicted PK outcomes switching between FVIII products.

PK outcomes (units)	Mean absolute relative error in % [range]								
	Advate to Novoeight			Novoeight to Advate			Advate to Eloctate		
	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3
Clearance (L/h)	30.3 [1–64]	28.9 [4–58]	19.8 [4–58]	35.7 [5–62]	33.6 [6–60]	16.7 [4–37]	31.5 [1–155]	29.1 [0–129]	27.3 [0–62]
Volume (L)	23.0 [2–47]	17.2 [4–50]	14.1 [1 − 32]	26.8 [10–45]	20.6 [3–38]	13.1 [1–26]	15.2 [1–37]	12.6 [0–29]	11.4 [0–27]
Half-life (h)	22.2 [3–58]	27.6 [0–63]	11.6 [0 − 33]	28.9 [2–93]	33.3 [5–96]	13.1 [0–48]	21.2 [2–68]	18.8 [3–66]	13.6 [0–34]
Time to 0.05 IU/mL (h)	33.5 [0–90]	35.3 [1–91]	13.0 [0–35]	39.9 [1 − 122]	41.5 [0 − 121]	14.9 [0–54]	21.6 [0–61]	19.7 [1–60]	15.2 [1–35]
Time to 0.02 IU/mL (h)	30.1 [1–79]	33.0 [1–83]	12.5 [1–34]	36.5 [2–114]	39.0 [2–114]	14.3 [1–52]	21.4 [1–63]	19.5 [1–62]	14.8 [1–35]
Time to 0.01 IU/mL (h)	28.0 [1–72]	31.5 [1–77]	12.2 [0–34]	34.4 [1–109]	37.4 [2–109]	13.9 [0–51]	21.3 [1–64]	19.3 [2–63]	14.5 [1–35]
Concentration at 24 h (IU/mL)	89.4 [4–290]	82.1 [1–253]	23.1 [0–56]	116.0 [1–455]	109.8 [1–431]	32.1 [0–129]	25.9 [1–82]	24.5 [0–82]	19.7 [1–49]
Concentration at 48 h (IU/mL)	126.8 [0–377]	134.8 [3–380]	30.2 [3–76]	161.7 [4–558]	167.4 [1–544]	43.8 [3 − 212]	46.4 [1–238]	43.3 [2–234]	28.1 [2–68]
Concentration at 72 h (IU/mL)	65.1 [2–143]	78.7 [3–184]	20.8 [0–69]	77.4 [6–163]	89.6 [6–184]	25.2 [0–88]	60.8 [1 − 321]	57.3 [1 − 312]	33.2 [4–66]

Table 3
Regression slope of predicted PK outcomes of each study.

PK outcomes (units)	Slope (95% CI)								
	Advate to Novoeight			Novoeight to Advate			Advate to Eloctate		
	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3
Clearance (L/h)	0	0.09 (0.02, 0.16)	0.81 (0.47, 1.14)	0	0.07 (−0.01, 0.15)	0.86 (0.50, 1.21)	0	0.16 (0.00, 0.32)	0.92 (0.68, 1.17)
Central volume (L)	0	0.08 (−0.25, 0.41)	0.47 (0.04, 0.90)	0	0.32 (0.00, 0.64)	0.68 (0.08, 1.27)	0	0.59 (0.40, 0.77)	0.85 (0.69, 1.02)
Half-life (h)	0	−0.12 (−0.30, 0.06)	0.84 (0.39, 1.28)	0	0.05 (−0.11, 0.22)	0.67 (0.31, 1.03)	0	0.15 (0.02, 0.29)	0.66 (0.51, 0.81)
Time to 0.05 IU/mL (h)	−0.08 (−0.23, 0.06)	−0.06 (−0.26, 0.13)	0.81 (0.42, 1.20)	0.05 (−0.10, 0.20)	0.12 (−0.08, 0.32)	0.73 (0.38, 1.09)	0.07 (0.00, 0.13)	0.18 (0.05, 0.31)	0.66 (0.52, 0.80)
Time to 0.02 IU/mL (h)	−0.07 (−0.17, 0.03)	−0.08 (−0.27, 0.11)	0.82 (0.42, 1.23)	0.03 (−0.08, 0.15)	0.10 (−0.09, 0.29)	0.71 (0.36, 1.07)	0.05 (0.00, 0.10)	0.17 (0.04, 0.30)	0.66 (0.52, 0.80)
Time to 0.01 IU/mL (h)	−0.06 (−0.14, 0.02)	−0.09 (−0.28, 0.10)	0.83 (0.42, 1.25)	0.03 (−0.06, 0.11)	0.09 (−0.09, 0.28)	0.70 (0.35, 1.06)	0.04 (0.00, 0.08)	0.17 (0.04, 0.30)	0.66 (0.52, 0.80)
Concentration at 24 h (IU/mL)	−0.15 (−0.45, 0.15)	−0.05 (−0.27, 0.18)	0.71 (0.35, 1.08)	0.14 (−0.22, 0.50)	0.20 (−0.05, 0.46)	0.80 (0.40, 1.19)	0.27 (0.07, 0.46)	0.26 (0.11, 0.40)	0.72 (0.58, 0.86)
Concentration at 48 h (IU/mL)	−0.12 (−0.31, 0.07)	−0.11 (−0.37, 0.15)	0.71 (0.35, 1.06)	0.06 (−0.18, 0.30)	0.15 (−0.17, 0.47)	0.81 (0.41, 1.22)	0.12 (0.02, 0.21)	0.20 (0.07, 0.33)	0.63 (0.50, 0.76)
Concentration at 72 h (IU/mL)	−0.08 (−0.23, 0.06)	−0.14 (−0.45, 0.17)	0.70 (0.35, 1.06)	0.03 (−0.15, 0.21)	0.12 (−0.26, 0.49)	0.81 (0.40, 1.21)	0.06 (0.01, 0.11)	0.16 (0.04, 0.27)	0.55 (0.43, 0.66)

half-life on the EHL FVIII product. On a population level, EHL products have been shown to have a longer half-life than SHL products, though this finding cannot be confirmed at an individual level. For instance, Young et al. have demonstrated that the individual SHL:EHL half-life ratio ranged from 0.79 to 2.98 concluding that some hemophilia patients exhibit a shorter half-life on an EHL product as compared to a SHL product while others have achieved near three-fold increase in half-life [27].

As there is a high inter-individual variability and low within-subject variability in factor concentrate PK, this suggests that using PK-tailored individualized dosing may be appropriate for optimizing hemophilia treatment [12,14]. The same variability comes into play when considering switching between different concentrates. We have shown that ignoring this variability (our Method 1), and dosing based on average population data is the least efficient approach, resulting in a high degree of imprecision when comparing estimated and measured PK outcomes. This is because there are individual factors that can influence the PK that are not taken into account. The differences in the predicted to observed half-life ranged up to 17 h, confirming that this approach is largely suboptimal for choosing a safe and effective dosing regimen for many individuals at the moment of switching.

The incorporation of covariates into the PopPK model that account for a portion of the BSV may lead to more precise estimated PK of individuals who are not represented by the typical patient in the population. Relevant covariates (such as age, body weight, blood type, and von Willebrand factor) have been shown to influence individual PK estimates and consequently factor concentrate activity levels [13,28–33]. Method 2 takes the covariate space into consideration when predicting individual PK across a switch. Some individuals were still not well represented from using this method, resulting in a mean relative error similar to that of Method 1 in terms of half-life (Table S3). For example, in the Advate to Eloctate study, the predicted half-life of one individual was 16 h lower than observed; this difference would have a substantial clinical impact when deciding on a patient's dosing regimen, and this potential error could be due to some unexplained variability or other contributing factors not included in the PopPK

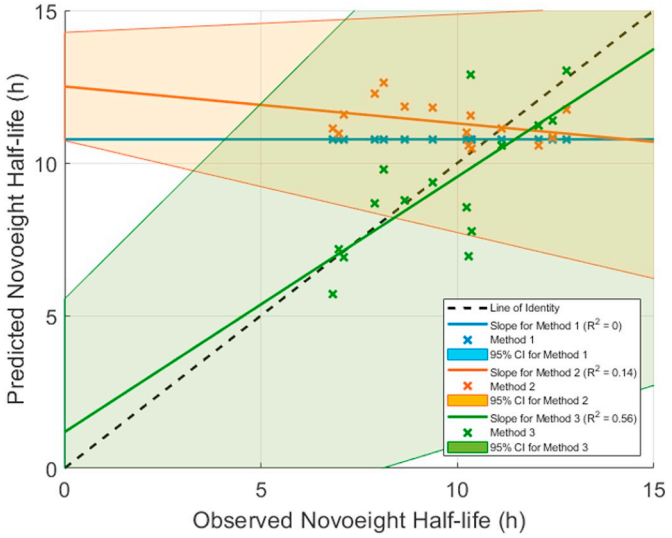

Fig. 3. Advate to Novoeight. Method 3 has the closest regression line compared to the line of identity (dashed line) and tends to better predict individuals with extreme half-life values. The coefficient of determination (R^2) refers to the fit to the line of identity. CI, confidence interval.

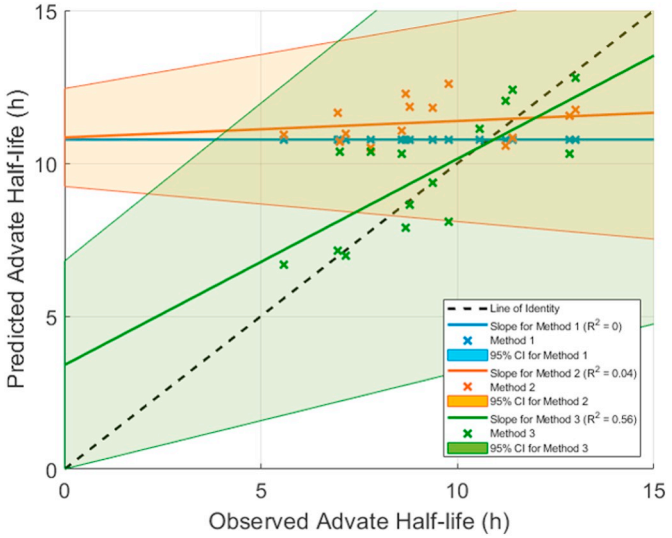

Fig. 4. Novoeight to Advate. Method 3 has the closest regression line compared to the line of identity (dashed line) and tends to better predict individuals with extreme half-life values. The coefficient of determination (R^2) refers to the fit to the line of identity. CI, confidence interval.

model.

Using prior PK knowledge along with the PopPK model of the second product and individual covariates (Method 3) resulted in the lowest mean relative error compared to the prior two methods (Table S3). This method is more often better at predicting half-life in comparison to the other two methods, and particularly so for subjects with extreme values of half-life (Fig. 3-5). This suggests that using prior individual PK information (gathered on the first product) to predict the PK of the second product provides a reasonable starting point for dose determination. The predicted individual half-life can still differ from 0 up to 10 h compared to the estimated Bayesian values, which is significantly less compared to 17 h for method 1 and 16 h for method 2.

4.1. Study limitations

Although using scaled η-values from the pre-switch concentrate in conjunction to the PopPK model of the second product and patient covariates has resulted in the lowest mean relative errors across all PK outcomes, none of the methods explored in this study was able to accurately predict PK outcomes to the extent where the observed vs. predicted regression line was equivalent to the line of identity. Since Method 3, thought to be the most precise, is not precise enough to be used in isolation, gathering blood samples and performing a new PK profile for the patient continues to be the recommended course of action for subjects switching factor concentrates. This method could be implemented into a platform such as WAPPS-Hemo and would provide valuable guidance around switching.

Another limitation is that this study only examined a limited number of hemophilia subjects. As hemophilia A is a rare disease, studies tend to be small and those that we used were no exception. Assessment of a higher number of patients across a wider breadth of factor concentrate products will be necessary to assess if method 3 would be useful in practice. Further, it is also unclear whether the normalized η-distribution of the current product could be assumed to be equivalent to the η-distribution of the future product. The η-values for CL or V1 depend on which covariates are being taken into account for in the PopPK model. While in this study, the PopPK models used for switching incorporated the same covariates (fat-free mass and age) on the same parameters, other PopPK models that do not have the same covariate structure would produce η-values that describe different variabilities.

Further, the methods looked specifically at three factor concentrate products, Advate, Novoeight and Eloctate. The method should be continuously tested for switching between other products when the data becomes available.

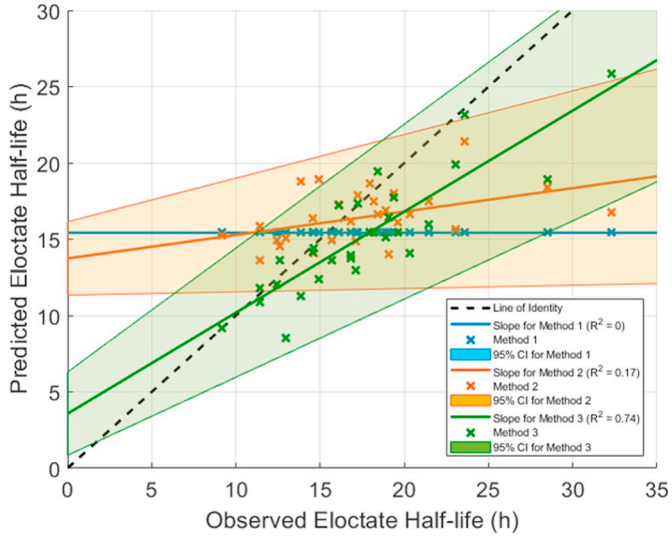

Fig. 5. Advate to Eloctate. Method 3 has the closest regression line compared to the line of identity (dashed line) and tends to better predict individuals with extreme half-life values. The coefficient of determination (R^2) refers to the fit to the line of identity. CI, confidence interval.

5. Conclusion

This novel approach of using prior PK knowledge of individual η-values in order to predict PK of a new concentrate may aid in determining a safe and effective dosing regimen. Using this methodology may result in better outcomes compared to current guidelines as it uses prior individual PK knowledge to develop the regimen as opposed to arbitrarily giving the same dose with a different frequency as suggested in the guidelines [11]. This switching algorithm can be implemented on the WAPPS-Hemo platform to guide clinicians in estimating the individual impact of switching between FVIII concentrates and tailoring

the initial regimen on the new concentrate while minimizing the time needed for dose optimization.

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Author contributions

JKY performed the study. All authors revised and approved the final and submitted version of the manuscript.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.10.023.

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