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Original Article

POPULATION PHARMACOKINETICS OF CONTINUOUS INFUSION OF FACTOR VIII IN HEMOPHILIA-A PATIENTS UNDERGOING ORTHOPEDIC SURGERY

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ABSTRACT

Objective: to develop a population pharmacokinetic model taking into account blood losses during and after orthopedic surgery in adult hemophilia A patients receiving infusion of coagulation factor VIII, and to evaluate the influence of potential covariates.

Methods: Factor VIII pharmacokinetic parameters were calculated from 24 patients. Among them, 7 were HIV+. The observations were analyzed with the mixed-effects compartment pharmacokinetic package NONMEM and the first-order conditional estimation method. To evaluate the stability and robustness of the final model the bootstrap method was used.

Results: During the model-building process, central volume of distribution (V_1) was related to body weight (P = 0.0263) and viral status (P = 0.0078). Moreover, the peripheral volume of distribution was related to body weight (P=0.0362). In the final model, only the viral status was significant for V_1 when compared with the base model. Posterior predictive checks and robustness analysis showed that the model adequately described the pharmacokinetic parameters. The HIV covariate accounted for 29.8% of the unexplained variation across patients for V_1. V_1 increased by 33.3% in HIV+ patients compared to HIV- patients.

Conclusion: A population pharmacokinetic model taking into account blood losses during and after orthopedic surgery was developed. The 33.3% increase in V_1 observed in HIV+ patients explained the need for higher doses in these patients.

Keywords: Factor VIII, Population pharmacokinetics, Hemophilia A, Orthopedic surgery.

INTRODUCTION

Hemophilia (A and B) is a recessively inherited bleeding disorder in which the blood does not clot normally. It is caused by a reduction in the amount or activity of factor VIII (FVIII-C; antihemophilic globulin), cofactor for factor IX in the activation of factor X in the coagulation cascade. The consequence is the formation of fibrin deficient clots which makes coagulation much more prolonged, and the clot more unstable. Hemophilia A is the most common form. In humans, factor VIII is encoded by the *F8* gene [1,2].

Treatment of hemorrhage and prophylaxis against bleeding following surgery is based on the infusion of factor VIII. A guidance for the management of hemophilia A patients undergoing surgical procedures has been published [3]. Both frequent bolus injections, intermittent or continuous infusions have been used to keep adequate factor VIII levels [4]. Several studies have demonstrated that continuous infusions provide improved coagulation factor cover [5-9]. Moreover, this mode of administration may be a further means of reducing the consumption of factor VIII. The short half-life of factor VIII is the main obstacle in maintaining adequate blood levels. The use of pharmacokinetics is a valuable tool to achieve the optimal treatment for an individual patient [4,10]. Either non-compartmental or compartmental (one- or two-compartment models) approach has been used to estimate factor VIII pharmacokinetic parameters [1,11-30]. In all of these studies, an important inter individual variability in pharmacokinetic parameters has been reported. The influence of age, body weight and plasma concentration of von Willebrand factor was investigated to explain this variability. A nomogram based on the factor VIII concentration measured at 10 h after preoperative loading dose has also been published to individualize factor VIII dosing requirements [31]. Bayesian estimates of the pharmacokinetic parameters have been reported [30-35]. In this study, a population pharmacokinetic model taking into account blood losses during and after orthopedic surgery was developed in adult patients with hemophilia A receiving a plasma-derived or recombinant factor VIII concentrate. The purpose was i) to determine accurate population pharmacokinetic parameters by using a two-compartmental open model, and ii) to accurately estimate both inter- and residual variability in pharmacokinetic parameters.

MATERIALS AND METHODS

Patients

The retrospective study was conducted in collaboration with the Regional Center of Hemophilia, Lyon, France. The study proceeded within the framework of the clinical practice in accordance with institutional guidelines.

Thirty Caucasian male hemophilia patients undergoing total knee prothesis were included. Mostly severe hemophilia patients over 18 years old were included, only two patients had moderate hemophilia. Nine patients (30%) were HIV+. Their average CD4 cell count was 496 ± 202 cells/mm^{3}and all of them had severe hemophilia. No patient had anti factor VIII antibodies detected and platelet counts were higher than 100x10^9 /L. Patients were from 25 to 61 years old and their body weight ranged from 49 to 95 kg. Factor VIII baseline concentration ranged from 0.005to 0.09 IU/mL (mean ± SD, 0.019 ± 0.024 IU/mL). The duration of the surgery was from 60 to 240 minutes.

Patients were treated with a plasma-derived (factane) or recombinant factor VIII concentrate (Advate®, Helivate®, ReFacto® or Kogenate®). Just before surgery (time 0), each patient received a loading dose of 25 to 103 IU/kg factor VIII, depending on the patient, administered by intravenous infusion over a 10-minute period followed by continuous infusions for at least one week. The total dose administered to the patients ranged from 314 to 962 IU/kg.

Sample collection and analytical method

Blood samples were collected in citrate-coated polypropylene tubes immediately before factor VIII injection and at repeated intervals during the infusion (T1, T6, T24, T48, T72, T96, T120, T126, T143 and T198 hours). The number of blood samples per patient ranged from 7 to 10.

Factor VIII concentrations were measured using an optic detection of clotting. The assay was performed on a MDA II automate (Bio Merieux, France). The quantification limit was 0.5% (0.005 IU/mL). Precision was lower than 4% for factor VIII concentrations from 0.027 to 1.18 IU/mL.

Population pharmacokinetic analysis

Factor VIII concentration versus time data were modeled using non-linear mixed-effects modeling in NONMEM 7 (Globomax LLC, Hanover, Md, USA) [36]. Estimation of typical population pharmacokinetic parameters and random inter-individual variability (IIV) associated with observed and predicted concentrations were done using a first-order conditional estimation method with ε-η interaction (FOCE INTER) [36]. Model discrimination was based i) on graphical assessment of goodness-of-fit plots [i. e. measured concentrations (DV) versus population (PRED) and individual predictions (IPRED), weighted residuals (WRES)versus PRED, and WRES versus time], and ii) on the basis of changes in –2 log-likelihood (OF). The difference in OFs between two hierarchical models was used as a likelihood ratio test statistic. This was approximately distributed as $\chi 2$ with the number of degrees of freedom equal to the difference in the number of parameters estimated between the two hierarchical models. Testing was performed at α level of 0.05. For nested models that differed by one parameter, a difference in OF of more than 3.84 favoured the model with more parameters.

A two-compartmental model fitted data better than a one-compartmental pharmacokinetic model. This model was parameterized in terms of central volume of distribution (V_1), clearance (CL), peripheral volume of distribution (V_2) and inter-compartmental clearance (Q).

Two additional parameters, α and β, were added to the structural model to take into account blood losses during and after surgery, respectively. The following equations were used:

$$V_1 = \begin{cases} V_0 + \alpha \dfrac{(Vols - PCHI)}{Vols} \rightarrow \textit{during surgery} \\ V_0 + \beta \dfrac{(Vols - POST)}{Vols} \rightarrow \textit{after surgery} \end{cases}$$

where V_0 is the baseline volume of distribution, Vols is the total blood volume estimated from weight and height [37], PCHI corresponds to blood loss during the surgery, and POST corresponds to the blood loss after the surgery. Blood losses were recorded manually in drains during and after surgery. IIV in pharmacokinetic parameters was assessed according to an exponential error model. The P_j parameter of the jth subject was described by the relationship:

$P_j = P_{mean} \times \exp(\eta_P)$

Where, P_j is the pharmacokinetic parameter of subject j, P_{mean} the population pharmacokinetic parameter, and η_P a Gaussian random variable with mean zero and variance of $\omega^2\eta_P$. The residual variability was estimated using a proportional error model. Importantly, the standard errors (SE) of these estimates were also obtained, providing a measure of goodness of fit for each parameter.

The following covariates HIV status, age, body surface area, weight and height were available for inclusion in the final model. The covariate analysis was done by a forward inclusion procedure followed by a backward deletion step. Bothlinear functions, power models, and allometric scaling were tested (covariates being centred or not around the mean values). The effect of each covariate was assessed by the likelihood ratio test.

Individual parameters were calculated as empirical Bayes estimates using the POSTHOC option in NONMEM. The terminal half-life was calculated from the individual primary pharmacokinetic parameters.

Performance of the model

The model's performance was assessed by examining the prediction error (PE). PE was defined as [(DV-IPRED or PRED)/IPRED or PRED] x 100%. Both MDPE (median of all PEs) and MDAPE (median of all absolute PEs) were calculated.

Using the final model, the visual predictive checks (VPCs) were carried out by simulating 1000 virtual data sets to assess the performance of the model.

This analysis was performed using PsN [38] and Xpose [39]. The 5th, 50th (population median response) and 95th percentile concentrations were plotted against time and the factor VIII concentrations were superimposed.

Validation of the final model

The bootstrap resampling procedure was used for evaluating the stability and robustness of the final model using PsN [40]. The bootstrap resampling was repeated 1000 times to evaluate whether an appreciable discrepancy existed between the parameter values estimated from the original data and the estimated bootstrap mean values. Final population parameters were compared with those obtained from the 1000 bootstrap analyses.

RESULTS

Out of 30 patients enrolled in the study, six were excluded. Four of them received packed red blood cells on 2 to 4 separate occasions over the 72 hours after surgery and two others were excluded for lacking information regarding blood losses. Thus, the pharmacokinetic model development data set consisted of 24 patients and 205 factor VIII concentrations. Among them, 7 patients (29.2%) were HIV+.

Table 1: It shows population pharmacokinetic parameters

	Population parameters before covariate inclusion		**Population parameters after covariate inclusion**	
	Mean (% RSE)	**IIV, % (% RSE)**	**Mean (% RSE)**	**IIV, % (% RSE)**
$V_1 = \theta_1$ (mL)	2650 (40.2)	55.9 (63.6)	-	-
$V_1 = \theta_1$ x VIH status + θ_7	-	-	θ_1 = 3020 (24.1) θ_7 = –1940 (61.2)	46.8 (76.3)
CL = θ_2 (mL h^{-1})	220 (5.8)	30.8 (38.6)	220 (5.9)	30.7 (38.6)
$V_2 = \theta_3$ (mL)	2471 (29.1)	79.2 (54.5)	2600 (28.1)	69.6 (60.4)
Q = θ_4 (mL h^{-1})	615 (48.7)	NE	616 (34.7)	NE
$\alpha = \theta_5$	901 (74.9)	-	1560 (70.9)	-
$\beta = \theta_6$	1621 (40.8)	-	1740 (32.2)	-
Residual variability (%)	0.15 (7.9)		0.15 (7.7)	

IIV, interindividual variability; RSE, relative standard error; CL, total clearance; V_1,central volume of distribution; V_2, peripheral volume of distribution; Q, inter-compartmental clearance; NE, not estimated, VIH status: negative = 1, positive = 2

It was not possible to estimate population parameter variability on Q. The elimination half-life before covariate inclusionaveraged 13.9 h (coefficient of variation, 28.6%).

Their means (± standard deviation) for age, weight, height and body surface area were 38.7 ± 9.6 years, 72.5 ± 14.7 kg, 176.2 ± 5.53 cm and 1.88 ±0.19 m^2, respectively. The mean duration of surgery was 1.8 h (0.83 to 4 h), and the mean duration of blood losses after the surgery was 48 h (24 to 96 h). Blood losses, during and after the surgery, averaged 295.8 mL (50 to 900 mL) and 1149.6 mL (320 to 3560 mL), respectively.

A two-compartment model with time-varying central volume of distribution (during or after surgery) best described the factor VIII data.

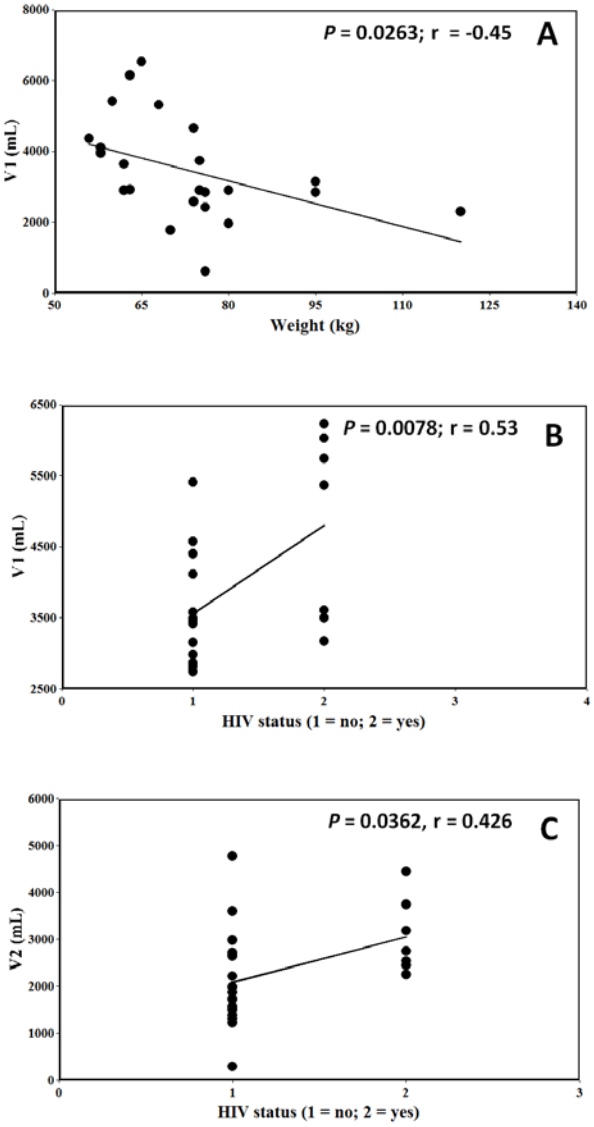

Fig. 1: It shows linear regression analysis between A) central volume of distribution (V_1) and patient body weight; B) central volume of distribution (V_1) and HIV status; C) peripheral volume of distribution (V_2) and HIV status

In forward inclusion, only the viral status was significant for V_1 when compared with the base model. Its inclusion in the model was justified by 10-point improvement of the objective function value.

(•) Observed concentrations (DV)

The elimination half-life after covariate inclusion averaged 14.5 h (coefficient of variation, 21.5%). The ratios of the between-subject variance predictable from covariate (BSVP = 0.093) to the total population parameter variance obtained without covariate analysis (PPV = 0.312) indicate that 29.8% of the overall variability in V_1 is predictable from covariate information.

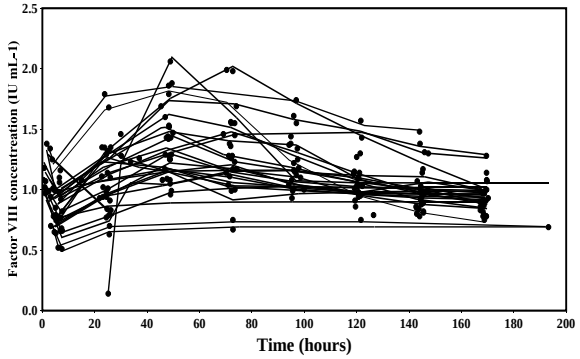

Fig. 2: It shows time evolution profiles of factor VIII in 24 patients undergoing orthopedic surgery. Lines are obtained from individual predicted concentrations connected point by point

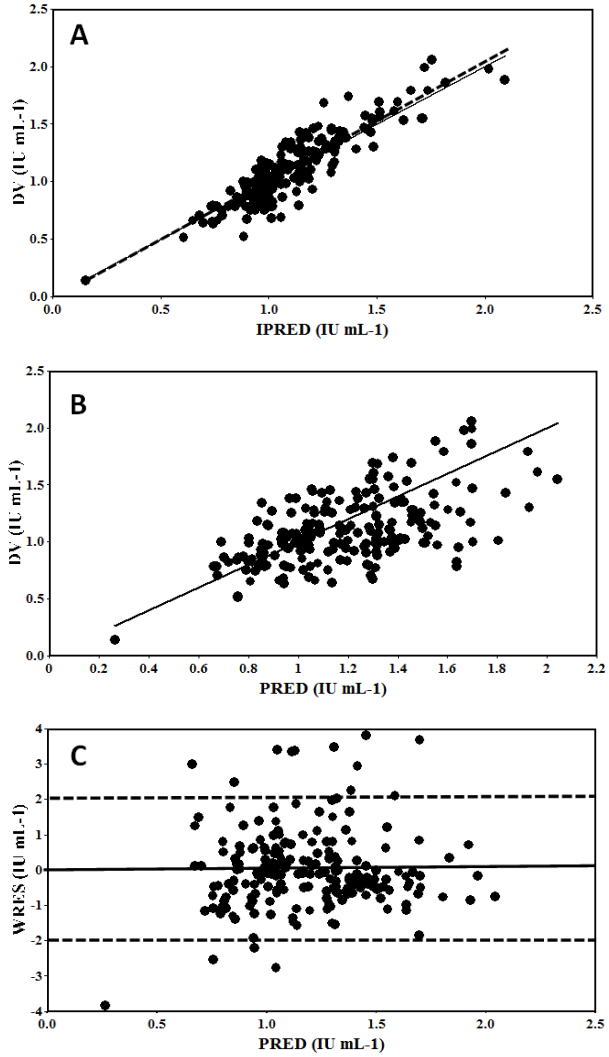

Fig. 3: It shows the goodness-of-fit plots for the final model. (A) Observed concentrations (DV) versus individual model predicted concentrations (IPRED); (B) DVversus model predicted concentrations (PRED); (C) Weighted residuals (WRES) versus PRED. The solid lines in (A) and (B) represent the line of unity and the dotted line in (A) the linear regression line

The goodness of fit has been evaluated by comparing the regression line estimated on the DV versus IPRED values (slope: 1.07, 95% confidence interval (C. I.): 0.999, 1.1; intercept: –0.07 IU mL^{-1}, 95% C. I.: –0.15, 0.008) to the reference line of slope = 1 and intercept = 0. No significant difference occurred. Most of the weighted residuals lay within 2 units of perfect agreement and were symmetrically distributed around the zero ordinate. By examining the PE values (IPRED *vs* DV), the MDPE was 1.09% (95% confidence interval: –0.96, 3.15) and the MDAPE was 7.6% (95% confidence interval: 6.3, 8.9). The MDPE and MDAPE of the population predictions PRED were 4.4% and 19.8%, respectively. These values were in a typical range for pharmacokinetic models. The plot of PEs versus time shows random distribution around the zero ordinate (data not shown).

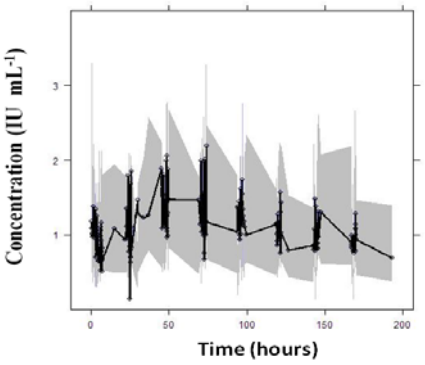

Fig. 4: It shows visual predictive check plot for the studied population. The middle line depicts the model predicted median. The other lines (above and below the median) present the 5th and 95th percentiles

The VPC plot confirms the adequacy of model predictions, showing no apparent deviations between model and data. About 98% of the data fit well within the 5th-95th percentiles band and the data were symmetrically distributed around the median. The final model was fitted repeatedly to 1000 bootstrap-resampled data sets.

DISCUSSION

The treatment of hemophilia with factor VIII is both effective and complex. The factor VIII concentration before the beginning of the perfusion was performed to know basal concentration. Then concentrations were determined during and after the surgery to adapt the rate of perfusion. So, many factor VIII concentrations were available for this retrospective study. Pharmacokinetic data may be fundamental to maximize efficacy and to minimize cost of this treatment. A recent joint report from the World Health Organization (WHO), World Federation of Hemophilia and International Society of Thrombosis and Haemostasis states that the use of coagulation products should be optimized and that pharmacokinetics is fundamental to dosing [41]. Factors affecting pharmacokinetic outcomes include inter- and intra-patient variability, the type of factor VIII formulation administered to the patients and also the analytical method used to quantify the compound.

In previous papers, either a one- [11-13,32] or a two-compartment model [27,28,30,31, 33,34] was used to describe factor VIII pharmacokinetics in human. This study is, to our knowledge, the first report of a population pharmacokinetic study of factor VIII carried out in patients during and after surgery. The two-compartment model taking into account blood losses during and after surgery was the best model adapting to experimental points. We choose to record blood losses manually because this method allows differentiating surgical and post surgical periods. Blood loss being not linear during and after surgery, we cannot use, in our model, the Brecher method which estimates the total losses.

Table 2: It shows bootstrap validation of the estimated population pharmacokinetic parameters in the final model

	Original data	**1000 Bootstrap replicates**	
Parameters	**Mean estimate**	**Median**	**2.5% quantile** **97.5% quantile**
$V_1 = \theta_1$ x VIH status+θ_7	θ_1 = 3020	θ_1 = 3006	1340-4376
	θ_1 = –1940	θ_1 = –1706	–4230-1270
$CL = \theta_2$ (mL h^{-1})	θ_1 = 220	229	195-246
$V_2 = \theta_3$ (mL)	θ_1 = 2600	2212	872-3776
$Q = \theta_4$ (mL h^{-1})	θ_1 = 618	601	343-1072
θ_5	θ_1 = 1560	1281	38.1-3141
θ_6	θ_1 = 1740	1647	709-3362
Inter-individual variability			
ω^2_{V1}	0.219	0.215	0.001-0.72
ω^2_{CL}	0.0942	0.0834	0.035-0.17
ω^2_{V2}	0.484	0.541	0.025-1.25
ω^2_{Q}	NE		
Residual variability, σ^2	0.15	0.15	0.12-0.17

CL, total clearance; V_1,central volume of distribution; V_2, peripheral volume of distribution; Q, inter-compartmental clearance; NE, not estimated, These results indicated the reliability and robustness of the estimated parameters and thus the population pharmacokinetic model was acceptable.

The number of patients (24)may seem not enough for population analysis, considering the clinical complexity of the patients. However, the pharmacokinetic parameters estimated using the bootstrap replicates are close to those obtained from the original data indicating that the model is acceptable. As previously reported, we found marked variation in pharmacokinetic parameters. In our population, the mean CL was 3.3 mL/ h/kg, mean V_{ss} was 66.5 mL/kg and mean $t_{1/2}$ elimination was 14.5 h. Similar pharmacokinetic parameters were reported in the literature [4,12,14-22,28,29,30, 33,34]. In these published studies, significant relationships between body weight, age and total clearance, and between body weight and the volume of distribution have been reported. Recently, Karafoulidou *et al* [33] showed that HIV status was a significant categorical predictor for V_1. In our study, a relationship was found between V_1 and weight (*P* = 0.0263) and between V_2 and weight (P = 0.0362) but they were not retained in the final model. Indeed, in forward inclusion, weight was not significant for both V_1 and V_2 when compared with the base model. As reported by Karafoulidou *et al*., we found that the central volume of distribution increased in HIV+ patients. The HIV covariate accounted for 29.8% of the unexplained variation across patients for V_1. V_1 increased by 33.3% (from 3550 mL to 4732 mL) in HIV+ patients compared to HIV- patients. This increase explained the need for higher doses in these patients. Indeed, the total administered dose increased by 26% in HIV+ patients (796 IU/kg) in regard to the other patients (632 IU/kg). Changes in the body mass / body fat ratio or possible distribution of the drug outside the blood volume due to the disease or endothelial inflammation following highly active antiretroviral therapy has been proposed to explain this increase [33,42]. Patients with haemophilia may also present other

clinical and pathological factor such as hepatitis C or liver cirrhosis. Too much data was missing, because of the retrospective nature of the study, to allow testing of these covariates in the model. Patients of this study received repeated continuous infusion of factor VIII, 88% of concentrations were in the range 0.75-1.5 IU/mL. These concentrations were near to those reported by Hay *et al* [43].

CONCLUSION

For the first time, clinicians could determine individual factor VIII pharmacokinetic parameters in taking into account blood loss. Stable concentrations over time can be of good efficacy and tolerance and decrease the infusion of concentrated red blood cells. This study may reduce the number of nursing procedures, optimize the amount of factor VIII used and thus reduce the cost of surgery.

CONFLICT OF INTERESTS

Declared None

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