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Pharmacokinetic variability of factor VIII concentrates in Chinese pediatric patients with moderate or severe hemophilia A

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ABSTRACT

Importance: The use of factor VIII (FVIII) concentrates under pharmacokinetic (PK) guidance has become the main approach for treatment of hemophilia. However, limited PK research has been conducted in Chinese pediatric patients.

Objective: To investigate the PK parameters of various FVIII concentrates in Chinese pediatric patients.

Methods: Seventy-nine patients were enrolled (28 treated with Kogenate FS®, 23 treated with Advate®, and 28 treated with GreenMono™). All enrolled patients participated in single-dose PK analysis after at least a 3-day washout period. Blood samples were collected predose, as well as at 1 h, 9 h, 24 h, and 48 h after infusion; FVIII levels were measured using a one-stage clotting assay. von Willebrand Factor Antigen (VWF:Ag) levels and blood types were also determined. PK parameters were evaluated by WAPPS-Hemo.

Results: Mean values of terminal elimination half-life time ($t_{1/2}$) for the Kogenate FS®, Advate®, and GreenMono™ FVIII groups were 12.24 h, 10.18 h, and 9.62 h; median clearance values were 4.16, 6.23, and 5.11 $mL \cdot kg^{-1} \cdot h^{-1}$; and median *in vivo* recovery values were 1.97, 1.55, and 1.61 IU/dL per IU/kg. Longer $t_{1/2}$, higher *in vivo* recovery, and lower clearance were observed in patients with higher VWF:Ag level who were treated with recombinant concentrates.

Interpretation: Chinese pediatric patients with hemophilia had FVIII PK characteristics similar to those previously observed in non-Chinese children, including large variation among individuals. VWF:Ag level and FVIII brand were associated with differences in FVIII PK. Thus, PK-guided dosing should be used to optimize individualized therapy in Chinese children.

KEYWORDS
Hemophilia A, Pharmacokinetics, Pediatric patients, FVIII concentrates

INTRODUCTION

Hemophilia A is an X-linked, inherited bleeding disorder caused by a deficiency in coagulation factor VIII (FVIII), which affects approximately 1 in 5000 live male births. As recommended by the International Society of Thrombosis

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and Hemostasis, regular replacement therapy (prophylaxis) has become the main treatment worldwide.[1] In 1965, Ahlberg noticed that patients with moderate and mild hemophilia A had fewer joint bleeds, compared with patients with severe hemophilia A; thus, he established the target trough level of 1 IU/dL as the initial goal of prophylaxis.[2] Compared with on-demand therapy, prophylaxis has been shown to reduce both clinical and subclinical bleeding, which are presumed to cause joint issues like pain and disfunction.[3-5] Based on the current understanding of factor concentrates, the Malmo protocol suggests the infusion of 20–40 IU/kg body weight at a rate of at least three times per week, and up to every other day.[6] However, this therapeutic regimen is resource-intensive and places a heavy venipuncture burden on patients, which may reduce treatment adherence (especially among pediatric patients).[7] Thus, some comparable treatments with less frequent infusion and lower doses have been adopted as alternatives to the standard prophylaxis regimen.[8-11] By using a combination of pharmacokinetic (PK) tests, the therapy can be adapted, such that it is more precise and individualized.

Dose calculation for most prophylactic regimens has been performed with the assumption that all patients exhibit similar PK characteristics. However, there is great inter-individual variability in various PK parameters,[12] such as half-life time ($t_{1/2}$), clearance (CL), and *in vivo* recovery (IVR). Bjorkman et al[13] performed PK analyses with a large number of patients, which revealed considerable differences among individuals. In their study, the $t_{1/2}$ of FVIII varied from 6 h to 25 h in patients with hemophilia A. Similar findings were more recently reported for a variety of concentrates; substantial variability was encountered regarding IVR and CL.[14] Furthermore, determinants of inter-individual variability (e.g., body mass composition) were also identified;[15] these findings indicated that dosing based on body weight may lead to under or over-dosing because of clearance variability among patients.[16] Thus, the use of individual PK parameters to optimize FVIII replacement therapy was adopted; this approach has been shown to improve important patient outcomes.[17] Knowledge of their own PK has helped patients to achieve better quality of life by either reducing unnecessary administration of FVIII or adding appropriate doses of FVIII, where necessary, to maintain the FVIII concentration above the target level.[18] Furthermore, patients may be able to choose a highly cost-effective product from among the range of available concentrates. With the aid of individual PK profiles, patients with different bleeding phenotypes can precisely determine their target FVIII levels, thus reducing bleeding during routine prophylaxis.

PK-guided prophylaxis is increasingly used and several affordable FVIII concentrates are available in China; however, there is very limited PK information concerning these FVIII concentrates in Chinese pediatric patients. A prior PK study conducted by Chen et al[19] involved performance of PK tests in 36 boys with hemophilia A, using different FVIII concentrates; it produced similar results of PK parameters. Based on the findings of the study by Chen et al, we performed this study involving 79 patients, grouped according to the FVIII concentrate brand used by each patient, instead of simply evaluating whether the patients used plasma-derived or recombinant FVIII concentrates. The aim of our study was to investigate PK variability in Chinese pediatric patients with hemophilia A by analysis of PK profiles from patients who were treated with different FVIII concentrates.

METHODS

Ethical approval

The study was approved by the Ethics Committee of Beijing Children's Hospital (2018-60). Written informed consent was obtained from each enrolled patient or their legally authorized guardian(s).

Patients

The patients were enrolled from January 2018 to February 2019 at Beijing Children's Hospital. Inclusion criteria were age <18 years; moderate or severe (FVIII activity < 2 IU/dL) hemophilia A; receipt of prophylactic treatment with a plasma-derived or recombinant FVIII concentrate for more than 50 exposure days; and current use of Kogenate FS®, Advate®, or GreenMono™ for treatment. Exclusion criteria were the presence of a current FVIII inhibitor (anti-FVIII antibody titer > 0.6 Bethesda units), fever, active bleeding, or a concurrent coagulation disorder.

Blood samples

After a washout period of at least 72 hours, each patient received a daily-use FVIII infusion of 40–50 IU/kg. Peripheral venous blood samples were drawn using vacutainer tubes (3.2% trisodium citrate, 2 mL). In accordance with the method of Blanchette et al,[20] a reduced blood sampling strategy was used (predose, as well as at 1 h, 9 h, 24 h, and 48 h after concentrate infusion). Blood samples were immediately centrifuged at 2500 g for 15 min at 20–25°C. Plasma was divided into three EP tubes (600 μL per tube) and stored in a −80°C freezer for further analysis. For each patient, FVIII level, FVIII inhibitor, blood type (ABO), and von Willebrand factor antigen (VWF:Ag) level were tested.

Laboratory assay

The one-stage-based activated partial thromboplastin time assay (Instrumentation Laboratory, Bedford, MA, USA) was used to measure FVIII activity in a multi-dilution mode, with FVIII-deficient plasma. The Nijmegen modification of the Bethesda Assay was used for the determination of FVIII inhibitors. An ACL TOP-

700 analyzer was used to perform all measurements (Instrumentation Laboratory, Bedford, MA, USA). A latex particle-enhanced immunoturbidimetric assay with HemosIL von Willebrand factor antigen kit (Instrumentation Laboratory, Bedford, MA, USA) was utilized to determine VWF:Ag levels.

PK evaluation

Individual PK profiles were estimated using WAPPS-Hemo,[21] a PK-guided dosing tool based on Bayesian methods and a population PK model that has been specifically designed for patients with hemophilia. In this study, the following information was entered into WAPPS: patient ID, height, body weight, date of birth, blood type, VWF:Ag level, endogenous baseline level, administered dose, FVIII level of all samples, FVIII measurement assay, and FVIII concentrate brand. Estimates for CL are not included in the standard WAPPS-Hemo report and were generously provided by Dr. Alfonso Iorio upon request; details regarding the population PK model used for estimation of individual profiles (i.e., the generic factor VIII described by McEneny-King et al[21]) were also provided by Dr. Alfonso Iorio. In brief, the model was derived by using 174 PK studies on recombinant concentrates and 49 PK studies on plasma-derived concentrates, all involving patients with severe hemophilia A. Baseline demographics were as follows: mean ages were 21 years for patients receiving recombinant concentrates and 21 years for patients receiving plasma-derived concentrates; the proportions of patients < 18 years of age were 14.3% (recombinant) and 12.2% (plasma-derived). Median bodyweights (min–max) were 68.1 kg (10.6–132.5 kg) for patients receiving recombinant concentrates and 58.2 kg (18.5–93.0 kg) for patients receiving plasma-derived concentrates. Median body mass index (min–max) values were 23.1 kg/m^2 (11.7–38.6 kg/m^2) for patients receiving recombinant concentrates and 20.9 kg/m^2 (14.0–30.5 kg/m^2) for patients receiving plasma-derived concentrates. Median numbers of measurements taken (min–max) were nine (4–11) for patients receiving recombinant concentrates and 10 (4–12) for patients receiving plasma-derived concentrates. FVIII as measured with a one-stage clotting test. The structural model constituted a two-compartment model, with a covariate term for the specific concentrate (Kogenate FS®, Advate®, or plasma-derived) on CL and Volume 1; for age on CL; and for fat-free mass on CL, Volume 1, and Volume 2. A term for between-participant variability was used on CL and Volume 1; no term was used for within-participant variability, and the residual unexplained variability term was structured as a combined error. The median relative error for $t_{1/2}$ estimates for the models was ≤ 1.5%, while the corresponding upper fifth percentile of the relative error was < 4.0%. IVR was calculated as follows: IVR (IU/dL per IU/kg) = (C_{max} − $FVIII_{preinfusion}$ [IU/dL])/ ($FVIII_{administered}$ [IU/dL]/bodyweight [kg]).[19]

Statistical analysis

The statistical analysis was performed by Graphpad Prism 8.0. Normally distributed data were reported as mean ± standard deviation and non-normally distributed data were reported as median (lower quartile, upper quartile). One way ANOVA and *t*-tests were employed to evaluate the difference among normally distributed data, and for non-normal data, Kruskal–Wallis and Mann–Whitney test were used to evaluate the difference. Categorical variables were compared by the Chi-squared test to detect statistical differences. Pearson (normal distributed data) or Spearman (non-normal distributed data) correlation coefficients were used to analyze the potential relations between PK parameters and the characteristics of patients. *P* values < 0.05 were considered statistically significant.

RESULTS

Patient characteristics

This study included 79 children with hemophilia A, aged 2–13 years; five patients exhibited moderate hemophilia A and 74 patients exhibited severe hemophilia A. Table 1 shows the patient characteristics according to treatment products (28 patients were treated with Kogenate FS® [age range, 2–15 years], 23 patients were treated with Advate® [age range, 2–10 years], and 28 patients were treated with GreenMono™ [age range, 4–9 years]). Age, bodyweight, body mass index, and blood-type distribution did not significantly differ among the three groups.

TABLE 1 Baseline characteristics of patients with hemophilia A in the three concentrate brand groups

Variables	Advate® (*n* = 23)	Kogenate FS® (*n* = 28)	GreenMono™ (*n* = 28)	Statistics	*P*
Age* (year)	6.25 (4.25, 8.33)	6.18 (4.52, 7.75)	6.50 (5.22, 8.48)	1.153#	0.47
Bodyweight* (kg)	22.0 (20.0, 28.0)	22.5 (18.0, 30.3)	23.5 (20.1, 28.8)	0.743#	0.80
BMI* (kg/m^2)	16.53 (14.42, 18.90)	16.09 (14.80, 17.47)	15.55 (14.51, 17.36)	0.434#	0.81
VWF:Ag* (IU/dL)	84.0 (74.2, 105.8)	83.9 (69.4, 107.8)	92.6 (80.0, 106.6)	1.955#	0.38
HA type (moderate/severe)	1/22	2/26	2/26	0.21†	0.90†
Blood type					
O type (*n*)	11	17	12	1.89†	0.39
Non-O type (*n*)	12	11	16		

*median (lower quartile, upper quartile); # Kruskal–Wallis test; † Chi–squared test. BMI, body mass index; HA, hemophilia A.

PK parameters of FVIII concentrates

The relationship between post-infusion FVIII levels and time after dosing is shown in Figure 1. Among all patients, the respective median values of $t_{1/2}$, IVR, and CL were 10.25 h, 1.66 IU/kg per IU/dL, and 4.89 $mL \cdot kg^{-1} \cdot h^{-1}$. Patients in the Kogenate FS® group had a longer mean $t_{1/2}$, compared with patients in the Advate® (12.24 vs 10.18 h, $P = 0.01$) and GreenMono™ (12.24 vs 9.62 h, $P < 0.01$) groups. Patients in the Kogenate FS® group had a higher median IVR, compared with patients in the Advate® (1.97 vs 1.55 IU/dL per IU/kg, $P < 0.01$) and GreenMono™ (1.97 vs 1.61 IU/dL per IU/kg, $P < 0.01$) groups. Lower CL was observed among patients in the Kogenate FS® group, compared with patients in the Advate® (4.16 vs 6.23 $mL \cdot kg^{-1} \cdot h^{-1}$, $P < 0.01$) and GreenMono™ (4.16 vs 5.11 $mL \cdot kg^{-1} \cdot h^{-1}$; $P = 0.02$) groups. There were no statistically significant differences between the GreenMono™ and Advate® groups in terms of $t_{1/2}$ (10.18 vs 9.62 h, $P = 0.71$), IVR (1.55 vs 1.61 IU/dL per IU/kg, $P > 0.99$), or CL (6.23 vs 5.11 $mL \cdot kg^{-1} \cdot h^{-1}$, $P > 0.99$) (Table 2, Figure 2).

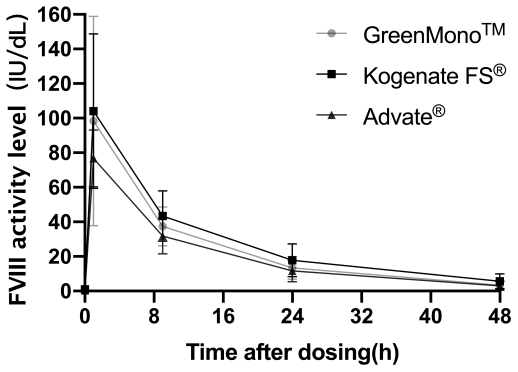

FIGURE 1 Plasma FVIII concentration (mean ± standard deviation) vs time curve of three FVIII concentrates after single infusion of 40–50 IU/kg FVIII. One-stage assay was used to determine FVIII activity.

Factors influencing PK parameters

Linear regression was initially conducted to identify factors correlated with PK parameters. $t_{1/2}$ was correlated with VWF:Ag ($P < 0.01$) and FVIII concentrate ($P < 0.01$); CL was correlated with VWF:Ag ($P < 0.01$), FVIII concentrate ($P < 0.01$), and age ($P = 0.04$). IVR was correlated with VWF:Ag ($P < 0.01$), body mass index ($P = 0.01$), and FVIII concentrate ($P < 0.01$).

The correlation between VWF:Ag level and individual PK parameters was evaluated further in each of the three FVIII concentrates. $t_{1/2}$ increased with increasing VWF:Ag level in all groups (Kogenate FS®: $r = 0.57$, $P < 0.01$; Advate®: $r = 0.78$, $P < 0.01$; GreenMono™: $r = 0.73$, $P < 0.01$). CL decreased with increasing VWF:Ag level in all groups (Kogenate FS®: $r = -0.53$, $P < 0.01$; Advate®: $r = -0.78$, $P < 0.01$; GreenMono™: $r = -0.54$, $P < 0.01$). IVR increased with increasing VWF:Ag level in two groups (Kogenate FS®: $r = 0.44$, $P = 0.02$; Advate®: $r = 0.78$, $P < 0.01$; Figure 3). The relationships between blood type and these PK parameters were also analyzed. $t_{1/2}$ tended to be shorter, whereas CL tended to be higher in patients with blood type O, compared with patients who exhibited non-O blood type, in all FVIII groups in our study; however, no statistical difference was found between IVR and blood type in our study (all $P > 0.05$; Table 3). Furthermore, CL decreased with age in the Kogenate FS® ($r = -0.41$, $P = 0.03$) and GreenMono™ ($r = -0.40$, $P = 0.04$) groups; IVR increased with age in the GreenMono™ group ($r = 0.38$, $P = 0.04$).

DISCUSSION

Because of the existence of inter-individual variability, individual PK testing has been a useful tool to guide individualized prophylaxis for patients with hemophilia. We have shown that the inter-individual differences of PK parameters in the Chinese pediatric population are similar to those observed in non-Chinese children. For each PK parameter, the maximum and minimum values differed greatly within the patient population. Furthermore, within FVIII concentrate groups, variability among patients was obvious. The respective ranges of $t_{1/2}$ in Kogenate FS®, Advate®, and GreenMono™ groups were 8.25–17.75 h, 6.25–16.00 h, and 5.75–16.00 h, fully overlapping with the ranges observed in non-Chinese populations. In each group, the longest $t_{1/2}$ was more than twofold greater, compared with the shortest $t_{1/2}$; comparable findings were also made concerning IVR and CL, which could lead to great discrepancies in FVIII dosing in traditional dosing regimens.

Inter-individual differences have been widely discussed in the literature.[14,16,22,23] PK studies of non-Chinese populations have also been conducted.[24,25] A PK study of Kogenate FS® in Canada revealed that the mean $t_{1/2}$, CL, and

TABLE 2 Pharmacokinetic parameters of patients with hemophilia A in the three concentrate brand groups

PK parameters	Total ($n = 79$)	Advate® ($n = 23$)	Kogenate FS® ($n = 28$)	GreenMono™ ($n = 28$)	Statistics	*P*
$t_{1/2}$ (h)	10.25 (8.75,12.75)	10.18 ± 2.55	12.24 ± 2.60	9.62 ± 2.44	8.24*	< 0.01
IVR (IU/kg per IU/dL)	1.66 (1.53, 1.98)	1.55 (1.48, 1.74)	1.97 (1.66, 2.23)	1.61 (1.45, 1.85)	3.54#	< 0.01
CL ($mL \cdot kg^{-1} \cdot h^{-1}$)	4.89 (3.93, 6.34)	6.23 (4.55, 6.86)	4.16 (2.93, 5.72)	5.11 (4.39, 6.67)	2.77#	< 0.01

*t-test; #Kruskal–Wallis test. $t_{1/2}$ for each of the three divided groups is shown as mean ± standard deviation, $t_{1/2}$ of all patients is shown as median (lower quartile, upper quartile); IVR and CL are both shown as median (lower quartile, upper quartile). PK, pharmacokinetic; $t_{1/2}$, half-life time; IVR, *in vivo* recovery; CL, clearance.

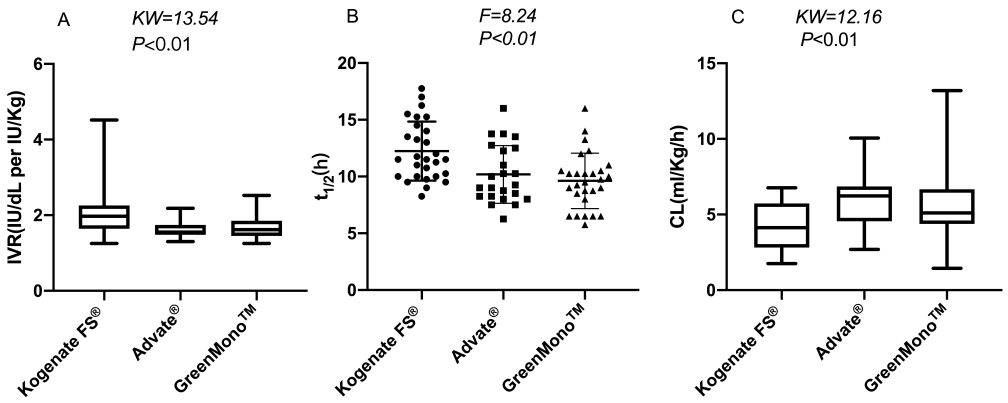

FIGURE 2 Comparison of IVR, $t_{1/2}$, and CL among the three concentrate brand groups. IVR and CL data are shown as median (range), while $t_{1/2}$ data are shown as mean ± standard deviation. $t_{1/2}$, half-life time; IVR, *in vivo* recovery; CL, clearance.

IVR were 10.7 h, 4.1 mL·kg^{-1}·h^{-1}, and 1.87 U/mL per IU/kg, respectively.[24] Our study revealed similar CL and IVR results, along with longer $t_{1/2}$ (12.24 h). When adjusted for their higher median age, Chinese pediatric patients seemed to have a longer $t_{1/2}$ while using Kogenate FS®. This may be due to ethnic differences, as well as variability in patient characteristics (e.g., age). Another study was conducted in Spain, involving 13 pediatric patients aged 7–15 years who were using Advate®; in that study, the reported mean $t_{1/2}$ and CL were 10.2 h and 4.3 mL·kg^{-1}·h^{-1}, respectively.[25] The $t_{1/2}$ was nearly identical to ours (10.18 h), whereas the CL was lower than in the present study; this discrepancy may be related to inter-individual variability, age difference, and ethnicity-related differences.[25,26] Further research is needed to compare PK among populations.

Kogenate FS®, Advate®, and GreenMono™ are three widely used concentrates in our center. Both Kogenate FS® and Advate® are full-length recombinant FVIII concentrates, while GreenMono™ is a plasma-derived FVIII product. Considerable variability was found among the FVIII concentrate groups. In the Advate® and GreenMono™ groups, the three PK parameters ($t_{1/2}$, IVR, and CL) showed no significant differences. Although Morfini et al[27] found no significant difference in $t_{1/2}$ between plasma-derived and recombinant FVIII concentrates, a statistical difference in $t_{1/2}$ was observed between the Kogenate FS® and GreenMono™ groups in our study. This difference may be attributable to the population difference between groups, as well as the difference between plasma-derived and recombinant FVIII products in our study. Morfini et al[27] concluded that complete bioequivalence was not achieved in their head-to-head study because a higher IVR was observed for recombinant FVIII concentrates, presumably because of activated molecules in the formulation of recombinant FVIII concentrates. Another study compared Advate® with a recombinant VIII single-chain product; latter had a more favorable PK profile, which permitted a longer dosing interval.[28] This may be partly related to different modifications in molecular structure. Some previous studies also demonstrated variability in PK parameters (e.g., $t_{1/2}$ and CL) among FVIII concentrates.[29-31] In our study, the Kogenate FS® group exhibited longer $t_{1/2}$, higher IVR, and lower CL, compared with the Advate® and GreenMono™ group; in contrast, PK parameters were very similar between the Advate® and GreenMono™ groups. Because improved glycosylation has been detected in patients using Kogenate FS® and extra VWF:Ag was only observed in patients using GreenMono™, differences in PK parameters may be related to distinct manufacturing technologies and other factors (e.g., extra VWF:Ag in GreenMono™), separate from inter-individual variability.[32]

Some factors that influence PK parameters were also analyzed in our study. Key characteristics that influenced $t_{1/2}$ and CL were patient age and the VWF:Ag level in plasma. In the Kogenate FS® and GreenMono™ groups, CL decreased with increasing age; IVR increased with age in the GreenMono™ group. According to Björkman et al and Kepa et al, $t_{1/2}$ is associated with age.[16,33] In studies by Björkman et al and Chen et al, respective enhancements of 0.4 h and 0.6 h per year in $t_{1/2}$ were observed in children with severe hemophilia A.[19,34] However, a study of patients using Advate®, in which patients were divided into three groups according to their age (<6 years, 6–12 years, and >12 years) revealed that the respective mean $t_{1/2}$ values of the three groups were 8.78 h, 9.44 h, and 8.52 h.[28] Thus, no obvious correlation between age and $t_{1/2}$ was identified. Furthermore, no significant correlation between $t_{1/2}$ and age was found in our study. This might be related to the narrow age distribution of our patients and considerable individual PK variability among children in the study.

VWF acts as a chaperone for FVIII and is known to protect FVIII from protease degradation.[35] In our study, PK parameters were affected by VWF:Ag levels in all three groups. Patients with a higher level of VWF:Ag tended to have longer $t_{1/2}$, higher IVR, and lower CL. A study conducted in Vienna reached a similar conclusion.[33]

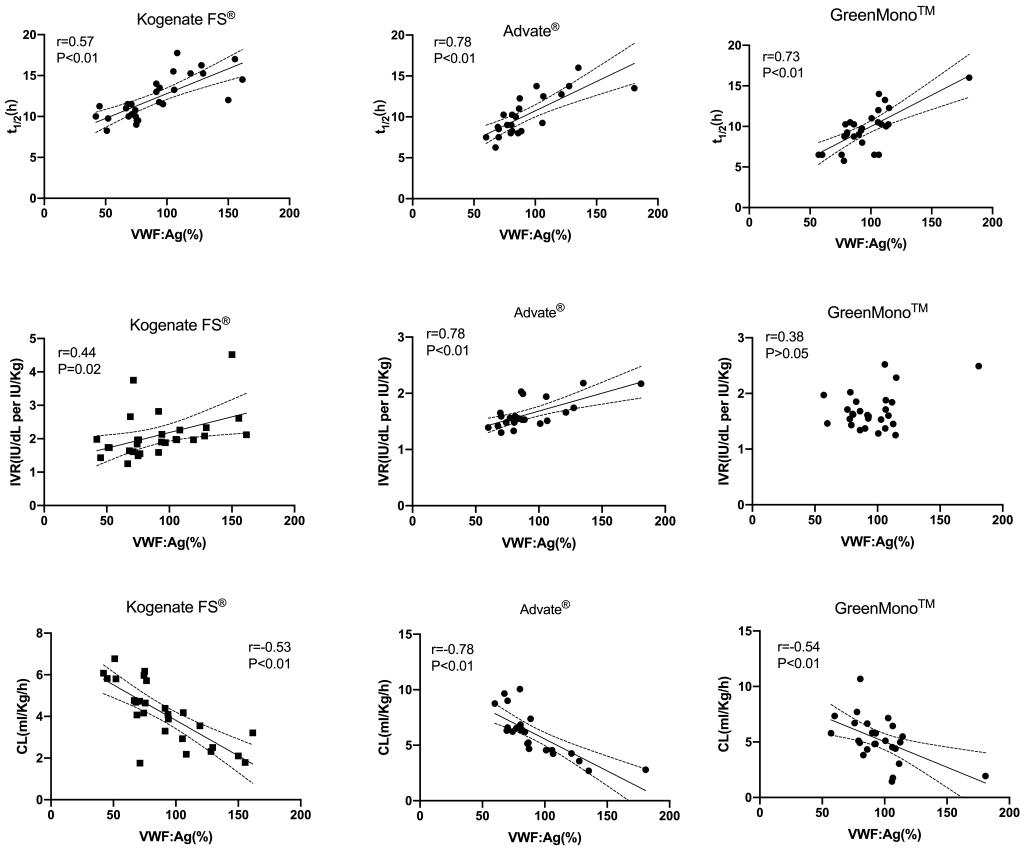

FIGURE 3 Correlations of VWF:Ag levels (%) with each of three PK parameters ($t_{1/2}$, IVR, and CL) among the three FVIII concentrate brands. $t_{1/2}$, half-life time; IVR, *in vivo* recovery; CL, clearance; PK, pharmacokinetic.

TABLE 3 Pharmacokinetic parameters of patients with hemophilia A who exhibit different blood types

PK parameters	FVIII	Blood group O	Blood group non-O	*t*	*P*
$t_{1/2}$ (h)	Kogenate FS®	10.29 ± 1.32	15.05 ± 1.76	−7.253	< 0.01
	Advate®	8.35 ± 1.29	11.60 ± 2.40	−3.641	< 0.01
	GreenMono™	8.67 ± 1.64	10.50 ± 2.51	−2.099	0.03
IVR (IU/kg per IU/dL)	Kogenate FS®	2.04 ± 0.62	2.43 ± 0.81	−1.288	0.21
	Advate®	1.58 ± 0.23	1.67 ± 0.27	−0.850	0.41
	GreenMono™	1.70 ± 0.34	1.69 ± 0.33	0.034	0.97
CL ($mL \cdot kg^{-1} \cdot h^{-1}$)	Kogenate FS®	6.36 ± 2.01	4.51 ± 1.21	2.576	0.02
	Advate®	10.94 ± 2.69	6.63 ± 2.01	4.171	< 0.01
	GreenMono™	9.66 ± 4.01	6.38 ± 3.62	2.580	0.02

PK, pharmacokinetic; $t_{1/2}$, half-life time; IVR, *in vivo* recovery; CL, clearance.

Our result was also in accordance with studies by Vlot et al and Fisher et al concerning the relationships of VWF:Ag level with PK parameters.[35,36] However, no statistically significant correlation was found between VWF:Ag level and IVR in the GreenMono™ group; this might have been due to the existence of extra VWF:Ag in plasma-derived FVIII concentrates, which was not present in recombinant FVIII products. The extra VWF:Ag in the GreenMono™ FVIII concentrate reduced the importance of endogenous levels of VWF:Ag and led to loss of the correlation between the endogenous VWF:Ag level and IVR. Investigation of the relationships of blood type with individual PK parameters revealed that patients with non-O blood types tended to have longer $t_{1/2}$ and lower CL, relative to patients with blood type O, which could help reduce FVIII consumption and venipuncture frequency. The effect of blood type maybe partly caused by differences in VWF:Ag levels among patients with different blood types. Notably, our results were consistent with those of Chen et al and Fischer et al.[19,36]

Our study had some limitations. First, only the one-

stage assay was used to test FVIII level, whereas the chromogenic assay was not used due to its high cost.[37] Although the use of chromogenic testing has implications for regulators, the one-stage clotting test is most commonly used in clinical practice. Second, although the demographic characteristics of patients were not significantly different among groups, the differences observed among concentrates may have reflected differences in the underlying population, rather than true differences among concentrates. Third, the WAPPS models used for individual PK estimation were derived from studies of non-Chinese populations with relatively limited pediatric representation. Formal demonstration of the presence or absence of an ethnicity-linked covariate effect would require derivation of a new set of models based on the pooled Caucasian and Chinese sample, thereby assessing the impact of ethnicity as a covariate.

Three considerations suggest that our results exhibit considerable accuracy. First, the observed variability demonstrated comparable magnitude with the derivation cohort. Second, the Chinese PK profiles were based on five time point curves, with a standard dose administration and a wash-out period; these conditions made the individual PK estimation closer to the individual estimates than to the underlying population estimates. Third, the generic model ensured adoption of a common structural base and covariate parametrization for the estimation, which would minimize the likelihood of model-associated differences in the observations.

Because China is a developing country, limited access to coagulation factor concentrates has been known to cause insufficient therapy for patients with hemophilia. However, several FVIII concentrate brands are now available; thus, patients can optimize their therapy with PK guidance and achieve better outcomes. The results of this study will be useful for adjustment of the participants' dosing regimens and could potentially aid in additional studies. We presume that the present study and future investigations will facilitate the application of PK-tailored dosing of FVIII concentrate in routine clinical practice. In addition, the submission of our data will enhance the accuracy of WAPPS-Hemo evaluated PK parameters, especially in Asian pediatric patients.

In conclusion, we have confirmed the existence of inter-individual variability among Chinese pediatric patients, irrespective of the specific FVIII concentrate they were receiving (limited to the Kogenate FS®, Advate®, and GreenMono™ concentrates). Both VWF:Ag and FVIII concentrate brand were independent influencing factors for FVIII PK.

CONFLICT OF INTEREST

The authors confirmed that there were no interests that might cause conflict or bias.

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