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Monitoring rFVIII Prophylaxis Dosing Using Global Hemostasis Assays

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Summary

Introduction—Secondary FVIII prophylaxis converts severe hemophiliacs (FVIII:C < 1 IU dL⁻¹) to a moderate phenotype (FVIII:C 1 IU dL⁻¹), however, plasma FVIII:C is a poor predictor of bleeding risk.

Aim—To study the use of thromboelastography (TEG) and thrombin generation assay (TGA) to quantify coagulation across a 48 hour rFVIII prophylaxis period.

Methods—10 severe hemophiliacs with varying clinical bleeding phenotypes received their standard rFVIII prophylaxis dose and blood samples were obtained over 48 hours. Measured parameters included FVIII:C, TEG, and TGA at each time point. FVIII:C pharmacokinetics (PK) and correlation between global assay parameters was performed.

Results—The FVIII:C PK parameters were consistent with previous literature. There was significant correlation between FVIII:C and TEG R-time and aPTT (both $p < 0.001$). Significant correlations existed between FVIII:C and TGA peak, ETP and velocity parameters (all $p < 0.001$). At 24 hours the TEG parameters were sub-therapeutic despite median FVIII:C of 13.0 IU dL⁻¹. TGA was sensitive to FVIII:C below 1 IU dL⁻¹. Those with the severest bleeding phenotype had the lowest TGA parameters.

Conclusion—There was significant correlation between FVIII:C and TEG and TGA. TEG lost sensitivity at 48 hours, but not TGA. Prospective studies are needed to determine whether these data can be used to design individualized rFVIII prophylaxis regimens.

Keywords

hemophilia A; TEG; thrombin generation assay; rFVIII prophylaxis

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Author Contributions

Research Study Design (MA, DFB)

Performed the Research (MA, EJM, JCB, MEN, JGK, DFB)

Data Analysis (DFB, MA, EJM, JV)

Wrote Paper (EFB, EJM)

Introduction

Despite prophylactic FVIII treatment in severe hemophiliacs, there remains wide inter-patient variability in clinical bleeding phenotype. For instance, many severe hemophiliacs with trough FVIII levels ≥ 1 IU dL⁻¹ frequently exhibit severe breakthrough bleeding; conversely, others rarely bleed even though their trough FVIII:C is <1 IU dL⁻¹. As such, plasma FVIII:C has been shown to be a poor predictor of preventing arthropathy [1]. This suggests that simply following the FVIII level to make clinical judgments regarding bleeding risk provides an incomplete picture. One potential explanation for this discrepancy is that the current monitoring parameters (e.g., FVIII:C and activated partial thromboplastin time (PTT)) are measured in the plasma matrix, which does not consider the critical contributions of platelets and tissue factor bearing cells to the coagulation processes. This is particularly important given the recognized cell based model of coagulation [2]. Therefore, the inherent variability in clinical efficacy suggests that the FVIII plasma level is best interpreted within the context of its pharmacodynamic effect on whole blood coagulation, platelet function and thrombin generation.

While there have been many elegant FVIII pharmacokinetic (PK) studies [3–12] comparatively few have assessed the FVIII level in relation to global coagulation measures. There is keen interest by the National Institutes of Health [13] and the International Society on Thrombosis and Hemostasis Scientific and Standardization Committee, to develop sensitive and specific laboratory monitoring parameters for hemophilia care. These include thromboelastography (TEG) and the thrombin generation assay (TGA) among others [14,15]. The use of these global measures of hemostasis appear to be complementary to the more traditional plasma based markers FVIII:C and aPTT.

The aim of the current study was to assess traditional and global measures of hemostasis across a 48-hour time period in severe FVIII deficiency patients receiving chronic rFVIII prophylaxis. These data could potentially be used in the future for personalized prophylaxis.

Materials and methods

Patients and study procedures

The Virginia Commonwealth University (VCU) Institutional Review Board approved this study, and it was conducted in compliance with the Declaration of Helsinki. Following written informed consent, 10 subjects > 18 years of age with severe FVIII deficiency without inhibitor antibodies were enrolled into this study. All participants were otherwise healthy, in a non-bleeding state and receiving prophylactic recombinant FVIII (rFVIII) therapy every two or three days. Participants were excluded if they reported factor replacement therapy within the previous 72 hours before study entry; had active bleeding; or had a medical- or family history of thrombosis. Demographics, medical history, bleeding phenotype and factor deficiency information were recorded for each participant. A severe bleeding phenotype was defined as having 1 or more bleeding episodes per month despite FVIII prophylaxis; mild bleeding was defined as 1 bleeding episode or less per year; and the moderate bleeding phenotype was considered between these two extremes.

Participants meeting eligibility criteria underwent a 48-hour FVIII dosing study using their regularly prescribed prophylaxis rFVIII dose administered by intravenous bolus over five minutes. Blood specimens were collected into 3.2% sodium citrate evacuated containers immediately before the FVIII dose, and then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours post-dose for the determination of FVIII:C, TEG and TGA analysis.

Assay Procedures

FVIII:C was determined using the one-stage clotting assay [16]. Thromboelastography was conducted on whole blood samples using the TEG[®] 5000 Hemostasis Analyzer (Haemoscope Corp., Niles, IL, USA) using kaolin, buffered stabilizers and phospholipids per manufacturer's instructions [17]. The reported values included the reaction time (R-time), kinetics time (K-time) and maximal amplitude (MA). The reference ranges for R, K and MA are 3–8 min, 1–3 min, and 51–69 mm, respectively [18].

Kinetics of thrombin generation was assessed in platelet poor plasma (PPP) by measuring the cleavage of the fluorogenic substrate Z-Gly-Gly-Arg-AMC according to the methods described by Hemker [19]. Low concentration tissue factor (PPP reagent-LOW, Thrombinoscope BV, Maastricht, The Netherlands) and PPP were pipetted in triplicate into 96-well round-bottom microtiter plates (Immulon 2HB plate; Diagnostica Stago, Parsippany, NJ, USA). The final concentration of tissue factor was 1 pMol L⁻¹. Thrombin generation was calculated using the Calibrated Automated Thrombogram software version v3.0.0.26 (CAT; Thrombinoscope BV, Maastricht, The Netherlands). Thrombin generation lag time (T-lag), peak thrombin concentration (C_{max}), endogenous thrombin potential (ETP), and the velocity of thrombin generation were reported.

Pharmacokinetic Analysis

Non-compartmental PK analysis was performed on each individual profile to estimate maximal FVIII:C activity (C_{max}), time to maximal activity (T_{max}), terminal half-life (t_{1/2}), total body clearance (CL_{tot}), mean residence time (MRT) and volume of distribution at steady-state (Vd_{ss}).

Statistical Analysis

Descriptive statistics were used when appropriate. When necessary, data were log-transformed to comply with the assumptions of normality. The relationship between variables was summarized using Pearson's correlation if the relationship was linear. When the relationship was linear on the log scale the correlation was calculated from the log-transformed values. The level of significance was pre-specified at p<0.05. All statistical analyses were performed using JMP[®] Pro version 10.0.0 (SAS Institute, Cary, NC).

Results

Ten severe FVIII deficient patients without inhibitory antibodies completed this study (Table 1). All subjects were receiving long-term rFVIII prophylaxis therapy. Five subjects had a moderate or severe clinical bleeding phenotype. The mean FVIII dose was 32.1 IU kg⁻¹ (range 21.4 to 54.4 IU kg⁻¹); the highest dose was used in the patient with the severest bleeding history. Table 2 shows the median (range) clotting parameters following rFVIII dosing through the 48-hour dosing period. The mean (S.D.) PK of FVIII:C included C_{max} 80 (29.8) IU dl⁻¹, CL_{tot} 2.9 (1.1) mL h⁻¹ kg⁻¹; t_{1/2} 11.3 (5.9) hours, and MRT 15.9 (7.8) hours.

There were significant curvilinear relationships between FVIII:C and log-R time and log-aPTT (r = -0.81 and r = -0.84, p<0.001, respectively, Figures 1a and b. A weaker correlation was noted between FVIII:C and MA (r = 0.56, p<0.001), however the trend was difficult to interpret as all MA values were in the normal range irrespective of FVIII:C activity.

The median (range) baseline peak thrombin concentration in the study population was 91.5 nM (19–247), while the baseline ETP was 1114.0 nM min⁻¹ (382.0–1805.0, Figures 2a and b). There was a significant correlation between log FVIII:C and log peak thrombin (r=0.51,

$p < 0.001$). Maximal median peak thrombin generation (330.5 nM) and ETP (median 1533.0 nMol min⁻¹) were achieved 30 minutes post-rFVIII dose and trended downward with FVIII:C clearance. Both peak thrombin and ETP returned to its baseline at 48 hours. Patients with a severe bleeding phenotype had the lowest baseline and 48-hour thrombin generation and ETP measurements, respectively. There was strong correlation ($r = 0.90$) between log FVIII:C and log thrombin generation velocity (Figures 3a and b), however there was inter-individual variability; patients #2 and #10 had markedly lower slopes and correspondingly lower correlations ($r = 0.31$ and $r = 0.65$, respectively).

Discussion

Hemophilia is by definition a disease of lack of thrombin generation, due to the inability to form the tenase and prothrombinase complexes during the amplification phase of coagulation. Deficient prothrombinase activity prevents the thrombin burst necessary for platelet activation and fibrin formation. Therefore, assays that can quantify and characterize not only thrombin generation but also whole blood viscoelasticity would be ideal to provide a complete picture of a patient's hemostatic response to factor therapy.

In this study, the PK of FVIII:C was consistent with previously published literature [3–14]. Following rFVIII dosing, the peak global response occurred at 30–60 minutes, and all measures returned to baseline by 48 hours. However, as early as 24 hours, the median TEG parameters R and K parameters fell below their target range, despite the median FVIII:C level of 13.0 IU dl⁻¹. Thus, these patients went another 24 hours with sub-therapeutic viscoelastic parameters until the completion of the study. Correspondingly, although the 48-hour median FVIII:C was 1.0 IU dl⁻¹ (the current goal trough level for prophylaxis), the blood viscoelasticity was virtually absent. This may be representative of the fact that TEG is activated under non-physiological conditions and is consequently insensitive to very low FVIII concentrations. Sorensen and colleagues have previously shown the TEG to be a useful monitor of recombinant activated factor VIIa and FVIII substitution [20–22], however, these studies did not assess TEG readings at the trough period.

On the contrary, similar to previous data [23–25] the TGA parameters ETP, thrombin peak and velocity were sensitive to FVIII:C below 1 IU dl⁻¹. There was variability in the individual subjects' TGA profile, which has been shown previously in healthy volunteers [26] and those with FVIII deficiency [24,25,27]. Our findings may be reflective of normal variance in patient thrombin generation profile, and/or the patient's rFVIII PK disposition. While the relatively small sample size in this single center pilot study precludes any statistical comparisons between patients with different bleeding phenotypes, it does shed light on the relevant question “was there a difference in TGA measures in patients with severe bleeding phenotypes, particularly at the 48 hour time point?” Patients with the severest bleeding phenotype had the lowest baseline and 48-hour TGA parameters. For example, patient #7, who had the severest bleeding history (59 documented bleeds and 118 rFVIII infusions in 2009), had baseline thrombin generation, ETP and time to peak thrombin (TTP) of 26 nM, 400 nM min⁻¹, and 16.3 min, respectively. At 48 hours, these parameters were 21 nM, 237 nM min⁻¹ and 16.0 min, respectively. On the other hand, patient #1, who experiences infrequent breakthrough bleeding events, had baseline thrombin generation, ETP and TTP of 103 nM, 1593 nM min⁻¹, and 17.3 min, respectively; at 48 hours these parameters were 177 nM, 1654 nM min⁻¹ and 13.4 min, respectively. Previous data have shown an association between clinical bleeding phenotype and TGA parameters in patients with hemophilia [23,28–30].

Taken as a whole, these data lend support to the opinion that achieving a trough FVIII:C level of 1 IU dl⁻¹ is not appropriate for all severe hemophilia A patients. A recent study

evaluated the frequency of joint bleeding as a function of FVIII activity [31]. The results showed that for those patients with FVIII:C of 1 IU dL⁻¹, the mean number of joint bleeds was 6 per year; for those with a level of 5 IU dL⁻¹ the number of bleeds dropped to approximately two per year; and 10–15 IU dL⁻¹ completely prevented joint bleeds. Our data may corroborate these findings. Indeed, at the 24-hour time point in the current study, the median FVIII:C was 13.1 IU dL⁻¹, which corresponded to near normal TEG and TGA readings. While achieving these trough levels would not be appropriate for all patients, those with a severe bleeding phenotype and active lifestyle may benefit from a more personalized pharmacotherapy approach.

This study has limitations that deserve comment. First, this was a relatively small pilot study; however it provides important preliminary data from which to design larger multi-centered personalized prophylaxis studies. Second, we studied the TGA in PPP without the use of corn trypsin inhibitor (CTI) to block the intrinsic pathway. While there is a body of literature supporting the use of CTI, when the present study began there were no formal standardized procedures for TGA. Nonetheless, our TGA data compared favorably to other studies that used PPP with and without CTI [23,24,27]. We believe these data to be representative given a previous study suggested that the influence of intrinsic pathway activation is minimal when TF concentrations are 0.5 pM [32].

Conclusion

In conclusion, we studied global hemostasis parameters using TEG and TGA across a 48 hour rFVIII prophylaxis dosing period. There was correlation between FVIII:C and TEG parameters, but sensitivity was lost at 48 hours. TGA maintained sensitivity across the entire period, but showed variability. Those with the most severe bleeding phenotypes had the lowest thrombin generation and ETP parameters. Further studies are needed to determine whether these collective data can be used to design individualized rFVIII prophylaxis regimens based on clinical bleeding phenotype.

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Figure 1. Correlation between FVIII:C, R and aPTT

Correlation between FVIII:C and R (Panel a, $r = -0.81$, $p < 0.001$) and FVIII:C and aPTT (Panel b, $r = -0.84$, $p < 0.001$)

Fig. 2.
TGA parameters in PPP following rFVIII prophylaxis

Figure 3. Correlation between thrombin velocity and FVIII:C

Correlation between log FVIII:C and log thrombin generation velocity (panel a, $r = 0.90$, $p < 0.001$) and individual patient correlation plots (panel b).

Table 1

Subject Demographics

Subject	Bleeding Phenotype	Ethnicity	Age (yrs)	PLT Count (x 10 ⁹ mL ⁻¹)	Plasma Fibrinogen (mg/dL)	Weight (kg)	Product	Weekly Doses	rFVIII Dose (IU)	rFVIII Dose (IU/kg)
1	Mild	AA	62	199	328	107	Kogenate FS	Two	2,300	21.4
2	Mild	Cauc	59	261	264	72	Kogenate FS	Three	2,058	28.7
3	Mild	Asian	33	274	313	69	Helixate FS	Three	1,628	23.4
4	Severe	Cauc	46	273	289	83	Advate	Two	1,973	24.4
5	Severe	Cauc	20	230	301	64	Helixate FS	Two	2,400	36.3
6	Moderate	Cauc	60	323	441	61	Recombinate	Two	1,560	25.6
7	Severe	Cauc	27	403	355	81	Kogenate FS	Two	4,464	54.4
8	Mild	Cauc	28	177	367	86	Recombinate	Two	3,520	40.9
9	Mild	AA	40	204	356	88	Kogenate FS	Two	3,000	34.1
10	Severe	Cauc	23	197	214	75	Advate	Three	2,200	29.3
Mean			39.8	254.1	322.8	78.7			2,510	32.1
S.D.			16.1	69.2	62.4	13.5			907	10.0

AA - African American; Cauc - Caucasian; PLT - platelet

Table 2

Median (range) coagulation parameters from Time 0 to 48 hours

Parameter	Time Following rFV/III Dosing (h)								
	0	0.5	1	2	4	8	12	24	48
Plasma FVIII:C (IU dL ⁻¹)	<1	91.0 (54–152)	76.0 (48–140)	65.0 (39–106)	58.5 (39–88)	40.5 (24–53)	27.5 (19–40)	13.0 (8–32)	1.0 (<1–16)
aPTT (sec)	58.5 (42–73)	31.5 (27–36)	32 (26–37)	32.0 (26–39)	33.0 (30–37)	34.5 (32–40)	36.0 (34–41)	41.0 (37–48)	51.5 (42–65)
R (min)	24.1 (9.8–37)	6.6 (3.4–11.1)	6.0 (3.8–9.6)	6.5 (3.9–12.5)	6.9 (4.6–10.5)	8.6 (6.8–13.6)	8.1 (6–11.3)	12.0 (6.2–18.9)	17.6 (12.3–29.5)
K (min)	5.5 (2.5–18.6)	1.9 (1.4–3.3)	2.1 (1.1–3.1)	1.8 (1.2–4.0)	2.2 (1.5–3.5)	2.5 (1.8–3.4)	2.3 (1.4–3.8)	3.1 (2.2–5.0)	4.4 (3.4–8.9)
MA (mm)	52.8 (44.4–63.5)	62.1 (56.1–67.3)	61.4 (58.2–62.6)	61.6 (52.6–68.0)	60.7 (52.6–68.0)	59.1 (52.7–67.1)	61.7 (51.0–71.4)	58.3 (54.0–64.3)	53.2 (47.1–60.3)