Association of Peak FVIII Levels and AUC with Bleeding in Patients with Hemophilia A on Every Third Day PK-Guided Prophylaxis

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Introduction & Objective

We previously demonstrated that 1) total hemorrhages and hemarthroses are linked to time spent with a factor (F) VIII concentration below 1%,[1] and that 2) targeting trough FVIII levels at ≥1% using pharmacokinetic-guided prophylaxis (PKP) FVIII 20-80 IU/kg given every third day and standard prophylaxis (SP) 20-40 IU/kg given every other day reduced the median annualized bleeding rate (ABR)[2] and the median annualized joint bleeding rate (AJBR)[3] as compared with on-demand treatment (OD). We further analyzed the data from the PKP group[4] to determine if peak FVIII levels, area under the curve (AUC), and time with FVIII levels in a hemostatically effective range (ie, >20-30%) were independent predictors of prophylactic efficacy.

Methods

Data for 34 subjects in the every third day intent-to-treat PKP arm and 32 subjects in the SP arm were evaluated. In the PKP arm, 4089 prophylactic infusions were administered during a median of 364 treatment days (range: 97–394). The median dose per infusion was 43.0 (range: 13.0–107.1) IU/ kg, and the median number of units administered per subject was 2979 (range: 1073-5600). In the SP arm, 5846 prophylactic infusions were administered during a median of 364 treatment days (range: 283-397). The median dose per infusion was 31.4 (range: 11.8-80.9) IU/ kg, and the median number of units administered per subject was 2095 (range: 967-3150). Average peak FVIII levels were estimated using individual in vitro recovery values and average dose/prophylactic infusion. Negative binomial multivariate regression model was used for analysis;[5] age and body mass index were covariates.

Results

A total of 845 bleeding episodes (188 traumatic, 657 spontaneous; 750 joint, 95 non-joint) occurred in the 34 patients during 6 months of OD that preceded PKP. The average ± SD (range; median) ABR and AJBR during on-demand treatment was 49.2 ± 20.7 (13-90.8; 44.8) and 43.5 ± 21.3 (6.5-90.8; 39.0), respectively. A total of 795 bleeding episodes (269 traumatic, 526 spontaneous, 661 joint, 134 non-joint) occurred in the 32 patients during 6 months of OD that preceded SP. The average ± SD (range; median) ABR and AJBR during OD was 48.7 ± 22.4 (24-120.5; 43.4) and 40.6 ± 21.7 (1.8-115; 36.8), respectively.

During PKP, 131 bleeding episodes occurred in 24/34 patients (70.6%). Among the 121 episodes of joint bleeding, 4 (all spontaneous) occurred within the first 12 hours after infusion, 20 (7 spontaneous) occurred 12-24 hours post-infusion, 49 (21 spontaneous) occurred 24-48 hours post-infusion, and 40 (22 spontaneous) occurred 48-72 hours post-infusion (**Table 1**). Interestingly, no significant increase was observed in the number of bleeding episodes occurring 48 hours after infusion as compared with earlier. Results from the SP arm were not statistically different from those obtained for the PKP arm.

The pattern of spontaneous and traumatic bleeding episodes over time was similar in both the PKP and SP arms. The median predicted concentration (range) at the time of bleeding among patients in the PKP arm was 2.71 (0-26.55) for 57 spontaneous hemorrhages, 3.57 (0-41.6) for 74 traumatic hemorrhages, 3.43 (0-41.67) for 121 hemarthroses, and 2.87 (0-11.26) for 10 non-joint bleeding events (**Figures 1** and **2**). Traumatic joint bleeding occurred with predicted FVIII levels as high as 41%, but the majority of hemarthroses occurred at levels <10%. The median predicted concentration (range) at the time of bleeding among patients in the SP arm was 4.42 (0-25.51) for 56 spontaneous hemorrhages, 10.60 (1-57.13) for 45 traumatic hemorrhages, 6.17 (0-57.13) for 79 hemarthroses, and .01 (0-43.19) for 10 non-joint bleeding events. The majority of traumatic joint bleeding occurred with predicted FVIII levels <10%, however hemarthroses occurred at levels as high as 58%.

Average peak FVIII levels in the PKP arm ranged from 24.3 to 167.5% (median: 70.9%), with lower values associated with an increased risk for all bleeding (P=0.0004) and joint bleeding (P=0.0013) (**Figure 3**).

An analysis of the relationship of bleeding events to AUC for both prophylaxis arms is shown in **Figure 4.** In the PKP arm, the median predicted AUC was 470 during the first 12 hours post-infusion, 190 between 12-24 hours, 136 between 24-48 hours, and 33 between 48-72 hours post-infusion. In the SP arm, the median predicted AUC was 339 during the first 12 hours post-infusion, 147 between 12-24 hours, 3 between 24-48 hours, and 30 between 48-72 hours post-infusion.

Among patients in the PKP arm, the median percent of time spent with FVIII levels >20% was 22.3% (range: 2.9-46.1), resulting in a median AUC of 1363 (range: 130-4265). Both values were significantly associated with a lower ABR. This relationship was even more pronounced when a higher percentage of time was spent with FVIII levels >30% (**Figure 5**). Values for the SP arm were similar.

In the PKP arm, the average peak level (IU/dL) and time spent with a FVIII level >30% FVIII were significantly correlated with reduced bleeding risk. Similarly, the average peak level (IU/dL) and weekly AUC (>5%, >10%, >20%, >30%, and >40%) showed a consistent and strong positive correlation (**Table 2**).

Table 1: Number of hemorrhages (patients) and time at which bleeding occurred post-infusion in the PKP arm.

Bleeding Type	12 hr	12-24 hr	24-48 hr	48-72 hr	>72 hr*	All
Spontaneous	4 (4)	7 (4)	21 (13)	22 (12)	3 (3)	57
Traumatic	0 (0)	14 (9)	31 (10)	22 (11)	7 (4)	74
Joint	4 (4)	20 (11)	49 (17)	40 (15)	2 (1)	121
Non-joint	0 (0)	1 (1)	3 (2)	4 (3)	2	10

*Indicates non-adherence to the treatment regimen.

Figure 1: Spontaneous and traumatic bleeding episodes over time in subjects on PKP.

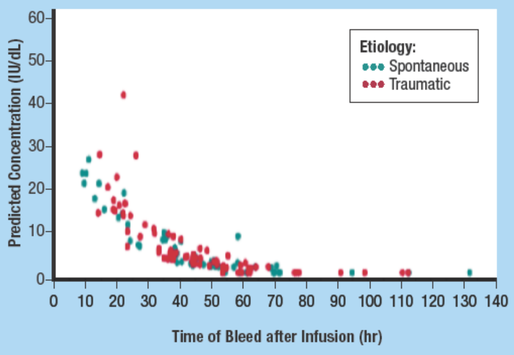


Figure 2: Joint/non-joint bleeding episodes over time in subjects on PKP.

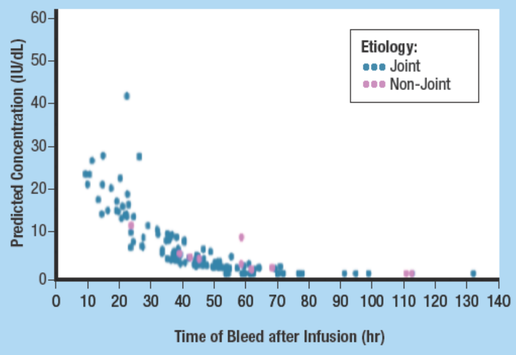
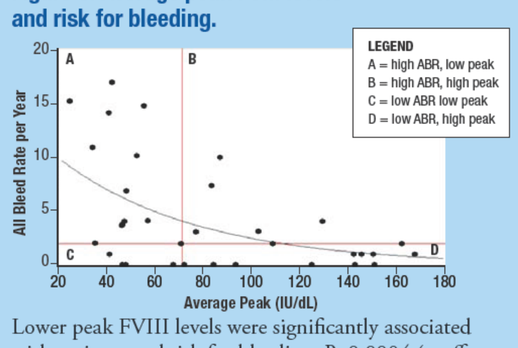
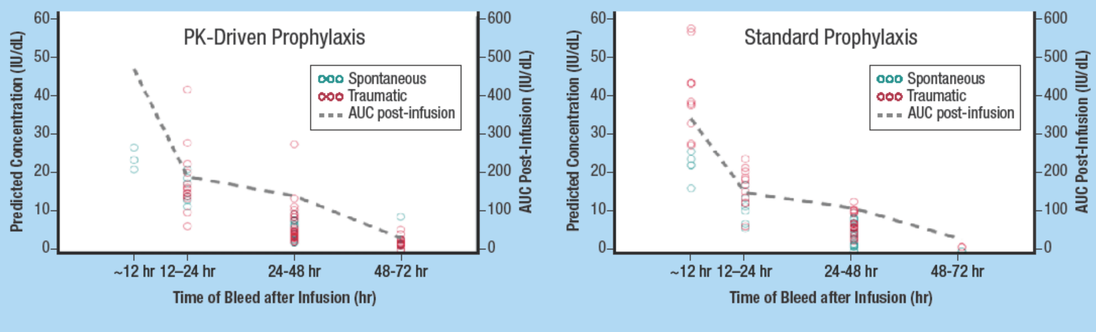


Figure 3: Average peak FVIII levels and risk for bleeding.



Lower peak FVIII levels were significantly associated with an increased risk for bleeding: P=0.0004 (coeff: -0.02) all bleeds; P=0.0013 (coeff: -0.02) joint bleeds.

Figure 4: Spontaneous and traumatic bleeding and AUC for PKP and standard prophylaxis.



Regimen	AUC 0-12 hr	AUC 12-24 hr	AUC 24-48 hr	AUC 48-72 hr
PKP	469.814	190.396	136.409	33.0903
SP	339.229	146.919	112.871	30.4046

Figure 5: Time spent post-infusion with FVIII levels >30% and bleeding risk in the PKP arm.

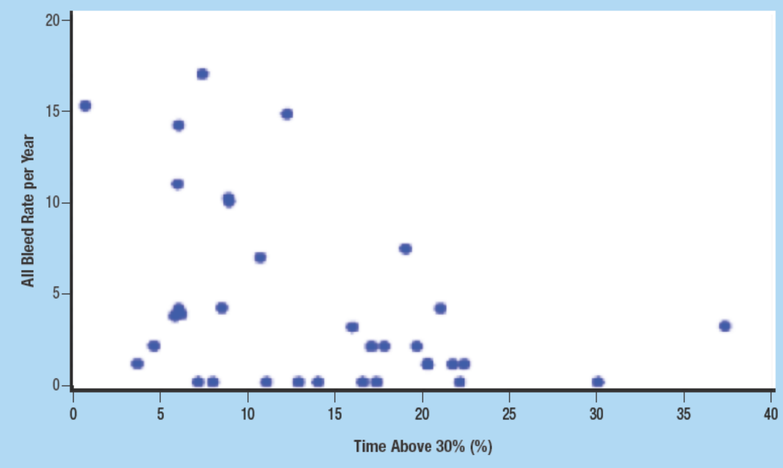


Table 2: Average peak level, time above %, and weekly AUC covariance in the PKP and SP arms.

	PKP (N=34)		SP (N=32)	
Variable	Time >5% Time >10% Time >20% Time >30% Time >40%	AUC >5% AUC >10% AUC >20% AUC >30% AUC >40%	Time >5% Time >10% Time >20% Time >30% Time >40%	AUC >5% AUC >10% AUC >20% AUC >30% AUC >40%
Average Peak (IU/dL)	---- (ns) 0.43 (s) 0.65 (s) 0.90 (s) 0.94 (s)	0.82 (s) 0.82 (s) 0.87 (s) 0.94 (s) 0.95 (s)	---- (ns) ---- (ns) 0.46 (s) 0.81 (s) 0.92 (s)	0.56 (s) 0.59 (s) 0.71 (s) 0.86 (s) 0.94 (s)
Time >5% Time >10% Time >20% Time >30% Time >40%	Not applicable	0.60 (s) 0.81 (s) 0.90 (s) 0.99 (s) 0.99 (s)	Not applicable	0.74 (s) 0.89 (s) 0.93 (s) 0.99 (s) 0.99 (s)

Non-parametric correlation coefficient: significant if = P <0.05.

Discussion & Conclusions

Patients receiving PKP every third day were dosed to maintain a target FVIII trough level of >1%, thereby eliminating time spent below 1% as a variable contributing to bleeding risk. Owing to the wider range of prescribed dosing in the PKP arm (20-80 IU/kg) versus the SP arm (20-40 IU/kg), PKP-treated patients demonstrated higher average peak FVIII levels, AUC, and time spent above various FVIII plasma level thresholds. Examination of these unique PK parameters in relation to the reported bleeding events showed that:

- **Higher peak FVIII levels and AUC provided increased protection from joint and non-joint bleeding.**
- **ABR was reduced as the percent of time spent weekly with FVIII levels >20-30% (ie, hemostatically effective range) increased.**
- **Traumatic bleeds occurred throughout the range of predicted FVIII plasma levels (as high as 58%), yet most occurred at FVIII levels <10% (median predicted value ~3%).**

These findings add to previous observations that time spent with FVIII levels <1% negatively correlates with bleeding risk by demonstrating that peak FVIII levels, AUC, and time spent at higher FVIII plasma levels are also associated with the risk for joint and non-joint bleeding. The data highlight the potential impact of variability in individual PK and the likelihood for hemorrhage and support the need for higher peak levels and AUC in some patients treated every third day, such as those with underlying joint disease, or during periods of increased activity.

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If you have any additional questions, please feel free to contact Baxter Bioscience Medical Information at medinfo@baxter.com.

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