ORIGINAL ARTICLE

WILEY

PK-tailored tertiary prophylaxis in patients with severe hemophilia A at Beijing Children's Hospital

Peijing Li [1] | Zhenping Chen [1] | Xiaoling Cheng [2] | Yan Wang [3] | Ningning Zhang [4] | Yingzi Zhen [1] | Xinyi Wu [5] Runhui Wu [1]

[1]Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[2]Department of Pharmacy, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[3]Physiatry Department, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[4]Department of Radiology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[5]Nursing Department, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence
Runhui Wu, Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China
Email: runhuiwu@hotmail.com

Received: 29 September, 2018
Accepted: 5 March, 2019

ABSTRACT

Importance: Tertiary prophylaxis using a low-dose regimen is usually insufficient to prevent recurrent joint bleeding and deterioration in joint diseases in children with severe hemophilia A. Pharmacokinetic (PK) dosing is a useful approach to increase the precision and efficiency of prophylaxis.

Objective: To explore the efficacy of PK-tailored tertiary prophylaxis in children with severe hemophilia A.

Methods: We implemented a PK-tailored tertiary prophylaxis program for 15 boys with severe hemophilia A aged 5–16 years at Beijing Children's Hospital. Following PK testing and a 6-month evaluation period (phase I), 15 patients were divided in two groups according to individual PK data and actual bleeding: (1) a PK-tailored group [modified prophylaxis regimen according to PK data for the next 6 months (phase II); $n = 8$] and (2) a maintenance group (continued the original regimen for the next 6 months; $n = 7$). We compared the bleeding rate, infusion frequency, and factor VIII (FVIII) consumption between the two groups.

Results: In the PK-tailored group, the median annual joint bleeding rate was reduced from 7.8 in phase I to 1.4 in phase II, mean annual total factor consumption increased from 1619.0 IU/kg in phase I to 2401.9 IU/kg in phase II, and median infusion frequency for prophylaxis increased from 104 times/year in phase I to 156 times/year in phase II ($P < 0.05$). Although the FVIII consumption increased, it remained at approximately half of the standard method.

Interpretation: PK-tailored prophylaxis may represent a more efficient approach to individual prophylaxis in China, but further studies are required to verify this.

KEYWORDS
Severe hemophilia, Pharmacokinetics, Tertiary prophylaxis

INTRODUCTION

Hemophilia A (HA) is a sex-linked coagulation disorder caused by a deficiency in the clotting factor VIII (FVIII). Children affected by the severe form of HA suffer from recurrent joint bleeding that eventually progresses to disability in adolescence in the absence of prophylactic treatment.[1] Tertiary prophylaxis[2] is an effective treatment

DOI: 10.1002/ped4.12122

strategy to prevent progression to disability in young children with HA, although its high cost limits its availability in developing countries.[3] Based on pharmacokinetics (PK), increasing infusion frequency will result in reduced FVIII consumption and a more stable factor level although it may have a negative impact on adherence.[4,5] Moreover, a significant positive association has been demonstrated between time spent with FVIII < 1 IU/dL of more than 30 h per week and bleeding frequency.[6] Implementing PK-driven prophylactic treatment for HA with increased infusion frequency and reducing the time spent with FVIII less than 1 IU/dL to 30 h per week for children with severe HA with target joint(s), defined in the present study as PK-tailored tertiary prophylaxis, may represent a cost-effective strategy in developing countries.

METHODS

This was a single center pragmatic trial conducted at Beijing Children's Hospital (BCH) by the Comprehensive Care Team of Hemophilia from January 2015 to May 2016. The study was approved by the ethics committee of BCH. Informed consent was obtained from all individual participants included in the study, and written permission to participate was obtained from parents or legal guardians in accordance with appropriate local laws, where applicable.

Inclusion/exclusion criteria

The inclusion criteria were as follows: (1) severe HA with a baseline FVIII level of < 1 IU/dL, (2) age 5–16 years, (3) > 50 exposure days (EDs) without inhibitor or inhibitor history, (4) ≥ 1 target joints, (5) close proximity to the comprehensive care center at BCH, (6) compliant to treatment, and (7) use of the pre-study prophylaxis regimen for ≥ 1 year prior to enrollment in the study.

The exclusion criteria were as follows: (1) history of FVIII inhibitor (titer > 0.6 Bethesda units [BU]) and detectable FVIII inhibitor at screening (titer > 0.6 BU), and (2) planned major surgery, and (3) concomitant serious conditions including symptomatic human immunodeficiency virus (HIV) infection, juvenile rheumatoid arthritis, metabolic bone disease, or other conditions known to mimic or cause joint diseases.

PK analysis

Following a bleed-free period of two weeks before the baseline assessment, patients did not undergo FVIII infusion for at least 72 h prior to treatment initiation. Each participant subsequently received a dose of 50 IU/kg FVIII by intravenous injection. Blood samples were collected and the concentration of FVIII was measured at 0.5 h before injection and 1 h, 9 h, 24 h, and 48 h after injection.

PK parameters and decay curves were generated using WinNonlin software (Pharsight Corp, Phoenix, Arizona, USA). The time below 1 IU/dL every week during prophylaxis was calculated as described previously[7] using the following PK equation for multiple infusions at regular intervals with steady-state levels:

$$\mathrm{FVIII}(t)=\mathrm{Dose}\times\mathrm{IVR}\times\frac{1}{(1-e^{-k\times\tau})}\times e^{-k(t-1)}$$

in which the additional term $1/(1-e^{-k\times\tau})$ represents the accumulation of FVIII during multiple dosing, τ denotes the time interval between doses, in vivo recovery (IVR) was calculated based on FVIII level at 1 h after infusion, and K was the elimination rate constant (ln2/half-life). Dose was measured in IU/kg and IVR was measured in IU/dL per IU/kg.

Treatment groups

Patients were divided into two groups based on PK data and bleeding phenotype. The PK-tailored group included patients with a time below 1 IU/dL of more than 30 h per week. The maintenance group included patients for whom the time below 1 IU/dL was less than 30 h per week. Patients with few joint bleeds (annual joint bleeding rate [AJBR] ≤ 3) were also included in the maintenance group even when the time below 1 IU/dL was more than 30 h per week.

Modified regimen for the PK-tailored group

Patients in the PK-tailored group had a stepwise increased infusion frequency of twice a week, to three times a week, to every other day, and then to every day. This method was selected instead of a strict PK-driven infusion time to ensure that the time below 1 IU/dL was less than 30 h per week, and also to allow alternations in infusion frequency for the convenience of the patient.

Study design

Baseline data were collected prior to treatment initiation. Therapy consisted of two phases. In phase I, all patients were treated with conventional low-dose prophylaxis regimens for 6 months. In phase II, the regimen was modified for patients in the PK-tailored group while the phase I prophylaxis regimen was maintained for patients in the maintenance group for a further 6 months. Recombinant FVIII (Baxter, Deerfield, Illinois, USA) was used in 11 patients and plasma-derived FVIII was used in 4 patients. The following data were collected from patient records for both phases: (1) number and site of joint bleeding as recorded in the patients' bleeding log; (2) factor concentrate consumption during each period, which was obtained from routinely submitted home therapy reports; and (3) infusion frequency as recorded in the patients' bleeding log. The following three outcomes were compared between the two groups: (1) AJBR, (2) factor

consumption, and (3) frequency of infusion.

Statistical analysis

SPSS software version 19.0 (SPSS Company, Chicago, IL, USA) was used for data analysis. Data following a normal distribution were presented as mean ± SD (standard deviation), while other data described by median and range. The Mann–Whitney *U* test was used to determine the significance of nonparametric data. Values of $P < 0.05$ were considered statistically significant.

RESULTS

A total of 15 patients were enrolled in the present study, and none of the patients reported life-threatening bleeding episodes during the study period. The time below 1 IU/dL was > 30 h for all 11 patients, but 3 patients had few joint bleedings (AJBR < 3). Therefore, 8 patients were assigned to the PK-tailored group and 7 to the maintenance group. The data for each patient in the two groups during Phase I and Phase II are shown in Table 1. Data for each group in Phase I and II are shown in Table 2.

The median single dose of prophylaxis regimens during Phase I were 11.3 (8.1–17.4) IU/kg in the PK-tailored group and 13.0 (10.9–23.3) IU/kg in the maintenance group. Infusion frequency varied from twice a week (BIW) to every other day (QOD), but 13/15 (86.7%) patients in

TABLE 1 Individualized data of both groups in Phase I and Phase II

Group	Phase I					Phase II				
	Prophylaxis regimen (IU/kg)	Trough level (IU/dL)	Time of FⅧ < 1 IU/ (dL · week)(h)	AJBR	Total factor consumption [IU/(kg · year)]	PK-tailored prophylaxis regimen (IU/kg)	Trough level (IU/ dL)	Time of FⅧ < 1 IU/ (dL · week)(h)	AJBR	Total Factor consumption [IU/(kg · year)]
PK-tailored group	13.2·BIW	0.51	102.3	12.0	1530.7	13.2·TIW	0.61	66.3	1.3	2076.7
	11.4·BIW	0.28	71.3	4.0	1226.9	11.4·TIW	1.05	0	6.7	1878.2
	8.1·QOD	0.34	71.7	6.0	1627.5	8.1·QD	2.26	0	10.8	3043.6
	12.5·BIW	0.15	95.4	4.0	1450.0	12.5·TIW	0.45	58.8	1.5	1968.8
	11.8·BIW	0.79	38.8	12.0	2023.0	11.8·TIW	1.97	0	9	2046.3
	17.4·BIW	0.34	84.4	9.6	2184.2	17.4·QOD	0.70	21.4	0	3173.7
	8.9·TIW	0.17	92.7	14.0	1643.1	8.9·QD	1.21	0	0	3250.5
	11.1·BIW	0.36	64.6	0[†]	1226.6	11.1·TIW	1.27	0	0	1777.6
Maintenance group	13.5·BIW	1.11	0	4.8	1523.7	-	-	-	6.0	1501.3
	12.4·BIW	1.97	0	10.0	1407.9	-	-	-	0	1284.4
	10.9·BIW	1.73	0	0	1130.5	-	-	-	2.0	1152.2
	15.4·BIW	1.35	0	0	1601.6	-	-	-	3.0	1670.8
	13.0·BIW	0.48	73.4	0	1352.0	-	-	-	1.0	1352.0
	23.3·TIW	0.66	40.4	1.0	3768.1	-	-	-	2.0	3768.1
	10.2·TIW	0.17	88.7	0	1591.2	-	-	-	2.0	1632.0

PK, pharmacokinetics; BIW, twice a week; TIW, three times a week; QOD, every other day; QD, every day; AJBR, annual joint bleeding rate; PK, pharmacokinetics; -, unadjusted. [†]The annual bleeding rate was 10.

TABLE 2 Summary on AJBR, factor consumption and infusion frequency of both groups in phases I and II

Variables	PK-tailored group (*n* = 8)		Maintenance group (*n* = 7)	
	Phase I	Phase II	Phase I	Phase II
Median AJBR (range)	7.8 (0–14.0)	1.4 (0–10.8)	0 (0–10.0)	2.0 (0–6.0)
Mean factor consumption ± SD [IU/(kg · year)]	1364.6 ± 211.6	2341.2 ± 663.4	1713.2 ± 860.9	1713.2 ± 860.9
Mean total[†] factor consumption ± SD [IU/(kg · year)]	1619.0 ± 337.6	2401.9 ± 633.7	1767.9 ± 897.0	1765.8 ± 902.4
Median infusion for prophylaxis (times/year) (range)	104 (104–182)	156 (104–365)	104 (104–156)	104 (104–156)
Median total infusion frequency (times/year) (range)	121 (108–203)	161 (106–376)	112 (104–160)	107 (104–158)

AJBR, annual joint bleeding rate; PK, pharmacokinetics; SD, standard deviation. [†]Factor consumption used for prophylaxis plus breakthrough bleeding treatment.

low-dose (< 30.0 IU/kg per week) regimen.

In phase I, the mean factor consumption was 1364.6 ± 211.6 IU/(kg · year) for the PK-tailored group and 1713.2 ± 860.9 IU/(kg · year) for the maintenance group. The median infusion frequency in the PK-tailored group was 121 (108–200) times/year and 112 (104–160) times/year in the maintenance group, and there was no significant difference between the groups. Median AJBR were 0 (range, 0–10.0) in the maintenance group compared with 7.8 (range, 0–14.0) in the PK-tailored group ($P = 0.054$). The mean trough level was 0.37 (0.15–0.79) IU/dL and the median time of < 1 IU/dL was 78.0 (38.8–102.3) h in PK-tailored group.

After increasing the frequency of infusion in the PK-tailored group, the trough level for 5 patients was > 1 IU/dL (1.05–2.26) IU/dL. Three patients remained at < 1 IU/dL, of which one patient had a trough level of 21.4 (< 30) h and the other 2 patients had a trough level of 66.3 and 58.8 (>30) h per week, respectively. The mean trough level in phase II for the PK-tailored group increased from 0.37 IU/dL to 1.19 IU/dL ($P < 0.05$), which was higher than that of the maintenance group (1.07 IU/dL).

In phase II, the median AJBR level was reduced to 1.4 (range, 0–10.8). The mean total consumption of factor increased to 2401.9 ± 633.7 IU/(kg · year), and the median infusion frequency for prophylaxis increased to 156 times/year. There was significant difference ($P < 0.05$) in the above aspects compared with phase I. The mean total consumption of factor in the PK-tailored group was 2401.9 ± 633.7 IU/(kg · year), which was higher than that in the maintenance group [1765.8 ± 902.4 IU/(kg · year)] ($P > 0.05$). The median total infusion frequency in the PK-tailored group was 161 times/year, which was significantly higher than the 107 times/year observed in the maintenance group ($P < 0.05$).

DISCUSSION

Prophylaxis, in theory, must maintain a plasma trough level of above 1 IU/dL.[2] However the high cost of this therapy hinders its application, especially in developing countries.[3] Factors such as PK can lead to individualized variations that can increase the cost effectiveness of prophylaxis.[8] As early as 1997, dose tailoring of FVIII according to individual PK data was described by Carlsson et al[9] in a study in which PK dosage reduced the utilization of FVIII from 4406 to 3000 IU/(kg · year) without further bleeding. In 2012, a randomized comparison study of PK-driven prophylaxis versus the standard regimen demonstrated a reduction in infusions but increased factor utilization with PK-driven prophylaxis.[4] Undoubtedly, PK-driven prophylaxis is more scientific and feasible than the standard regimen, although the above two methods are both too expensive for widespread application in developing countries.[3] One PK characteristic of FVIII is that an increase in infusion frequency is associated with a more stable and higher trough level at the same dose. Daily prophylaxis is therefore associated with improved clinical outcomes, without extra factor consumption.[10]

Given that the primary objective of prophylaxis is to reduce bleeding and bleeding frequency when an AJBR > 3 beyond 30 h duration occurs at a FVIII:C level under 1 IU/dL per week,[6] a more cost-effective regimen for patients in developing countries may be to keep the duration to less than 30 h per week and increase the infusion frequency rather than increasing the dosage in PK-driven prophylaxis, referred to as PK-tailored prophylaxis in the present study.

We divided patients according to FVIII activity < 1 IU/dL for more than 30 h per week into a PK-tailored group and a maintenance group. Increased infusion frequency in the PK-tailored group was also considered by bleeding phenotype. During phase I, no difference was observed between the groups in prophylaxis regimen, factor consumption, and infusion frequency with higher AJBR. During phase II, AJBR in the PK-tailored group was reduced without a significant increase in the consumption of factor [approximately 2000 IU/(kg · year)] or infusion frequency. However, PK was not completely indicative of bleeding phenotype: the time (FVIII activity < 1 IU/dL, more than 30 h per week) in three patients was longer than 30 h but with low AJBR, whereas in three other patients, the trough level was higher than 1 IU/dL despite more frequent hemorrhage. The point at which to intervene for PK dosing thus requires further investigation.

To the best of our knowledge, this is the first study to incorporate PK dosing into individualized low-to-moderate-dose prophylaxis. This is not a strictly designed study, however, clinical outcomes were acceptable and the cases in practice can contribute to further studies in this patient population.

The PK-tailored regimen was cost-effective in reducing bleeding, but further studies of this regimen are required.

CONFLICT OF INTEREST

The authors have no conflict of interests related to this article.

REFERENCES

1. Ahlberg A. Haemophilia in Sweden. VII. Incidence, treatment and prophylaxis of arthropathy and other musculo-skeletal manifestations of haemophilia A and B. Acta Orthop Scand Suppl.1965;Suppl 77:3-132.
2. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007;357:535-544.
3. Schrijvers LH, Uitslager N, Schuurmans MJ, Fischer K. Barriers and motivators of adherence to prophylactic

treatment in haemophilia: a systematic review. Haemophilia. 2013;19:355-361.
4. Valentino LA, Mamonov V, Hellmann A, Quon DV, Chybicka A, Schroth P, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. J Thromb Haemost. 2012;10:359-367.
5. Lindvall K, AstermarkJ, BjörkmanS, Ljung R, Carlsson KS, Persson S, et al. Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy. Haemophilia. 2012;18:855-859.
6. Collins PW, Blanchette VS, Fischer K, Björkman S, Oh M, Fritsch S, et al. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. J Thromb Haemost. 2009;7:413-420.
7. Collins PW, Björkman S, Fischer K, Blanchette V, Oh M, Schroth P, et al. Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: influences of variance in pharmacokinetics and treatment regimens. J Thromb Haemost. 2010;8:269-275.
8. Reininger AJ, Chehadeh HE. The principles of PK-tailored prophylaxis. Hamostaseologie. 2013;33 Suppl 1:S32-35.
9. Carlsson M, Berntorp E, Björkman S, Lethagen S, Ljung R. Improved cost-effectiveness by pharmacokinetic dosing of factor VIII in prophylactic treatment of haemophilia A. Haemophilia. 1997;3:96-101.
10. Mizrahi T, St-Louis J, Young NL, Ménard F, Zourikian N, Dubé E, et al. Adherence to treatment regimen and bleeding rates in a prospective cohort of youth and young adults on low-dose daily prophylaxis for severe hemophilia A. BMC Hematol. 2016;16:26.

How to cite this article: Li P, Chen Z, Cheng X, et al. PK-tailored tertiary prophylaxis in patients with severe hemophilia A at Beijing Children's Hospital. Pediatr Invest. 2019;3:45-49. https://doi.org/10.1002/ped4.12122