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Improved clinical outcome after PK-Guided Personalised Prophylaxis with my-PKFIT® in patients with hemophilia A without inhibitors

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ABSTRACT

Objective: Prophylaxis is the gold standard in patients with severe hemophilia. In recent years, personalisation of prophylaxis treatment according to pharmacokinetic properties has been used in treatment. In this study, personalisation treatment experience based on the pharmacokinetic dosing tool my-PKfit results in pediatric and adult patients from three centers is shared.

Material and Methods: myPKfit (www1.mypkfit.com) was used to evaluate pharmacokinetic parameters in hemophilia A patients receiving recombinant Factor VIII (Takeda Advate ®) prophylaxis. 75 samples in 34 patients (3 samples in 7 patients, 2 samples in 27 patients) were analysed for pharmacokinetic evaluation. Age, weight and baseline FVIII level of the patients were recorded. Pharmacokinetic curves were obtained after entering sampling times, factor dose and sample results. The annual bleeding rate (ABR) of the patients were evaluated before and after the changes made after the pharmacokinetic evaluation.

Results: The median age of 34 patients with severe hemophilia A without inhibitors was 12.3±8.7 (1.5-37) years, and the mean weight was 40.0±22.0 (10-83) kg. All patients had a baseline FVIII level of less than or equal to 2 IU/dl. All patients were receiving primary or secondary/tertiary prophylaxis. The mean half-life of the factors of the patients was 9.6±1.4 (7.0-13.4) hours, and the mean time reached below 1 IU/dl was 48.9±11.2 (16.0-77.0) hours. Prophylactic factor therapy was changed in 17 patients after mypk-fit, dose increased in 9 patients, the frequency increased in 6 patients, and both dose and frequency increased in 2 patients. With a mean follow-up period of 23.7 +16 (2-49) months, in 17 patients whose prophylaxis regimen was changed after the PK evaluation by myPkyfit, ABR was found to be significantly lower in the post-change period, compared to the last one year before the change of regimen (2.94 + 2.19 and 0.58 + 1.00 respectively) P: 0.028.

Discussion: A pharmacokinetic study by the Bayesian method is an increasingly used method for personalised prophylaxis regimen. We believe that myPKfit is beneficial in providing effective and appropriate prophylaxis.

Key words: Pharmacokinetic, myPKfit, hemophilia, prophylaxis

Research Article

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INTRODUCTION

In individuals with severe hemophilia, recurrent bleeding episodes in joints causes chronic arthropathy, pain and loss of function. No matter how effective is the treatment after bleeding, bleeding episodes can cause synovial damage to the joint and lead to permanent joint sequelae in long-term. Prophylaxis is the gold standard in the treatment of adults and children with hemophilia (1). Prophylactic treatment is based on the almost absence of joint problems in patients with mild disease and the rare occurrence of permanent joint damage in patients with moderate clinical course. In the 1950s, the concept of prevention of bleeding in hemophilia was first introduced by Nillsson et al. in Sweden and prophylaxis has been widely applied afterwards first in children and then in adults (2).

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The World Federation of Hemophilia (WFH) and the World Health Organization recommend prophylaxis as the "first-line" treatment for the prevention of hemophilic arthropathy in patients with severe hemophilia (3,4). World Federation of Hemophilia Guideline has classified prophylactic therapy in the hemophilia treatment as primary, secondary or tertiary according to the time of initiation of treatment. Currently, it has been shown that the most effective and safe treatment for patients is primary prophylaxis (5). However, there is no single formula on which treatment regimen is most suitable for which patient. Different centers have different approaches regarding the age, dose and frequency of prophylaxis (6). In recent years, there have been publications that "prophylaxis can be individualised" in line with different characteristics such as the patient's age, clinical bleeding characteristics, pharmacokinetic studies, target joint status, activity, lifestyle, and also the availability of the factor. (7-10).

myPKFiT® is a web-based application developed by Baxalta (Shire) (now part of Takeda) as a PK and dose calculator for Advate®. This device helps customise dosage with only 2 blood samples compared to 11 with standard PK sampling (11,12). In this study, we evaluated whether PK-specific prophylaxis is an effective option to reduce bleeding rates in children and adults with severe hemophilia A (HA) without inhibitors.

MATERIAL and METHODS

Thirty-four severe HA (FVIII <2 IU/dl) patients without inhibitors were included from three centers in Istanbul, Turkey. All patients were receiving prophylaxis with Advate®. The mean age of the patients was 12.3±8.7 years (1.5-37). Seventeen patients were on primary prophylaxis, 17 were on secondary/tertiary prophylaxis. myPKfit (www1.mypkfit.com) was used to evaluate pharmacokinetic parameters in patients with hemophilia A receiving Takeda Advate® prophylaxis. No patient had a previous pharmacokinetic study. Age, body weight, baseline FVIII levels, infused FVIII dose, infusion time were collected and loaded onto the myPKFiT medical device. After entering the date and time of collection and the FVIII level (IU) for each sample, the tool estimated the PK profile for each patient.

The target minimum FVIII trough level was chosen as 1 IU/dl because the time spent with FVIII is below 1 IU/dl as shown to be associated with an increased risk of bleeding in patients. After entering the target trough levels, the myPKFiT dosage calculation simulator provided a weekly chart with individual dosing. The suggested individual dosing was discussed with the patient and/or family to plan a new prophylactic regimen.

Annual bleeding rate (ABR) was obtained before and after adjustments according to mypk-fit using patients' clinical data. A total of 75 samples were analysed in 34 patients (3 samples in 7 patients, two samples in 27 patients) for pharmacokinetic evaluation.

Statistical Analyses: Data were calculated as median and interquartile range (25-75 percent) for continuous variables and as percentages for frequency and discrete variables. Comparison of clinical outcomes was made with the Wilcoxon rank test for paired samples, and changes in FVIII consumption were analysed using the student's t test. Significance level was determined as $P < .05$.

RESULTS

Thirty-four patients with severe HA who received regular prophylactic factor therapy (with Takeda Advate ®) from three hemophilia centers in Istanbul, Turkey were included in the study. The mean age of the patients was 12.3±8.7 (1.5-37) years, and mean body weight was 40.0±22.0 (10-83) kg (**table 1**). The prophylaxis doses of the patients were 50.08±13.26 (22-86) units per week, the prophylaxis frequency was every 78.82±23.45 (48-144) hour (between 1-3 per week), and the mean ABR at baseline 2.20+1.88 (10-0) (**table 2**).

A total of 75 blood samples were taken from 34 patients. Mean baseline factor levels were 0.95±1.41 (0-8) IU. The pharmacokinetic profiles of patients were calculated by myPKfit with basal, 4th and 24th hour factor levels and the mean factor VIII dose recommended by the program is 92.88±30.51 (61.5-181.8) unit/kg per week and mean factor prophylaxis frequency was every 50.11±6.90 (48-72) hour (**table 2**, **figure 1,2,3**). The mean half-life of the factors of the patients was 9.6±1.4 (7.0-13.4) hours, and the mean time reached below 1 IU/dl was 48.9±11.2 (16.0-77.0) hours (**table1**).

A change in dose or frequency was recommended in 30 patients in the myPKfit program and no change was recommended in the current prophylactic dose or frequency in 4 patients. Evaluating the clinical status, bleeding frequency and treatment compliance of the patients, the prophylaxis program was changed in 17 of the 30 patients by discussing with patient and/or family. It was determined that frequency increased in 6 patients, frequency and dose increased in 2 patients, only dose increased in 9 patients.

The current prophylaxis program was continued although an increase in frequency was recommended by myPKfit program in 13 patients according to the choice of the treating physician and the patient/family. It was determined that the annual bleeding frequency was low in 10 of these 13 patients, the patient or his parents did not accept the increase in the frequency of prophylaxis in 2 of them,

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and the same prophylaxis regimen was continued in one patient due to vascular access problem. With a mean follow-up period of 23.7 +16 (2-49) months, in 17 patients whose prophylaxis regimen was changed after the PK evaluation by myPkyfit, ABR was found to be significantly lower in the post-change period, compared to the last 1 year before the change of regimen (2.94 + 2.19 and 0.58 + 1.00 respectively) P: 0.028.

Table 1. Demographic characteristics of hemophilia A patients undergoing pharmacokinetic evaluation

Age (years) (Mean ± SS)	12.3±8.7 (1.5-37)
Age to start prophylaxis (years) (Mean ± SS)	4.15±4.48 (0-19)
Annual bleeding rate (Mean ± SS)	2,20±1,88 (10-0)
Target joint development %	23.5
Body weight (kg) (Mean ± SS)	40.0±22.0 (10-83)
Basal FVIII level (IU/dl), (Mean ± SS)	0.95±1.41 (0-8)
Faktör VIII half-life (hour), (Mean ± SS)	9.6±1.4 (7.0-13.4)
The mean time reached below 1 IU/dl (Mean ± SS)	48.9±11.2 (16.0-77.0)

Table-2: Treatment schedule of patients before and after pharmacokinetic evaluation (with myPKfit)

	Before PK evaluation	Recommended by myPKfit	After PK evaluation
Frequency of Prophylaxis Mean ± SS (hours)	78.82±23.45 (48-144)	50.11±6.90 (48-72)	66.35±17.78 (48-144)
Prophylaxis dose Mean ± SS (IU/kg/week)	50.08±13.26 (22-86)	92.88±30.51 (61.5-181.8)	56.56±19.00 (22.00-93.75)

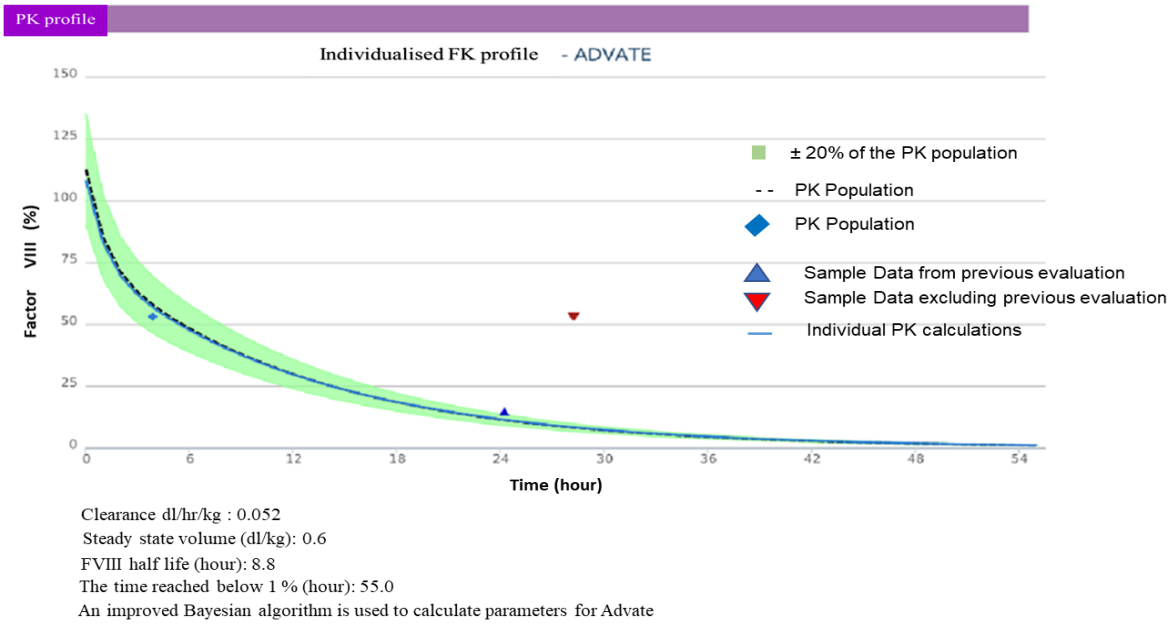

Figure 1: individualised FK profile

1.Week	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Dose (IU)	500 IU		500 IU		500 IU		500 IU
Dose (IU/kg)	43,5 IU/kg		43,5 IU/kg		43,5 IU/kg		43,5 IU/kg
Targeted Trough Value Above Baseline Level	1,4 %		1,5 %		1,5 %		1,5 %
Time Above Factor VIII % 10	23 hours		23 hours		23 hours		23 hours
Time Below Factor VIII % 5	16 hours		16 hours		16 hours		16 hours
2.Week							
Dose (IU)		500 IU		500 IU		500 IU	
Dose (IU/kg)		43,5 IU/kg		43,5 IU/kg		43,5 IU/kg	
Targeted Trough Value Above Baseline Level		1,5 %		1,5 %		1,5 %	
Time Above Factor VIII % 10		23 hours		23 hours		23 hours	
Time Below Factor VIII % 5		16 hours		16 hours		16 hours	

Figure 2: Individualised FK profile, dose adjustments

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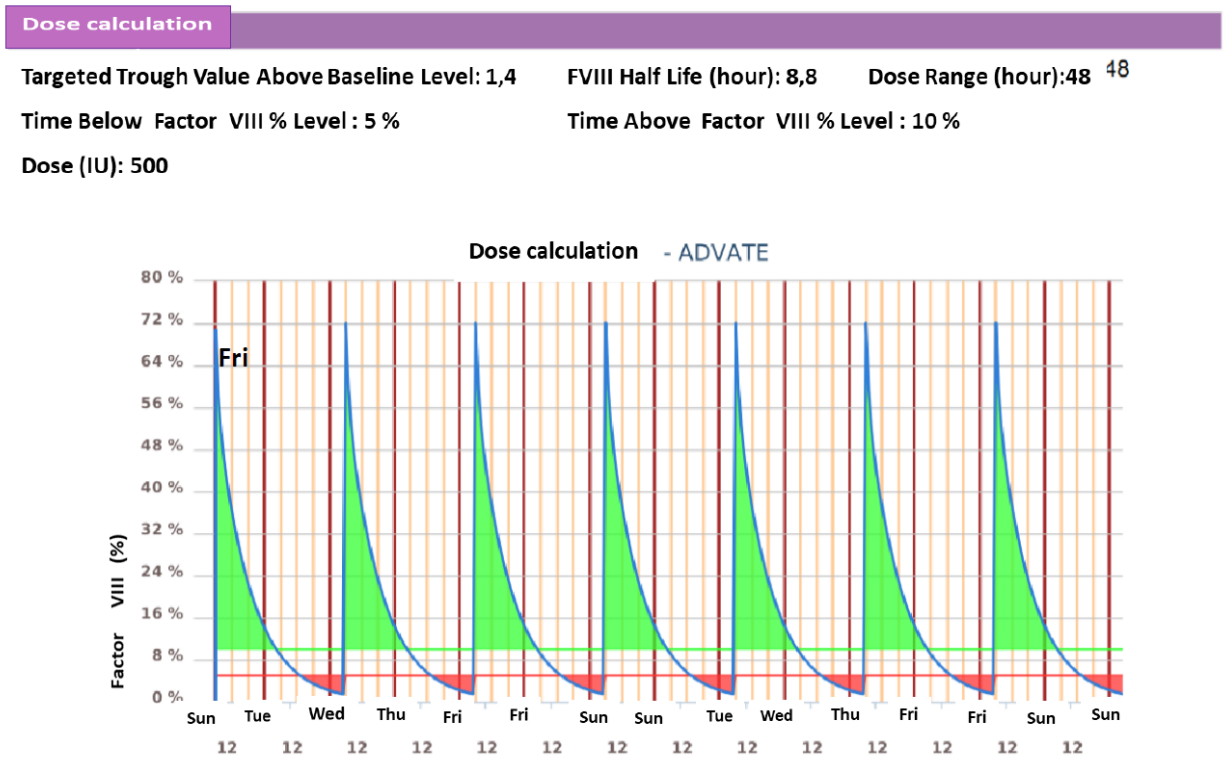

Figure 3: Shema of suggested weekly prophylaxis by myPKFiT® of one of the patients

DISCUSSION

Due to inter-patient variability, the standard dosing of prophylaxis based on body weight may result in over- or under-dosing in prophylaxis haemophilia therapy. Pharmacokinetic study using the Bayesian method is an increasingly popular method for individualisation of treatment in hemophilia (13). The Bayesian approach not only reduces the need for many samples for PK study, but also minimises interindividual variability by including variables such as age, weight, and von Willebrand factor levels in a multivariate model of the patient population. Generally, only two samples are required at 4 to 48 hours after infusion for FVIII products with standard half-life, and even single samples have been evaluated.

myPKFiT and Web-Accessible Population Pharmacokinetics Service-Hemophilia (WAPPS-Hemo) are web-based population-based applications developed to help physicians personalise and optimise their replacement therapy in hemophilia (14). myPKFiT was originally developed for use only with Octocog alfa (Advate, Takeda Pharma), but more recently it has also been used for the pegylated form of this molecule (rurioctocog alfa pegol, Adynovi, Takeda Pharma). WAPPS-Hemo can be used for all available factor concentrate products. Estimated dosing and frequency of administration are provided to achieve specific target levels for each. Implementation of individual pharmacokinetic (PK)-based adaptation may improve treatment guideline adherence and thus clinical outcomes.

Apart from the PK profile, other factors such as bleeding phenotype, musculoskeletal system status are also important in personalising the treatment. The objective and clear information provided by myPKFiT® is useful for discussing the treatment regimen between the healthcare team and the patient or their parents and making changes as needed. In our study, we showed that PK-guided prophylaxis using myPKFiT® resulted in individually improved clinical outcome and optimised FVIII consumption in a study population with a choice of 1 IU/dl trough level. As a result of the PK data obtained with myPKFiT®, half of the patients required modification (frequency and/or dose increase) in the treatment in our study. After this change, a significant reduction in ABR was observed, with an overall beneficial effect on clinical outcomes. The results of our study are consistent with those previously reported. Castellano et al. recruited 36 patients in their study in 3 centers in Spain. (15). Patients' ABR and annual joint bleeding rate were significantly reduced after pharmacokinetic dosing. Adjustment had an impact on most patients' individual FVIII consumption: the annual amount was reduced in 18 cases and increased in 14 cases. In our study, modifications significantly increased total FVIII consumption. A possible cause may be that most patients received insufficient dose and frequency of prophylaxis. A total of 27 patients with severe hemophilia A without inhibitors were included in the study by Alverez et al. (12). A change in prophylaxis was made after a PK

study using mypkfit in 10 patients. The use of mypfit has increased in their center after the study. Our study also increased the number of PK studies in patients treated at our centres, thus providing an objective tool for the recommended adaptation of prophylaxis. We have observed that the graphs obtained by mypk-fit are helpful, especially when discussing prophylaxis regimens with families and patients. In our series, we thought that good clinical outcomes were also associated with better patient compliance. As previously suggested, the graphical output of myPKFiT® is a useful tool for educating patients and their families in the hematology clinic. These data can be used to promote adherence to treatment (16). In this context, resources can help facilitate communication, and our experience of using these tools and applications is that the graphics produced by myPKFiT® are very helpful.

Standard pharmacokinetic (PK) assessments for people with hemophilia A are challenging, requiring a 72 hour washout and 5 to 11 blood samples. With myPKFiT®, PK parameters can be obtained with a small number of blood samples to adapt prophylaxis regimens as suggested by previous studies and the user manual (17,18). Blanchette et al. compared PK parameters in people with severe hemophilia A receiving Advate® obtained with a conventional washout, 6-sampling time-point PK protocol and a protocol without wash, only single clinic visit and 2 samples (19). A total of 39 inhibitor-negative males (factor VIII activity [FVIII:C] <2%) were enrolled in PK study. As a result, it has been shown that the two methods give similar results. In our study, only two blood samples were sufficient in the majority of patients.

We did not perform a pharmacoeconomic evaluation in this study, but other authors have reported a cost reduction associated with PK evaluation. Pasca et al. performed PK evaluations of 14 patients. (20). The weekly infusion frequency was decreased in three severe patients, increased in four patients, and remained the same in the other five patients. It was shown that the annual concentrate consumption decreased in 81.8% of the patients. A subsequent economic evaluation of each of the twelve patients with severe hemophilia A included in this analysis comparing standard and PK-guided prophylaxis showed that an optimised treatment could result in an average annual savings of €20.525 (-%15,8). The main goal of hemophilia treatment is to combine efficacy, safety, improvement in quality of life and cost savings. Cost savings are especially important in developing and middle-developed countries. WHEN pharmacoeconomic calculations are made, it is necessary to consider not only the amount of factor use, but also other factors such as absence from work or school due to bleeding or joint problems, surgical and/or arthroscopic interventions, hospitalisation and hospital visits. Many additional costs will be reduced by effective prophylaxis and reduction of bleeding. For these reasons, we consider our results to be even more important.

Our results may reflect real life experience as they are demonstrated by clinical experiences in three different large tertiary hospitals in Istanbul. Despite the small number of patients and only 1 year follow-up, we believe that this information is useful. Long follow-up clinical results will provide more information on this subject.

CONCLUSION

PK-guided dosing allows physicians to evaluate the FVIII half-life and clearance in patients with severe hemophilia without inhibitors and modify prescribed Advate® prophylaxis to ensure a good patient care. Requirement of only two samples to estimate pharmacokinetic parameters makes it easy to use in routine clinical practice with little inconvenience for patients and caregivers. Our results suggest that pharmacokinetic prophylaxis may be an effective option for reducing bleeding rates for children and adults in severe HA without inhibitor. In addition, we observed that giving the graphical printout to the patients and showing the pharmacokinetic results improved adherence to treatment. Further studies on pharmacoeconomic evaluation based on these results may guide us on factor consumption, especially in countries with limited resources.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. The Ethics Committee of the Cemil Tasçıoğlu City Hospital approved the study.

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