

ORIGINAL ARTICLE

Extended half-life factor VIII concentrates in adults with hemophilia A: Comparative pharmacokinetics of two products

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Abstract

Background: The use of pharmacokinetic (PK) studies to help design personalized prophylaxis regimens for factor VIII (FVIII) concentrate in individuals with hemophilia A has been recognized for many years but only became practical for routine clinical use with the availability of web-accessible population PK applications based on Bayesian analysis.

Objective: To compare PK variables using population PK studies done on 2 extended half-life recombinant FVIII concentrates in 23 individuals with hemophilia A after switching from one product to the other.

Methods: We retrospectively analyzed PK parameters derived from the Web-Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-HEMO) application on 23 individuals with severe or moderately severe hemophilia A who were required to switch from recombinant FVIII Fc (Eloctate; Biogen, Cambridge, MA, USA) to recombinant antihemophilic factor PEGylated (Adynovate; Takeda Pharmaceutical Company, Osaka, Japan) between 2016 and 2017.

Results: There were minor PK differences between Eloctate and Adynovate, but some parameters did reach statistical significance, namely in vivo recovery (mean, 2.73 IU/dL per IU/kg vs 2.41 IU/dL per IU/kg), clearance (mean, 0.163 mL/h vs 0.194 mL/h), and volume of distribution at steady state (mean, 42.5 mL/kg vs 49.8 mL/kg). Smaller nonsignificant trends toward higher values for Adynovate were seen in terminal half-life, area under the curve, and predicted times to 5% and 1% residual FVIII after infusion.

Conclusion: Population PK analysis revealed differences between the two extended half-life FVIII concentrates, reaching significance for in vivo recovery, clearance, and volume of distribution.

KEYWORDS

Bayesian analysis, factor VIII concentrate, hemophilia A, pharmacokinetics, prophylaxis

Essentials

- Different extended half-life factor VIII concentrates display different properties in vivo.
- We studied factor VIII responses in 23 individuals with hemophilia A on two different concentrates.
- We found differences in some of the measured outcomes, but these were minor in degree.
- Switching between these two concentrates did not compromise hemophilia care.

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1 | INTRODUCTION

The principle of prophylaxis in hemophilia replacement therapy is that the regular administration of factor concentrate in nonbleeding patients can prevent repeated hemarthroses and the crippling damage resulting from them. This strategy was pioneered by Swedish investigators in the 1960s.¹ Prophylaxis has been universally accepted as the optimal clinical practice for severely affected and selected nonseverely affected individuals with hemophilia. The variables that can be adjusted in prescribing prophylaxis regimens in hemophilia A are the choice of factor VIII (FVIII) product, the dosage of the FVIII concentrate, and the dosing interval. To design prophylaxis regimens, practitioners traditionally relied solely on the patient's body weight and knowledge of the published pharmacokinetic (PK) parameters for the clotting factor concentrate of interest. However, published values conducted to demonstrate bioequivalence derived from PK studies or from phase 3 clinical trials, may not be appropriate for an individual patient. Bjorkman and colleagues demonstrated substantial interindividual variation in PK parameters of FVIII concentrate in individuals with hemophilia A, with terminal half-lives ranging from 6 to 25 hours.^{2,3} The PK of factor VIII is influenced by body weight, age, von Willebrand factor concentration, and ABO blood group.⁴⁻⁶

Given this degree of interindividual variability, tailored prophylaxis regimens based on personalized PK parameters are theoretically preferable approaches to optimize efficacy, efficiency, and acceptability of clotting factor replacement therapy. Traditional PK studies are impractical for routine clinical use because of the requirement for multiple blood samples taken over several days and the need for washout before performing the study. However, the recent advent of population PK calculators based on Bayesian analysis has made it practical to perform individual PK studies of factor concentrates in individuals with hemophilia. Web-Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-HEMO), developed at McMaster University, is a web-based population PK application that can be used for many of the commercial FVIII (and factor IX) concentrates used around the world.^{7,8} Guidance for the use of online applications such as WAPPS-HEMO has been provided by the Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) on Factor VIII, Factor IX, and Rare Coagulation Disorders.^{9,10}

We used the WAPPS-HEMO application to compare several variables from PK studies performed in a cohort of patients from a single adult Canadian hemophilia treatment center (HTC) before and after a nationally mandated product switch from one extended half-life FVIII concentrate, recombinant FVIII Fc (Eloctate; Biogen, Cambridge, MA, USA) to another, recombinant antihemophilic factor PEGylated (Adynovate; Takeda Pharmaceutical Company, Osaka, Japan).

2 | METHODS

Population PK studies were performed between August 2016 and June 2017 on patients in our HTC who were using Eloctate FVIII

concentrate in varying prophylaxis schedules. The studies were done to help individualize their prophylaxis regimens. The dose of Eloctate, timing of blood sampling, and number of samples for conducting the PK studies were not prescribed. Because of the results of a national tender, all these patients were required to switch to an alternative factor VIII concentrate in 2018. The majority switched to Adynovate, as it was the only available extended half-life option available in Canada at the time. The patients reported here are those who then had another PK study, again done to optimize clinical management, and again with the same variability in conduct of the study.

Factor VIII infusions and blood sampling for all PK studies were performed in our hemophilia clinic by one of our hemophilia nurses. The factor VIII concentrates were all in date and were reconstituted immediately before infusion. For all PK studies, FVIII was measured in the special coagulation laboratory at St. Michael's hospital, Toronto, Canada, by one-stage assay using the HemosIL SynthASil activated partial thromboplastin time reagent (Instrumentation Laboratory, Bedford, MA, USA) with FVIII-deficient plasma (Precision BioLogic, Bethesda, MD, USA) on the ACL TOP 700 instrument (Werfen, Barcelona, Spain). The assay methodology did not change over the time of the study. All PK analyses were calculated by the WAPPS-HEMO program. The PK parameters reported herein are terminal half-life ($t_{1/2}$), clearance (CL), volume of distribution at steady state (V_{ss}), area under the curve (AUC), and predicted time from infusion until factor VIII activity of 5 and 1 IU/dL. AUC and times to 5% and 1% FVIII were calculated based on infusions of 30 IU/kg Eloctate or Adynovate. All PK variables were reported by the WAPPS-HEMO program except for in vivo recovery (IVR) of FVIII, which was calculated as the increment in FVIII activity in IU/dL per IU/kg infused, based on peak FVIII levels drawn at a mean of 14.6 min (Eloctate) and 21.9 min (Adynovate) after infusion. Descriptive statistics were used (mean, median, standard deviation and range, confidence intervals). Paired *t* tests were used to compare PK variables between the two studies.

3 | RESULTS

Twenty of the 23 individuals have severe hemophilia A with baseline endogenous FVIII level < 1% by the one-stage assay. The other 3 have moderately severe disease, with historical baseline FVIII measured at 2%. Three of the individuals with severe hemophilia A have a history of a FVIII inhibitor (two in childhood, one as a young adult); all responded to immune tolerance induction and have subsequently had no detectable inhibitor activity by Bethesda assay. PK studies were done on all individuals while they were using Eloctate and repeated after they had switched to Adynovate. Their ages ranged from 19 to 64 (median, 35) at the time of the Eloctate PK study, and 21 to 66 (median, 37) at the time of the Adynovate PK study. The number of samples taken after infusion of the FVIII concentrates varied from two to five, with the last samples drawn at means of 24.8 h \pm SD 14.3 (Eloctate) and 37.8 h \pm SD 17.5 (Adynovate) following infusion. For

the time to 1% data, the number of analyzable patients is only 21, as baseline FVIII levels in the other 2 patients exceed 1%.

Table 1 shows the ages of the individuals at the time of the sequential PK studies, and the minor change in weight over the interval. As these were all adults, their height was assumed to have been stable. Because this was an observational study, the number of samples and sampling times for the PK studies varied. These are also shown in the table.

Overall results are shown in Table 2. Adynovate showed significantly greater IVR, less rapid clearance, and smaller V_{ss} than Eloctate. The mean IVR was 2.73 IU/dL per IU/kg for Adynovate and 2.41 for Eloctate; 17 of the 23 individuals (74%) had greater recovery of Adynovate, and the mean difference of -0.32 represented a 13.3% increase after switching from Eloctate. The mean values for clearance were 0.194 dL/h for Eloctate and 0.163 dL/h for Adynovate; clearance was more rapid for Eloctate in 14 individuals and for Adynovate in 9. The mean difference of 0.031 dL/h represented a reduction of 16% after switching to Adynovate. The mean values for V_{ss} were 49.8 mL/kg for Eloctate and 42.5 mL/kg for Adynovate; V_{ss} was greater for Eloctate in 19 of the 23 individuals (83%), and the mean difference of 7.24 mL/kg represented a 14.5% reduction after the switch to Adynovate.

The differences between the two FVIII concentrates in $t_{1/2}$, AUC, and predicted times to 5% and 1% residual FVIII after infusion showed nonsignificant trends toward higher values for Adynovate. The confidence intervals for mean differences for all these variables crossed zero.

The individual results for these variables are shown in Figure 1A-G, in which values for Adynovate are plotted on the X-axis and those for Eloctate on the Y-axis.

Two of the individuals infused FVIII on demand, and the remaining 21 were on prophylactic regimens. Sixteen of these 21 remained on the same regimen (in varying dosages and schedules) after switching from Eloctate to Adynovate. In 5 individuals, we recommended changes in the regimens within 1 year of switching. In 4 of them, the FVIII dose was increased by an average of 34% without a change in infusion frequency; in the fifth individual, we increased the dosage but decreased the frequency of infusion, such that the total FVIII dose was unchanged. These adjustments were based on breakthrough bleeding frequency rather than PK results. In fact, in 4 of the 5 individuals, the average PK parameters were superior on Adynovate. The average values for Eloctate and Adynovate, respectively, were 15.7 hours and 16.9 hours for $t_{1/2}$; 1,312 IU.h/dL and 1,670 IU.h/dL for AUC; 55.9 hours and 64.0 hours for time to 5%.

TABLE 1 Patient and methodological differences in PK studies

	Eloctate	Adynovate
Age, y, median (IQR)	36.0 (19.54)	38.0 (19.45)
Weight, kg, median (IQR)	83 (29)	80 (31)
Sample number, mean (min, max)	4.3 (3, 6)	2.7 (2, 3)
Last sample in h, mean (min, max)	23.4 (4, 56)	37.0 (4, 73)

Abbreviations: IQR, interquartile range; PK, pharmacokinetic.

TABLE 2 Values from PK studies done on 23 patients for Adynovate and Eloctate (calculated by WAPPS-HEMO)

	Adynovate Median/mean (range)	Eloctate Median/mean (range)	P value for difference	Mean difference ^a (SD)	CI of difference (lower/upper)
Terminal half-life, h	16.8/16.6 (10.9-22.9)	15.7/16.3 (6.0-26.4)	.60	0.33 (2.97)	-0.95, 1.61
In vivo recovery (IU/dL per IU/kg)	2.61/2.73 (1.84-4.24)	2.36/2.41 (1.34-0.400)	0.01	0.32 (0.56)	0.08, 0.57
AUC (IU.h/dL)	1,716/1,677 (1,031-2,423)	1,477/1,513 (489-3,085)	0.09	157.3 (437.6)	-27.5, 342.1
Time to 1%, h	128.9/119.5 (79.6-164.6)	117.1/118.8 (40.9-193.5)	0.90	0.7 (26.1)	-10.4, 11.7
Time to 5%, hr	69.4/65.6 (43.0-91.9)	62.8/63.7 (21.8-109.8)	0.56	1.8 (15.0)	-4.5, 8.2
CL (dL/h)	0.142/0.163 (0.099-0.248)	0.187/0.194 (0.098-0.417)	0.03	-0.031 (0.061)	-0.004, -0.057
V_{ss} (mL/kg)	44.5/42.5 (28.8-51.4)	50.2/49.8 (35.8-69.1)	0.00	-7.24 (7.68)	-10.55, -3.93

Abbreviations: AUC, area under the curve; CI, confidence interval; CL, clearance; PK, pharmacokinetics; SD, standard deviation; V_{ss} , volume of distribution at steady state; WAPPS-HEMO, Web-Accessible Population Pharmacokinetic Service-Hemophilia.

^aAdynovate minus Eloctate.

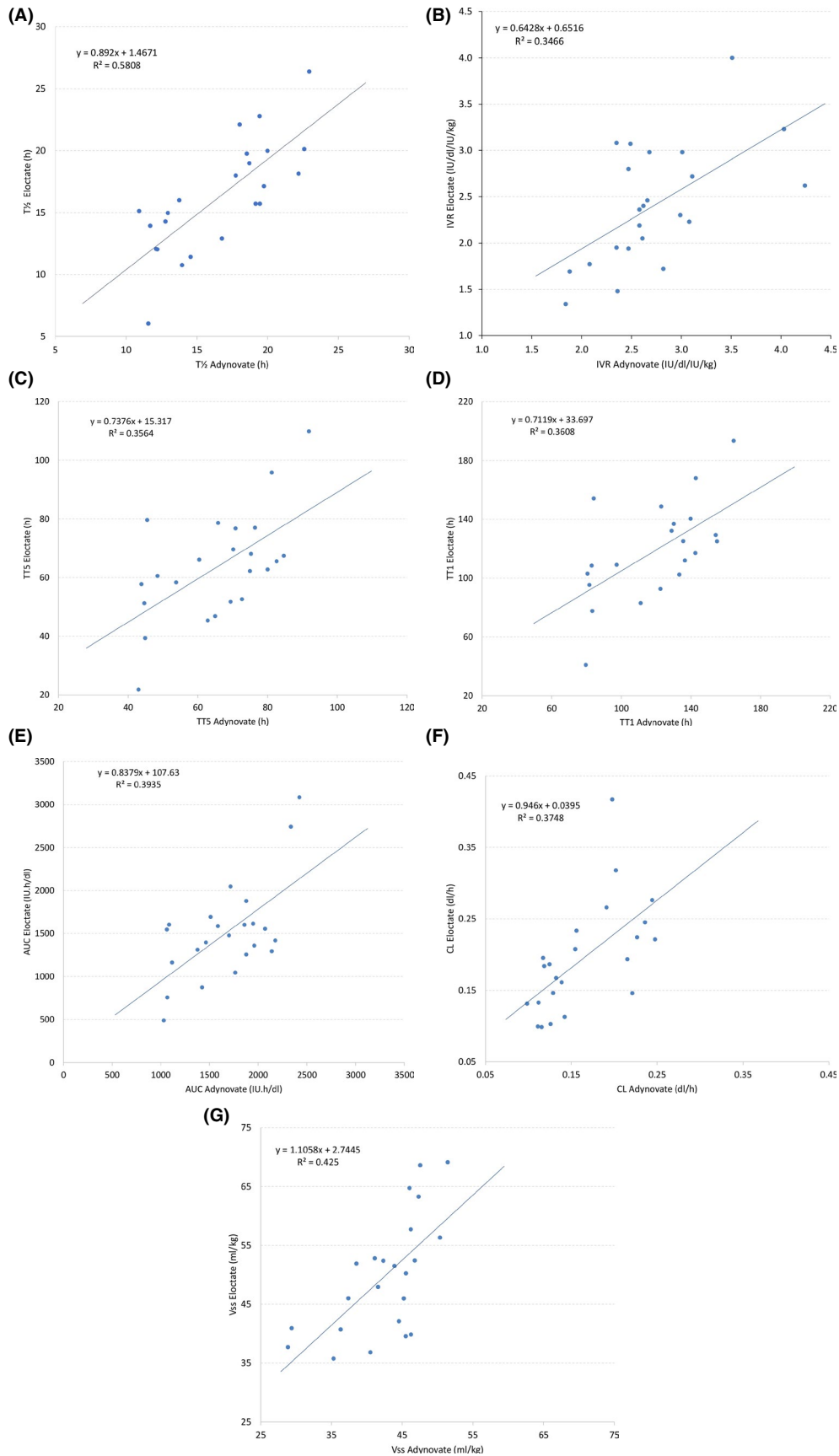


FIGURE 1 Individual patient values (filled circles) and regression lines for PK variables for Eloctate and Adynovate. Regression formulas are shown as inserts. (A) half-life ($t_{1/2}$); (B) in vivo recovery (IVR); (C) time to 5% FVIII; (D) time to 1% FVIII; (E) area under the curve (AUC); (F) clearance (CL); (G) volume of distribution at steady state (V_{ss})

4 | DISCUSSION

The value of PK as a strategy to achieve greater individualization of prophylaxis regimens was demonstrated in the 1990s, in a crossover study of 21 individuals with hemophilia A treated prophylactically for successive 6-month intervals with standard FVIII dosing (25-40 IU/kg three times per week) followed by dosing guided by conventional PK studies.¹¹ During the PK-guided interval, alternate-day dosing was given to target trough FVIII levels of approximately 1%. Measured trough levels were higher during PK-guided dosing despite a significant reduction in FVIII consumption. Breakthrough bleeding rates were similar during both treatment periods. However, the use of conventional PK studies to achieve tailored replacement regimens found limited clinical applicability. These studies require that multiple blood samples be taken over prolonged intervals,¹² which is often impractical outside of research settings; furthermore, the need for washout before administering the FVIII concentrate may put severely affected individuals at undue risk of bleeding.

Bjorkman showed that these limitations could be largely avoided with the use of population PK studies created using Bayesian analysis, which require only limited numbers of blood samples and no washout period.¹³ In these models, covariates are identified that explain interindividual variability, and precision is further improved as patient numbers are enriched. Bjorkman et al showed that three samples taken between 4 and 48 hours after FVIII infusion gave PK values almost indistinguishable from conventional PK studies, and even a single blood sample taken 24 hours after infusion led to prophylaxis protocols superior to regimens based on body weight alone.¹³ A further benefit is that once models are constructed, sampling times are flexible, greatly increasing convenience for both patients and health care workers. The benefits and limitations of PK-guided prophylaxis in hemophilia have been recently reviewed.¹⁴ WAPPS-HEMO has become a widely accepted web-based population PK application, based on its easy accessibility and its applicability to a wide range of plasma-derived and recombinant FVIII and factor IX concentrates.⁷ Another web-based population PK application, MyPKfit, is applicable to only two FVIII concentrates, Advate and Adynovate.¹⁵

The utility of personalized PK was shown in a small Spanish study of 21 individuals with hemophilia A treated with Advate, in which the adoption of PK-guided prophylactic regimens using MyPKfit led to a tendency to fewer spontaneous bleeds, and abolished the highly significant correlation between individual half-life values and joint bleeds that had existed in the retrospective period before implementation of PK guidance.¹⁶ Overall median FVIII consumption increased modestly by 4.4% in the year following PK-guided therapy compared to the year before.

Comparative assessments of clotting factor concentrates have been done using various population PK calculators. Preijers et al¹⁷ derived a PK model from data from published PK studies using NONMEM software (ICON plc, Dublin, Ireland), and compared its predictions to those derived from the WAPPS-Hemo and MyPKfit portals. For 30 individuals with hemophilia A treated with Advate, among other parameters the half-life as determined

by WAPPS-HEMO was shorter than as determined by NONMEM (median, 11.2 hours vs 13.0 hours; $P < .001$). In this study, MyPKfit did not provide PK estimates for 6 of the individuals treated with Advate, as their FVIII measurements were outside the limits of prediction of the population model. For the remaining 24 individuals, the median half-life estimate was 12.6 hours, shorter than the 30 hours predicted by NONMEM ($P < .001$).

Gringeri et al¹⁸ used two independent population PK models that were derived using different covariates to estimate PK parameters in individuals treated with an extended half-life FVIII concentrate, recombinant FVIII Fc (Eloctate), and a standard half-life product, recombinant antihemophilic factor PEGylated (Advate). Applying these models to simulated populations of 1000 severe individuals with hemophilia A, they compared predicted percentages of time spent above specified FVIII plasma levels when treated with various prophylactic infusion schedules.

As biopharmaceuticals, FVIII concentrates may be biosimilar, but they are not bioequivalent.¹⁹ Several hemophilia studies have demonstrated that when individuals switch from one factor concentrate to another, the average PK parameters can be similar, but individuals can have very different concentration-time profiles on the two products.¹⁹⁻²¹ Yu et al¹⁹ reviewed WAPPS-HEMO data through late 2018 for individuals who switched products, and noted the lack of evidence for longer FVIII half-lives on products labeled as extended half-life concentrates as compared to standard half-life concentrates. The ISTH Subcommittee on factor VIII and factor IX recommended that a population PK study using an application such as WAPPS-HEMO be done after switching individuals from standard to extended-half-life factor concentrates.¹⁰ Our data showed only limited intraindividual correlation of PK parameters over the two studies (Figure 1A-G), emphasizing that it is equally important to repeat PK studies after switching between extended half-life products. This intraindividual variability is not surprising given the structural differences of Eloctate and Adynovate, which emphasize the lack of bioequivalence of the two products, both of which are described as "extended half-life FVIII." Eloctate is a B domain-deleted FVIII produced in a human cell line (human embryonic kidney) and modified by the fusion of the IgG Fc domain to the C-terminal C2 domain of the FVIII. Adynovate is a full-length FVIII generated in a hamster cell line (Chinese hamster ovary) with one or more 20-kDa branched polyethylene glycol molecules linked to amino acids in the FVIII B domain.

Carcao and colleagues²² reported population PK values calculated by WAPPS-Hemo for a cohort of adolescents aged 12-18 years with severe hemophilia A who made the same product switch as our patients, from Eloctate to Adynovate, after the tender process in Canada. They used the same blood sampling schedule for all 23 evaluable individuals, approximately 3, 24, 48, and 72 hours after FVIII infusion. The mean terminal half-lives were very similar for the two concentrates when FVIII was measured by one-stage assay, 16.1 hour for Eloctate and 16.7 h for Adynovate. These are very similar to the mean half-lives that we report herein for a similar number of adults, 16.3 and 16.6 hours. However, when they measured FVIII by a chromogenic

assay the mean half-life was significantly shorter for Adynovate, at 16 hours compared to 18 hours for Eloctate ($P < .001$). They found considerable interindividual variability, with roughly equal numbers having slightly better PK variables with one or the other FVIII concentrate. Our results were again similar, with 12 of the 23 patients having longer half-lives for Adynovate and 11 for Eloctate.

We found only minor differences in PK parameters, which nevertheless did achieve conventional levels of statistical significance differences for clearance, V_{ss} , and IVR. We do not feel that these minor differences have practical relevance, although given the nature of the study we are unable to analyze clinical responses. When calculated using the chromogenic assay, Carcao and colleagues²³ also found significant differences in V_{ss} and IVR. Although we did not perform chromogenic assays as part of this study, we have found that the two assays yield essentially identical results when applied to our patients with severe hemophilia A (unpublished). Overall, the discrepancies between our results and those of Carcao et al were only minor. The prospective methodology of their study, with fixed doses and sampling times for PK studies, was an important difference between the two studies. Another major source of differences between the studies is the age of the patients, which has important effects on FVIII PK. The patients in their study were adolescents between ages 12 and 18; ours were adults, age 19 and over at the time of the first PK study. Given the small sizes of both our studies, it is also possible that distributions of ABO blood groups and von Willebrand factor concentration were sufficiently different to affect the results.

Shah et al²⁴ compared PK characteristics of Eloctate to another extended half-life FVIII concentrate, BAY 94 (Jivi; Bayer LLC, Leverkusen, Germany) in a randomized crossover study in 18 adults with severe hemophilia A. PK was calculated using non-compartmental analysis (WinNonlin software; Certara, Princeton, NJ, USA) with FVIII measured by one-stage assay on 12 samples collected out to 120 hours after infusion of the concentrates. They found significant differences for AUC, CL, IVR, and $t_{1/2}$. The difference in V_{ss} just failed to reach statistical significance. They also used these PK profiles to derive a one-compartment population PK model for BAY 94 and a two-compartment PK model for Eloctate, using NONMEM software.

Clinical implications of the PK studies are uncertain. Although we did recommend changes in prophylaxis in five individuals after switching to Adynovate (to more intensive regimens in four of them), this was based on reported breakthrough bleeding rather than on PK results. In fact, on average, the PK parameters were better on Adynovate than on Eloctate (only one of them had a longer $t_{1/2}$ and time to 5% on Eloctate). The occurrence of reported bleeds in these few patients should not be taken as evidence of differences in product efficacy, for several reasons. Breakthrough bleeds are self-reported events, based on symptoms that can be difficult to distinguish from synovitis and arthritic pain in individuals who have chronic hemophilic arthropathy. In addition, bleeds were variably reported as spontaneous or provoked, and most often occurred in target joints. Furthermore, we are reporting our prescribed prophylaxis regimens, and in a "real-world" setting such as this, patients may not have been

completely adherent to our recommendations. Analysis of bleeding rates of the entire cohort would have provided added value, but given the retrospective design we believe that the bleed data recorded in our patients' treatment diaries are insufficiently complete and informative to allow us to provide reliable estimates.

Our study has several limitations. The patient numbers were relatively small, and represented only those in whom we were able to perform PK studies on both treatment products. The sequence of PK (Eloctate first) was not random but was a function of the mandated product switch. The doses of the concentrates were not fixed, nor were the sampling times. Although our FVIII assay methodology did not change over the course of the study, we cannot exclude the possibility of minor systematic differences related to different lot numbers of commercial reagents. In addition, we calculated PK values based on the FVIII unitage provided by the manufacturers. We did not assay the factor concentrates to validate the actual FVIII content.

In summary, we found slightly higher AUC, longer times to 5% and 1% FVIII, and reduced clearance for Adynovate than for Eloctate, but none of these variables reached statistical significance, nor do we consider them to have major clinical significance. Differences in IVR, clearance and V_{ss} did achieve significance, which was not unexpected, given that the polyethylene glycol moiety bound to the Adynovate molecule effectively increases its molecular size. The magnitude of the PK differences between the two extended-half-life FVIII concentrates were not great, and we were reassured that, at least based on observed and predicted FVIII levels, the efficacy of our patients' prophylactic management was not compromised by the mandated product switch. Our observations also emphasize the value of population PK analyses, and they provide insight into the PK characteristics of extended-half-life FVIII concentrates in adults with hemophilia A in a real-world setting.

RELATIONSHIP DISCLOSURE

JT has served on advisory boards for Takeda. MS has received grant and personal support from Takeda. AI has received grant support from Sanofi and Takeda.

AUTHOR CONTRIBUTIONS

JT conceived the study, analyzed the data, and drafted the manuscript. AI performed the PK calculations and assisted in analyzing the data and editing the manuscript. MS assisted in analyzing the data and editing the manuscript.

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