Original article

Pharmacokinetics of recombinant factor VIII among pediatric patients with hemophilia A, a multicenter study in Thailand

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Abstract:

Background: *Recombinant FVIII (rFVIII), the synthetic recombinant antihemophilic factor VIII, was developed due to concern of adverse effects of plasma derived products. In Thailand, the number of children with hemophilia A (HA) treated with rFVIII has gradually increased. However, related pharmacokinetic studies on rFVIII are mostly conducted among adults and few studies in a Thai pediatric population.* ***Objectives:*** *This study aimed to evaluate the pharmacokinetic parameters of standard half-life (SHL) rFVIII and identify the correlation between pharmacokinetic parameters and baseline characteristics among children with HA.* ***Methods:*** *A prospective multicenter cohort study was conducted. Pediatric patients with severe HA treated at King Chulalongkorn Memorial Hospital, Prapokklao and Sawanpracharak Hospitals were enrolled. Factor VIII activity was measured by validated one stage clotting assay before and at 0.25, 0.5, 1, 12 and 24 hours after a single dose of Recombinate® infusion (50±5 units per kilogram).* ***Results****: Thirteen patients with severe HA treated and had regular follow-up were enrolled. Pharmacokinetic parameters revealed mean percentage of maximum FVIII of 84.55 U/dL, volume of distribution of 66.35 mL/kg, half-life of 8.53 hours, clearance of 5.49 mL/hr/kg, AUC_{0-24} of 777.93 U.hr/dL and AUC of 928.01 U.hr/dL. The results showed statistically significant correlation between dose per kilogram and maximum concentration (p-value = 0.002). We also observed the trend of dose per kilogram and AUC_{0-24} correlation (p-value = 0.057).* ***Conclusion****: Our study reported concerning the pharmacokinetic parameters of recombinant FVIII in a Thai pediatric population and also showed variation among different studies.*

Keywords : ● *Pharmacokinetic* ● *Pediatric* ● *Hemophilia* ● *Recombinant factor VIII*

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นิพนธ์ต้นฉบับ

เภสัชจลนศาสตร์ของแฟคเตอร์แปดที่ได้มาจากการสังเคราะห์โดยเทคโนโลยีรีคอมบิแนนท์ในผู้ป่วยเด็กที่เป็นโรคฮีโมฟีเลีย เอ, การศึกษาแบบหลายสถาบันในประเทศไทย

นลิตา ดีพิจารย์[1,2] ปาจรีย์ จริยวิลาศกุล[3,4] ปกป้อง ณ สงขลา[5] กิตติมา กาญจนกำแหง[6] และ ดารินทร์ ซอโสตถิกุล[1,2]

[1]สาขาวิชาโลหิตวิทยาและมะเร็งเด็ก ภาควิชากุมารเวชศาสตร์ [2]หน่วยปฏิบัติการวิจัยเพื่อการบูรณาการและนวัตกรรมทางโลหิตวิทยาและมะเร็งเด็ก [3]หน่วยปฏิบัติการวิจัยเภสัชจลนศาสตร์คลินิก [4]ฝ่ายเภสัชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย [5]กลุ่มงานกุมารเวชกรรม โรงพยาบาลสวรรค์ประชารักษ์ นครสวรรค์ [6]กลุ่มงานกุมารเวชกรรม โรงพยาบาลพระปกเกล้า จันทบุรี

บทคัดย่อ

บทนำ *แฟคเตอร์แปดที่ได้มาจากการสังเคราะห์โดยเทคโนโลยีรีคอมบิแนนท์ (rFVIII) ถูกสร้างขึ้นมาเพื่อลดผลข้างเคียงที่เกิดจากการให้ผลิตพันธุ์ที่ผลิตจากพลาสมาซึ่งผู้ป่วยเด็กฮีโมฟีเลียเอในประเทศไทยมีการใช้ rFVIII เพื่อรักษามากขึ้น อย่างไรก็ตามการศึกษาเกี่ยวกับเภสัชจลนศาสตร์ของ rFVIII ส่วนใหญ่เป็นการศึกษาในผู้ใหญ่ และมีการศึกษาน้อยมากที่ทำในเด็กไทย* ***วัตถุประสงค์*** *เพื่อศึกษาเภสัชจลนศาสตร์ของ standard half-life (SHL) rFVIII และหาความสัมพันธ์ของค่าทางเภสัชจลศาสตร์กับลักษณะพื้นฐานของผู้ป่วยเด็กฮีโมฟีเลีย เอ* ***วิธีการศึกษา*** *การศึกษาไปข้างหน้าโดยศึกษาในหลายสถาบัน ผู้ป่วยที่เข้าร่วมการศึกษาคือ เด็กฮีโมฟีเลียเอ ชนิดรุนแรงที่เข้ารับรักษาที่โรงพยาบาลจุฬาลงกรณ์ โรงพยาบาลพระปกเกล้า และโรงพยาบาลสวรรค์ประชารักษ์ ซึ่งจะได้รับการตรวจระดับแฟคเตอร์แปดก่อนและหลังจากการให้ Recombinate® (50±5 ยูนิตต่อน้ำหนักตัว) ที่ 0.25, 0.5, 1, 12 และ 24 ชั่วโมง* ***ผลการศึกษา*** *เด็กฮีโมฟีเลียเอชนิดรุนแรง13คนที่เข้าร่วมการศึกษา ซึ่งมีค่าทางเภสัชจลนศาสตร์ คือ ค่าเฉลี่ยระดับแฟคเตอร์แปดสูงสุด 84.55 ยูนิต/เดซิลิตร ปริมาตรกระจายตัว 66.35 มิลลิลิตร/กิโลกรัม ค่าครึ่งชีวิต 8.53 ชั่วโมง อัตราการกำจัดยา 5.49 มิลลิลิตร/ชั่วโมง/กิโลกรัม AUC_{0-24} 777.93 ยูนิต.ชั่วโมง/เดซิลิตร และ AUC 928.01 ยูนิต.ชั่วโมง/เดซิลิตร จากผลการศึกษายังพบว่าปริมาณ rFVIII ต่อน้ำหนักมีความสัมพันธ์ทางสถิติอย่างมีนัยสำคัญกับระดับแฟคเตอร์แปดสูงสุด (p-value = 0.002) และ AUC_{0-24} (p-value = 0.057)* ***สรุป*** *การศึกษานี้เป็นการศึกษาทางเภสัชจลศาสตร์ของ rFVIII ในเด็กไทย จากผลการศึกษาพบว่ามีความแตกต่างจากการศึกษาก่อนหน้า*

คำสำคัญ : ● *เภสัชจลนศาสตร์* ● *แฟคเตอร์แปดเข้มข้นชนิดเตรียมจากพันธุวิศวกรรม* ● *ผู้ป่วยเด็ก* ● *โรคฮีโมฟีเลียเอ*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2565;32:227-33.

Introduction

Hemophilia A (HA) is an inherited bleeding disorder resulting from the deficiency of Factor VIII (FVIII).[1] Approximately 400,000 people in the world are reported to have HA.[2-3] In Thailand, the key elements in treating hemophilia are to prevent and treat bleeding episodes using synthetic clotting factors. Recombinate® is rFVIII, a synthetic form of recombinant DNA-derived FVIII prepared for clinical use. It has been synthesized from a genetically engineered Chinese hamster ovary cell line to solve the problem of blood-borne infection from plasma-derived clotting factors, especially viral infections caused by the hepatitis virus, human immunodeficiency virus and parvovirus.[1,4-7] Recombinate® has undergone safety studies that have shown no serious side effects and incidence of inhibitor to FVIII development only 11.9% in previously treated patients and 0.123% in previously untreated or minimally treated patients.[8-9] Due to this advantage, treating HA with the Recombinate® has been increasingly used among adults and in pediatric populations.

The recognition of FVIII's pharmacokinetics (PK) is the cornerstone in managing HA cases concerning providing sufficient factor replacement to patients. Unfortunately, the PK data of rFVIII remain limited and have been reported in only a few studies. White et al. reported the PK data of rFVIII in two adult patients. The mean half-lives (T1/2) of rFVIII were 16.1±0.1 hours.[10] Lee et al. studied the PK of rFVIII among patients with HA. T1/2 was 13.1 hours; area under the plasma concentration time curve (AUC) was 7.95; volume of distribution at steady state (Vd) was 60.3 mL/kg and recovery was 131 IU/mL.[11] The PK data of rFVIII among children was studied by Chen et al. Maximal plasma concentration (Cmax) was 102.66±9.94 U/dL; T1/2 was 10.87±0.65 hours and clearance (CL) of 4.69±0.29 mL/hr/kg. Mostly, recent studies showed the PK parameters of rFVIII only in an adult population. Currently, little information is available regarding pediatric patients with HA.[12] We therefore conducted a prospective cohort study to evaluate the PK of rFVIII among Thai pediatric patients diagnosed with severe HA. The second aim was to evaluate PK variability by identifying the correlation between PK parameters and baseline characteristics of patients.

Materials and Methods

The study design constituted a multicenter, prospective cohort. The subjects were enrolled from three hospitals in Thailand, i.e., King Chulalongkorn Memorial Hospital (KCMH), Prapokklao Hospital and Sawanpracharak Hospital.

Inclusion criteria included patients with severe HA with ages ranging between 1 and 20 years treated with Recombinate® and regular follow-up at multicenter hospitals.

Exclusion criteria included patients with HA presenting FVIII inhibitor within six months before being enrolled, having a history of hypersensitivity to Recombinate® or mouse/hamster proteins, or developing all types of bleeding within one month before the test or patients receiving a diagnosis with bleeding diathesis from other medical conditions.

Upon approval by the Institutional Review Board, medical records of the patients were retrospectively reviewed. Clinical information was collected including age, weight (kg), height (cm), body surface area (m^2), blood group and dose per kg of the patients.

Specimen collection

Each patient received a single dose of Recombinate® infusion with the dose of 50±5 units per kg of body weight. Three milliliters of blood was collected before infusion and again at 15 minutes, 30 minutes, 1 hour, 12 hours and 24 hours after infusion. The samples were collected in plastic tubes containing 3.2% sodium citrate and immediately mixed. The collected samples were capped, and transported on ice to the laboratory where plasma was separated and stored at -20°C until the FVIII assay was performed. Samples were stored for not more than one week to assay. All plasma samples were analyzed for FVIII activity using validated one-stage clotting assay, performed on the CS-1600 Sysmex (Fully Automated Coagulation Analyzer) at KCMH laboratories.

Pharmacokinetics analysis

The PK parameters were calculated using noncompartmental analysis for each participant using Microsoft excel and expressed in terms described below.Area under the plasma concentration time curve from 0 to 24 hours post infusion (AUC_{0-24}) computed using the linear trapezoidal rule, area under the plasma concentration-time curve from time 0 to the timepoint of the last measured concentration (AUC_{0-inf}), computed as Cinf/βCinf is the last measured concentration and β is the slope of the terminal portion of the log concentration-time curve.

Total area under the plasma concentration-time curve from time 0 to infinite time (AUC), computed as follows: Total AUC = AUC_{0-24} + AUC_{24-inf}; plasma half-life (T1/2) computed as 2.303log2/k ,Note: k = β *(-2.303); volume of distribution (Vd), computed as Dose/Concentration at time 0; clearance (CL) as determined by k* Vd.

Statistical analysis

This study employed descriptive analysis. Demographic data (age, body weight, height, BMI, weight for height and dose per kilogram of body weight) and PK parameters (Cmax, Vd, T1/2, CL, AUC0-24 and AUC) were statistically calculated using mean and median. The correlation between demographic data and PK parameters was performed using Spearman's rho correlation, and level of significant of *p*-value was below 0.05.

Results

Patient characteristics

In this study, 13 patients with severe HA were enrolled. The median age was 10 years (range between 2 and 20). The mean infusion dose was 49.39 IU/kg (range between 44.11 and 57.69), with no FVIII inhibitor demonstrated among all subjects before rFVIII infusion.

Pharmacokinetic data

The PK results of each patient are shown in Table 1. Our study reported a mean percentage of Cmax of 84.55 U/dL, Vd of 66.35 mL/kg, T1/2 of 8.53 hours, CL of 5.49 mL/hr/kg, AUC_{0-24} of 777.93 U.hr/dL and AUC 928.01 U.hr/dL. Graphic data of FVIII concentration and time among all patients are shown in Figure 1. Semi log graph of FVIII concentration and time are shown in Figure 2.

Table 1 Pharmacokinetic data

Subject No.	Age (years)	BW (kg)	Dose/kg	Cmax (u/dL)	Vd (mL/kg)	$T_{1/2}$ (hr)	Clearance (mL/hr/kg)	AUC_{0-24} (U.hr/dL)	AUC (U.hr/dL)
1	2	13	57.69	96.6	65.00	6.63	6.76	775.82	852.44
2	4	18	46.87	69.9	71.93	11.14	3.94	787.81	1,036.98
3	5	17	44.11	58.8	84.11	10.05	5.76	588.85	734
4	5	16	46.87	90.3	60.37	6.85	6.06	685.28	761.42
5	5	20	50.00	88.1	69.00	6.81	7.00	626.67	693.55
6	10	31	53.57	93.0	75.60	8.19	6.39	684.15	804.79
7	10	20	50.00	78.9	70.95	10.27	4.75	800.03	1,017.91
8	14	45	44.44	72.7	62.00	6.92	6.20	677.51	748.41
9	16	45	44.44	88.7	63.68	9.35	4.71	732.91	904.28
10	19	50	50.00	75.0	67.30	7.67	6.06	744.38	844.09
11	19	63	55.55	112.0	54.66	10.35	3.64	1,192.5	1,521.31
12	20	49	51.02	102.4	52.51	9.78	3.71	1,116.21	1,374.73
13	20	42	47.61	72.8	65.45	6.95	6.50	701.02	770.28
Mean	11.46	33	49.39	84.55	66.35	8.53	5.49	777.93	928.01
SEM	1.89	4.61	1.18	4.1	2.33	0.46	0.33	49.48	70.59

BW: body weight; Cmax: maximum concentration; Vd: volume of distribution; $T_{1/2}$: half-life; AUC_{0-24}: area under the plasma concentration time curve from time 0-24 hours; AUC: total area under the plasma concentration time curve from time 0 to infinite time; SEM: standard error of the mean

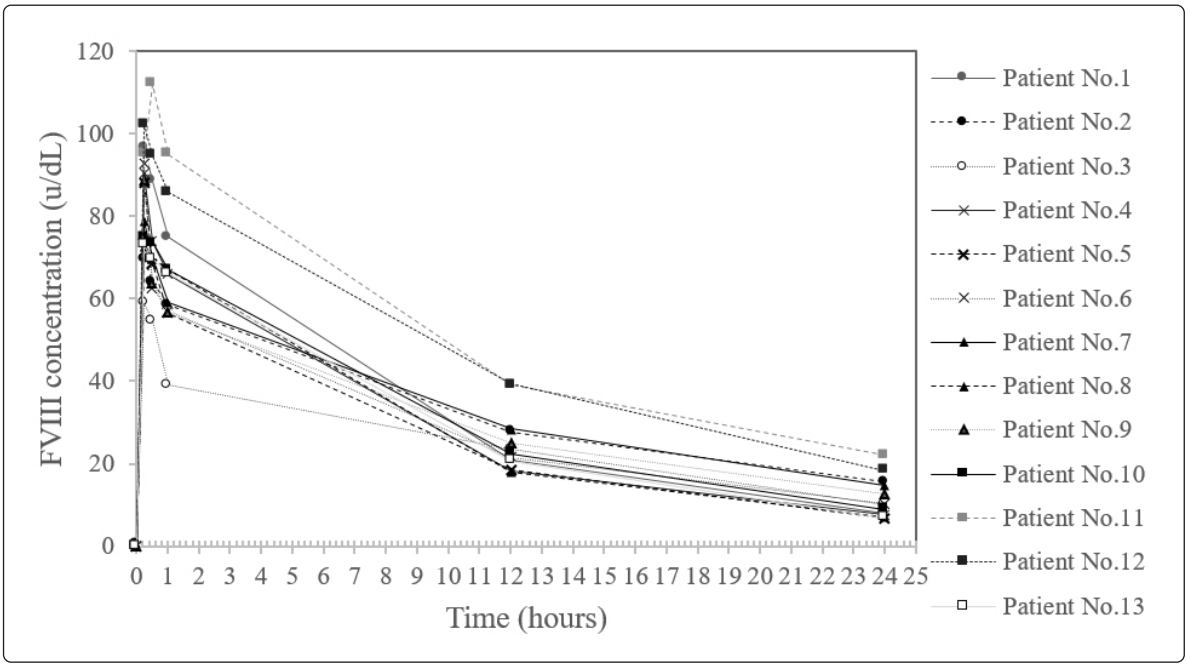

Figure 1 FVIII concentration and time of all patients

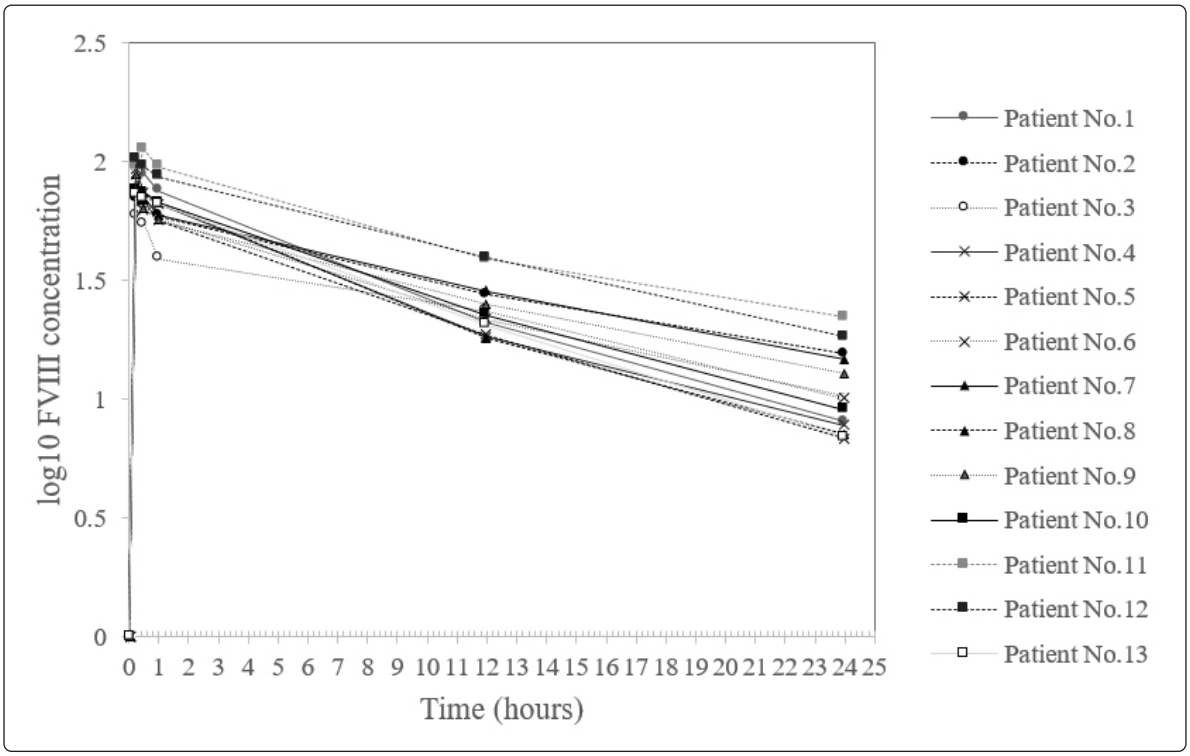

Figure 2 Graphic on semi log graph of FVIII concentration and time of all patients

Pharmacokinetic variability

Interestingly, we observed a correlation between response to rFVIII and some patients' characteristics. Dose per kilogram significantly correlated with Cmax (correlation value 0.765, $p = 0.002$) and tended to correlate with AUC_{0-24} (correlation value 0.540, $p = 0.057$).

Discussion

This study revealed two important findings. First, our study reported the PK data of rFVIII among Thai pediatric patients with HA differing from the adult population. Second, we found a statistically significant correlation between dose per kilogram and Cmax of rFVIII and also observed a trend of dose per kilogram and AUC_{0-24} correlation. Conversely, BMI was not correlated with AUC_{0-24} or Cmax of rFVIII. No studies conducted before our study demonstrated the PK parameters of rFVIII among Thai pediatric patients with HA. The related studies reported PK data among adults and one study reported PK among children. In our study, T1/2 tended to be shorter; in this study T1/2 of rFVIII was 8.53 hr but in related studies of White, et al. among people with severe HA aged 18 and 39 years, mean T1/2 of FVIII was 16.1 hr. The study of Chen, et al., conducted among people with severe HA younger than 18 years, reported that T1/2 of FVIII among patients with pediatric HA was 10.87 hr.).[10,12] Vd was not associated with age, weight for height or blood group. In this study CL increased (CL was 5.49 mL/hr/kg), but related studies of White, et al. showed the CL of rFVIII was 1.9 mL/hr/kg, and the study of Chen, et al., reported the CL of FVIII among pediatric patients with HA was 4.69 mL/hr/kg.[10,12] In contrast, the study results of Chen, et al. found age and blood group O were important predictive factors of factor FVIII T1/2.[12] Because this study was conducted in a Thai pediatric population, genetics and patient's age might be contributing factors underlying the difference in results among these studies. The PK of rFVIII was found to correlate with the dose per kilogram constituting the second interesting point.

Regarding its strengths, this constitutes the first study reporting the PK parameters of rFVIII in a Thai pediatric population. In addition, no patient was lost to follow-up. However, our study encountered limitations due to the small number of participants enrolled. This might explain the statistically insignificant correlation between most of the PK parameters and baseline characteristics. For further studies, we suggest enrolling a larger group of subjects and comparing other rFVIII data. Another limitation was the vWF:Ag was not taken to determine the correlation to the PK of rFVIII. The vWF level may have had an interesting correlation with the PK of rFVIII. In summary, our study reported PK data of rFVIII in a Thai pediatric population and revealed PK variability. We found that the body weight might be a factor contributing to the variation of PK. For clinical application, because of the variable PK of rFVIII, factor level monitoring remains an important tool to evaluate the clinical effects of treatment especially in pediatric populations. The core of treatment should be individualized and tailor-made.[1]

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