

The pharmacology of a new pasteurized antihemophilic factor concentrate derived from human blood plasma

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The pharmacology of a new pasteurized factor VIII (FVIII) concentrate derived from human blood plasma was studied in 23 adults with hemophilia A. In Part 1 of the study involving six nonbleeding subjects, the mean increase in FVIII activity was 1.43 ± 0.34 U per ml 10 minutes after an intravenous dose of 50 U per kg. The intravascular survival kinetics in these six patients showed a biphasic decay curve with an initial mean half-life of 5.1 ± 1.2 hours probably representing early redistribution, and a late half-life of 13.3 ± 4.9 hours. In Part 2 of the study, the activity at 10 minutes was measured in another 17 patients, as well as in one patient already studied in Part 1. The mean increase in activity with the 24 observations was 1.13 ± 0.37 U per ml with a mean FVIII dosage of 51.0 ± 2.6 U per kg of body weight. Only one patient had an allergic reaction, which did not recur when the patient was given a second lot. **TRANSFUSION** 1989;29:208-212.

ANTIHEMOPHILIC FACTOR (factor VIII: FVIII) concentrates became available in the early and middle 1960s.¹⁻⁶ By the early 1970s, the transmission of hepatitis B through these concentrates was evident.⁷ In 1972, Mozen et al.⁸ demonstrated that, during Cohn's cold ethanol fractionation of plasma,^{9,10} hepatitis B virus concentrated more in certain fractions (including that containing FVIII) than in others. By the late 1970s, after donor screening tests for hepatitis B were established, non-A, non-B hepatitis remained the major viral disease transmissible by clotting factor concentrates.¹¹⁻¹³ At about this time, plasma fractionators began exploring various methods of inactivating viruses that might contaminate plasma, including heat and chemical treatments. This research was given added impetus in the 1980s by reports that concentrates also could transmit the agent causing acquired immune deficiency syndrome (AIDS).¹⁴⁻¹⁹

All methods of viral inactivation are not equally effective. Heating dried (lyophilized) concentrate initially appeared to inactivate the human immunodeficiency virus (HIV) fairly well,²⁰⁻²³ but not the viruses responsible for non-A, non-B hepatitis^{22,24,25} or hepatitis B.²² More recently, heating lyophilized products at higher temperatures for longer periods of time seemed more likely to inactivate HIV thoroughly.^{20,26}

Heating concentrates in solution for 10 hours at 60°C (pasteurization) seems to inactivate completely a variety of viral agents, including the viruses of hepatitis A, B, and non-A, non-B, as well as cytomegalovirus, Epstein-Barr virus, and HIV.^{20-22,27-29}

Chemical treatment, which in the United States has been limited to the use of organic solvents and deter-

gents to dissolve viral lipid envelopes, also appears to be highly effective.²²

Given the rigors of the above viral inactivation methods, one may wonder if FVIII that has undergone such treatment is still as effective and has plasma recovery and survival as good as FVIII concentrates not subjected to such steps. Pasteurization is probably the most rigorous of the viral inactivation methods. Hilfenhaus and Weidmann²⁹ reported a mean half-life of 12.1 ± 5.06 hours and a recovery of 74 percent for a pasteurized FVIII manufactured in Germany, but they do not supply much study detail. We therefore present details of the in vivo recovery and plasma half-life of a new pasteurized FVIII concentrate (Koate-HS, Cutter Biological, Berkeley, CA) in patients with hemophilia A.

Materials and Methods

Studies reporting FVIII pharmacokinetics have collected and evaluated their data in slightly different ways. In 1984, Kjellman³⁰ reported that differences between laboratories in in vivo recovery could be due to the timing of blood sampling, the FVIII:C assay methods, the FVIII:C plasma standard, and the estimation of the patients' plasma volumes, as well as the potency attributed to the FVIII concentrate used. He also discussed the validity of using a one-compartment or two-compartment model to calculate FVIII half-life. Subsequently, Matucci et al.³¹ presented FVIII kinetics using a noncompartmental method based upon the area under the plasma-concentration-time curve and the area under the moment curve. They advanced cogent arguments for using the model-independent methods. Messori et al.³² reviewed the entire field in 1987, highlighting problems of compartmental analysis in past kinetic studies. They too advocate a model-independent, noncompartmental approach.

Despite these proposals, we chose to evaluate our data using the two-compartment model. The decay curves in all six of our subjects were biphasic (bi-exponential). We also felt that this model enabled us better to compare our results with those published previously by others.

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Patients

The study population consisted of 23 adult subjects with hemophilia A, all of whom gave informed consent to inclusion in the study. Their mean age was 37.2 ± 14.9 years (range, 20–68 years); their mean weight was 69.1 ± 14.3 kg (range, 49.1–106.8 kg).

Study design

The study consisted of two parts. Six nonbleeding hemophiliacs participated in Part 1, which consisted of an uncontrolled, nonblind study to assess the *in vivo* recovery and half-life of the FVIII administered. Part 2 was also an open study in which one patient already included in Part 1 was investigated along with 17 new patients. Four of the patients participating in Part 2 were being treated for mild hemorrhage.

Study drug and dosage

The FVIII concentrate used in this study was manufactured by a modification of the method originally described by Hersgold et al.³ The final preparation is heated in solution for 10 hours at 60°C using a modification of the method described by Ng and Dobkin.³³ We used throughout a standard dosage of 50 U per kg of body weight administered by intravenous injection over approximately 5 minutes. The actual mean dosage used was 51.0 ± 2.6 U per kg. Two different lots (PR 3056 and PR 3063) of pasteurized anti hemophilic factor (AHF) concentrate (AHF-HS/Koate-HS) were used in this study.

Only lot PR 3056 was used in Part 1 of the study; it was also given to 10 subjects (seven nonbleeding and three bleeding) in Part 2, while the other eight subjects in Part 2 (seven nonbleeding and one bleeding) received a single infusion of lot PR 3063. All subjects were evaluated clinically before and after the infusion.

FVIII assays

The FVIII in the Koate-HS vial was quantitated by the manufacturer's quality assurance laboratory with a modified one-stage FVIII assay. The FVIII reference used was a concentrate standard (Mega 1, Travenol Laboratories, Glendale, CA) containing 10.2 FVIII units per ml. The Mega 1 concentrate standard is calibrated against the World Health Organization (WHO) Third International Standard established in 1982.³⁴

Blood samples were collected in Ware's balanced citrate solution. This consists of three parts of 0.1 *M* sodium citrate with two parts of 0.1 *M* citric acid.

Plasma samples were also assayed in our quality assurance laboratories using the one-stage prothrombin time (PTT) method. These samples were run in duplicate against two standards. The FVIII reference was normal pooled plasma, HL 783 (Cutter Biological), calibrated against the WHO First International Reference Standard.³⁵

In Part 1 of the study, to estimate the plasma half-life and recovery of the AHF concentrate, blood samples were taken (each by separate venipuncture) before and then at 10 and 30 minutes and 1, 2, 4, 6, 12, 24, and 30 hours after infusion. In Part 2 of the study, samples were taken before and then at 10 and 30 minutes after each injection. Human research guidelines for obtaining blood samples were observed throughout.

Statistical methods

The estimation of the early and late plasma half-lives of FVIII in the individual subjects was accomplished by a least-squares linear regression of time versus the natural logarithm of the observed FVIII level. The early half-life pertained to the first hours (up to but not beyond the 6-hour values), and the late half-life pertained to the FVIII decline including and subsequent to the 6-hour values. This half-life division was based upon previous observations that FVIII levels fall faster in the first few hours after infusion than in the later hours, which suggests a biphasic exponential decay.^{36,37} The model assumed that FVIII levels declined exponentially with time. Under this assumption, the half-life of FVIII was: $-\ln(2)/\beta_T$, where β_T was the least-squares slope of the decline of the natural logarithm of the percentage of recovery. A different β was calculated for the early and late phase of half-lives.

The expected FVIII level in units per ml was calculated by dividing the total number of AHF units infused by the total plasma volume if no FVIII is lost and then adding the preinfusion level. It has been shown that about 20 percent of the administered FVIII is not found in the plasma after administration; hence, the expected response is 0.02 U per ml per unit per kg of FVIII administered.

In *vivo* recoveries of the two lots of AHF-HS used in this study were compared using the *t* test, calculated on the fractional rise per unit per kg achieved at 10 minutes after each infusion. Analysis of covariance was used to analyze the effect of the subject's weight on *in vivo* recovery.

Dunnett's *t* test³⁸ was used to make multiple comparisons to baseline (preinfusion) vital signs, blood counts, and blood chemistry values.

Tests were determined to be significant only if the results were $p < 0.05$ (two-tailed).

Table 1. Mean *in vivo* recoveries 10 minutes after completion of the infusions

Study phase	FVIII lot number	Number of subjects	Weight (kg)	FVIII dose units/kg	Increase in FVIII activity 10 minutes after infusion (U/ml)		Percentage of rise in FVIII/unit/kg
					Expected	Actual	
1	PR 3056	6*	$75.1 \pm 19.6^\dagger$	49.7 ± 1.4	0.99 ± 0.03	1.43 ± 0.03	2.0 ± 0.7
2	PR 3056	10	68.0 ± 14.0	52.3 ± 3.4	1.05 ± 0.07	1.12 ± 0.20	2.2 ± 0.4
2	PR 3063	8*	66.1 ± 9.9	50.4 ± 1.5	1.01 ± 0.03	0.91 ± 0.44	1.8 ± 0.9
	TOTALS	24	69.1 ± 14.3	51.0 ± 2.6	1.02 ± 0.05	1.13 ± 0.37	2.2 ± 0.8

* One subject received an infusion from both FVIII lots used.

† Mean $\pm$ SD.

Table 2. *In vivo* percentage increase in FVIII at 10 and 30 minutes after infusion for two lots of AHF-HS

AHF-HS lot number	Number of observations	In vivo percentage rise in FVIII levels (per U of FVIII administered per kg)	
		10 minutes	30 minutes
PR 3056	16	2.43 ± 0.64	2.35 ± 0.78
PR 3063	8	1.81 ± 0.91	1.71 ± 0.32
Mean ± SD	24	2.22 ± 0.78	2.13 ± 0.72
p value (PR 3056 compared with PR 3063)		0.0651*	0.0093†

* T test based on equal variances.

† T test based on unequal variances.

Results

In vivo increase in FVIII activity

The mean *in vivo* increase in FVIII activity for each part of the study is shown in Table 1. The actual mean *in vivo* increase in FVIII activity for all 24 infusions was 1.13 ± 0.37 U per ml. Each unit of FVIII infused per kg of body weight caused a 2.2 ± 0.78 percent increase in the plasma FVIII level.

Table 2 compares the mean *in vivo* percentage increases in plasma FVIII levels per unit of FVIII administered per kg of body weight for the two lots used in this study. The *in vivo* recovery for lot PR 3056 was significantly greater than that for lot PR 3063 ($p=0.0093$) at 30 minutes. The difference between the two lots in recovery at 10 minutes

did not, however, quite reach significance because of the greater variations in individual subjects' recoveries at that time.

Analysis of covariance revealed that the weight of the subject had a major influence on the *in vivo* recovery ($p = 0.0013$). In general, when plasma volume was estimated as 40 ml per kg of body weight, heavier patients tended to have an actual recovery far greater than expected. When the weight of the subject is removed as a variable, there is no significant difference in the *in vivo* recoveries of lot PR 3056 and lot PR 3063 ($p = 0.149$) or between the first phase ($n = 6$) and the second phase ($n = 18$) of the study ($p = 0.155$). This is seen in Table 1, where the actual recovery of the 6 patients with an average body weight of 75.1 kg is greater than that of the 10 patients with an average weight

Table 3. Mean increase in FVIII activity (U/ml) following infusion of AHF-HS

Time after infusion	Number of observations*	Mean increase in activity	Standard deviation
10 minutes	6	1.43	0.33
30 minutes	6	1.41	0.51
1 hour	6	1.16	0.26
2 hours	6	1.03	0.28
4 hours	6	0.83	0.18
6 hours	6	0.77	0.18
12 hours	6	0.52	0.18
24 hours	6	0.27	0.13
30 hours	6	0.21	0.14

* Subjects 1 to 6.

Table 4. *In vivo* FVIII survival in individual subjects*

Patient	FVIII half-life (hours)	
	Early	Late
1	6.0	22.3
2	6.6	11.4
3	5.0	10.6
4	5.8	15.1
5	3.6	9.5
6	4.0	9.2
Mean ± SD	5.2 ± 1.2	13.0 ± 5.0

* All studies conducted with PR 3056.

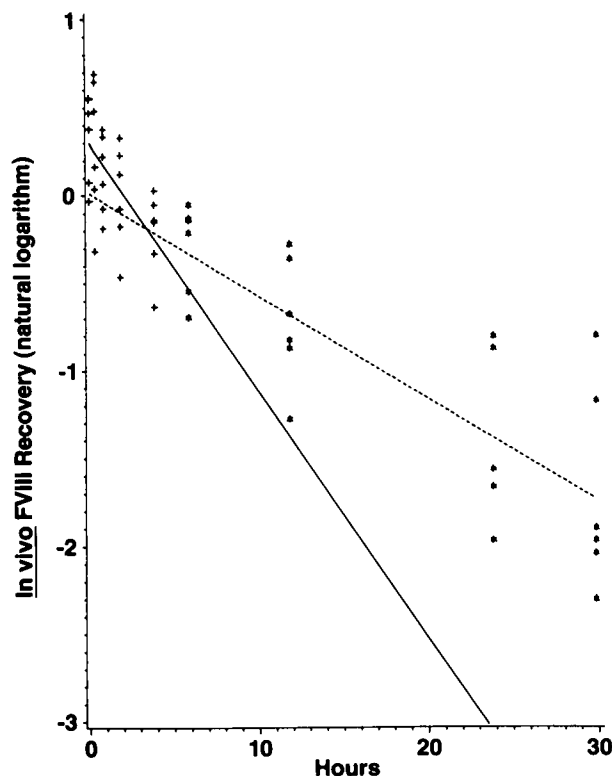


FIG. 1. Disappearance of FVIII from the circulation over time. + = individual FVIII recoveries up to 6 hours used to construct early (—) decay curve. * = individual recoveries 6 hours and more used to construct late (---) decay curve.

of 68.0 kg, which in turn is greater than that of the 8 patients with an average weight of 66.1 kg (recoveries of 144.4 vs. 106.7 vs. 90.1%).

We evaluated the likelihood that differences in hematocrit might also affect recovery, with subjects with higher hematocrits having a lesser plasma volume and hence a greater *in vivo* recovery. A regression of FVIII levels versus weight and hematocrit again confirmed that there was a significant correlation between weight and *in vivo* recovery ($p = 0.042$) in contrast to hematocrit ($p = 0.465$). There was also a weak but significant correlation between weight and hematocrit, with heavier patients tending to have higher hematocrits ($p = 0.031$). The mean hematocrit for subjects in study Part 1 (Lot PR 3056) was 45.0 ± 2.7 percent; in Part 2 (Lot PR 3056), 36.4 ± 5.3 percent; and in Part 2 (Lot PR 3063), 39.9 ± 4.8 percent.

Plasma half-life

The mean *in vivo* increase in FVIII activity after infusion of AHF-HS over time is shown in Table 3 and Figure 1. From these data, the mean early and late plasma FVIII half-lives were estimated to be 5.2 ± 1.2 and 13.0 ± 5.0 hours, respectively. The half-lives of the plasma in the six patients included in this part of the study are shown in Table 4.

Hemostatic effect

Four of the patients included in Part 2 of the study were given a standard 50-U per kg dose of AHF-HS to control a bleeding problem. This dosage completely controlled the bleeding in each incident.

Side effects

One of the six patients included in Part 1 of the study developed mild headache, hives, itching, and conjunctival and nasal congestion with rhinorrhea about 2 minutes after completion of the infusion. He was treated with 50 mg of oral Benadryl (Parke-Davis, Morris Plains, NJ) and had complete resolution of the symptoms in 2 hours. No other patient in either part of the study had any unusual symptoms. The patient with side effects in Part 1 of the study was also included in Part 2 and received treatment with another lot of AHF-HS without problem.

Discussion

The *in vivo* increases in FVIII activity and half-life for this new pasteurized antihemophilic factor concentrate are similar to those reported previously for unheated concentrate. For example, in 1974, studies³⁶ on an early concentrate showed that each FVIII unit infused per kg of body weight caused an approximate 2 percent rise in plasma FVIII. The pasteurized concentrate studied here caused a 2.2 percent rise in plasma FVIII for each FVIII unit infused per kg of body weight. In the 1974 study, the mean initial plasma half-disappearance time was 5.2 hours (range, 3.2 to 8 hours) and the mean biologic half-life was 17.2 hours (range, 13.2 to 25.6 hours). In our study, the initial plasma half-disappearance time was 5.1 hours (range, 3.6 to 6.6 hours) and the mean bi-

ologic half-life was 13.3 hours (range, 9.1 to 22.4 hours). In our six hemophiliac subjects, the median biologic half-life was 11.0 hours, which is below the lower limit of the range reported by Britton et al.³⁶ However, in 1979, Aronson³⁷ reviewed FVIII half-life studies and found that the initial equilibration phase was about 4 hours and the later biologic phase was about 12 hours in almost all instances.

No previous reports of the plasma recovery and half-life of coagulation factor concentrates have dealt with the influence of obesity on the results. This study demonstrates the problems that can occur if a standardized estimation of plasma volume, based on weight alone, is used. An obese individual has less plasma per kg of body weight than does a person of normal weight. Because it is not practical to measure actual plasma volumes in individuals in studies of this nature, a more accurate plasma volume might be estimated from a formula including both weight and height, or obese individuals might be excluded. We were unable to detect any influence of hematocrit on plasma recovery, which could be attributable to the few subjects evaluated.

One patient experienced a mild allergic side effect. This appeared to be an idiosyncratic reaction, and the patient did not react to a subsequent infusion with a different lot. Such reactions do occur on occasion in individual hemophiliacs and do not appear to be either product- or lot-related. Usually the person does not react to a subsequent administration of either another lot or another product. No satisfactory explanation can be advanced.

The hemostatic effect of this pasteurized AHF appears to be adequate. All four bleeding patients responded satisfactorily to a single dose.

The half-life of this pasteurized (heated in solution at 60°C for 10 hours) FVIII preparation is comparable to that described for other FVIII concentrates. Thus, no major adjustments in dosage regimens are likely to be necessary when this product is used for therapy. Moreover, the preparation retains hemostatic activity. Additional studies are needed to confirm its long-term safety.

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