Pharmacokinetics (PK) of recombinant and plasma-derived factor VIII (FVIII) products in pediatric patients with severe hemophilia A

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Introduction:

In North America, there are several FVIII products that are used to treat both children and adults with Hemophilia A. However, studies to determine the pharmacokinetic properties of these FVIII products focus primarily on adult patients, while the pharmacokinetic data for pediatric populations is rather limited. A review of the current literature and FVIII product inserts was conducted to determine if the half-lives of available recombinant and plasma-derived FVIII products are comparable in pediatric patients. Although there is widespread PK data for FVIII use in adults, this data cannot be applied to pediatric patients due to several significant physiologic differences. Specifically, Advate, Kogenate FS and Xyntha demonstrate three variable PK trends, which include a lower area-under-the-curve, a higher clearance rate, and a lower half-life.

Literature Review:

The pharmacokinetic parameters for pediatric patients derived from the package inserts of Advate, Kogenate FS and Xyntha are presented below (Table 1). Additional studies from the literature are presented here.

Advate

Blanchette *et al.* evaluated the pharmacokinetic data of Advate in a group of 53 children <6 years of age with severe hemophilia A . The mean half-life was 9.88±1.89 h, with a range of 6.8-15.4 h. Furthermore, the age of the child was found to impact the half-life by an increase of 0.4 h/year.

Kogenate FS

Although pharmacokinetic data is not listed for children less than 4.4 years old, a prospective randomized control study was performed with 65 male hemophilia A patients, less than 2.5 years old with no previous joint damage [3]. Results showed that even without knowing the half-life of Kogenate FS in this age group, there are still significant clinical benefits to taking Kogenate FS prophylactically rather than episodically.

Xyntha™/ReFacto AF

The pharmacokinetic parameters of Xyntha in pediatric patients under the age of 6 is currently being studied, but the results are not yet available.
Clinical studies done for FDA approval illustrated pharmacokinetic equivalence between Xyntha and Advate. However, this study consisted of subjects ≥12 years of age [4]. Pharmacokinetic equivalence between Xyntha and Advate has not been studied in pediatric patients less than 12 years of age.

Recombinate

No pediatric pharmacokinetic data is available for Recombinate, however, the Recombinate Study Group demonstrated the safety and efficacy of Recombinate in young children between the ages of 2 days old to 50 months old [10].

Plasma-Derived Factor VIII Products

A review of the literature was conducted for three plasma-derived factor VIII products, including Octanate, Humate-P and Optivate. There is no pediatric pharmacokinetic data available for any of these products.

One ongoing prospective clinical study consisting of previously untreated patients with hemophilia A ages 0.0-5.6 have thus far demonstrated that Octanate is both effective and well-tolerated [11]. Furthermore, Matysiak *et al.* determined through a study of twenty-five children ages 1-6 that Optivate is safe for use in children with hemophilia A . In contrast, the product monograph of Humate-P specifically states that for von Willebrand disease, Humate-P is indicated in both adult and pediatric patients; but for Hemophilia A, it is only indicated in adults. This is due to the lack of long-term evaluation of joint damage in pediatric patients treated with Humate-P.

Results:

Table 1. Pharmacokinetic parameters of recombinant FVIII products in various age groups.

Product	Age	Mean Half-life (hrs)	Mean AUC (IU*hr/dL)	Mean Clearance (dL/hr/kg)	Reference
Advate	1 month to <2 years	8.86 ± 1.78	1385 ± 476	0.039 ± 0.015	[2]
	2 to <5 years	10.27 ± 1.94	1545 ± 616	0.038 ± 0.016	
	5 to <12 years	10.89 ± 1.60	1282 ± 509	0.044 ± 0.012	
	12 to <16 years	11.70 ± 3.72	1447 ± 528	0.038 ± 0.012	
Kogenate FS	4.4 to 18.1 years	10.7 (7.8-15.3)	1320.0	0.041	[3]
	12 to 33 years	14.60 ± 4.38	1487.08 ± 381.73	NA	
Xyntha	12 to 16 years	8.03 ± 2.44	1150 ± 520	0.052 ± 0.024	[4]

NA, not available

Conclusions:

Pediatric PK studies are available for Advate, Kogenate FS, and Xyntha . However, each FVIII product defines their age groups differently when reporting PK data (Table 1), thereby making it difficult to compare their half-lives. Moreover, there is no pediatric PK data for any of the plasma-derived products, thus excluding possible comparisons with recombinant-derived products.

Currently there is strong evidence that reducing the number of bleeds in young children is vital in the prevention of haemophilic arthropathy. Furthermore, clinical trials with pediatric patients demonstrate that tailoring dosing frequency to an individual's half-life can have clinically significant outcomes in terms of bleeding prevention. We recommend that future research involves defining uniform age groups that every FVIII product will adhere to when reporting PK data. This will allow health care providers to compare the products and make evidence based decisions regarding patient care.

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WFH2012 40--Tu

Clotting Factor Concentrates

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DOI: 10.3252/pso.eu.WFH2012.2012

Poster presented at: WFH 2012 World Congress, Paris, France, Sunday, July 8 - Thursday, July 12

PosterSessionOnline.com