Comparison of pharmacokinetic (PK)-guided prophylactic dosing tools in hemophilia A - a pilot study

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Introduction

- Severe and moderate-severe hemophilia A patients administer clotting factor VIII (FVIII) concentrates prophylactically to prevent bleeding events.
- Pharmacokinetic (PK)-guided dosing using Bayesian analysis is used to individualize prophylactic dosing of FVIII.
- In the Bayesian analysis individual PK parameters are calculated by combination of a population PK model and individual observed concentrations.
- Individual PK parameters are used to attain a dosing regime which maintains FVIII plasma trough levels >0.01 IUmL^{-1}.
- For FVIII several dosing regimes using Bayesian analysis are available.

Objectives

- To compare the performance of Bayesian PK dosing tools for dose individualization of FVIII during prophylaxis.

Methods

Bayesian analysis

- Following a dose of 50 IU/kg Advate three samples were obtained at t=6, 24 and 48 hours (*Table 1*, *Figure 1*).[1]
- Individual PK parameters were calculated using the following tools:
  1. Bayesian analysis in NONMEM®-software
     - Population PK parameters for Advate were taken from literature.[2]
  2. MyPKFiT®, developed by Baxalta/Shire©
  3. WAPPS-Hemo portal

Evaluation of performance

- Clearance (CL), distribution volume in steady-state (Vss), half-life, time to 0.01 IU/mL (1%), and calculated dose were evaluated.

Table 1. Patient characteristics

N	7
Age (years, median [range])	33 [8.7 - 70]
Body weight (kg, median [range])	85.3 [56.8 - 103]
Baseline plasma level (IUmL^{-1})[a]	≤ 0.03
Product[a]	Advate®
Dose (IUkg^{-1} [range])	48.5 [46.2 – 55.6]

[a]For each patient

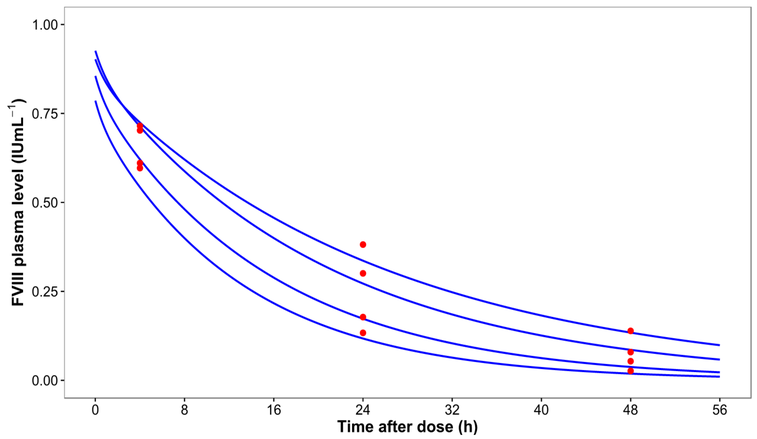

Figure 1. FVIII plasma levels (red dots) of four patients with their corresponding individual PK fits (blue line), after 50IUkg^{-1} intravenous infusion, using Bayesian analysis in NONMEM® (method 1).[2]

Table 2. Bayesian estimates of PK parameters

	CL[a] (mL/h)		Vss[b] (mL)		Half-life[c] (h)		
Patient	Method 1	Method 2	Method 1	Method 2	Method 1	Method 2	Method 3
1	325	247	3598	4265	7.8	12.7	11
2	198	195	3341	3720	11.8	14.9	12
3	304	278	4828	5150	11.1	14.1	11
4	177	214	2894	3780	11.4	12.8	12
5	124	118	1411	1400	8	9.7	8.5
6	127	130	2235	2600	12.3	11.9	13
7	294	274	4153	4425	9.8	10.4	11

[a] Clearance; [b] Distribution volume in steady state; [c] Terminal elimination half-life.
Method 1: Bayesian analysis using NONMEM®. Method 2: MyPKFiT®. Method 3: WAPPS-Hemo portal.

Conclusions

1. Differences may exist between the population PK models implemented in the current PK tools, leading to differences in estimation of PK parameters.
2. Larger prospective studies are necessary to gain more insight into the difference between the PK tools and its clinical consequences.

Results

Estimated clearance (CL), distribution volume in steady-state (Vss), and terminal elimination half-life are shown in *Table 2*.

In comparison with method (1) CL was generally estimated lower by (2), although not statistically significant, with a mean difference of 6.9 mLh^{-1} (95% CI: -14.5, 28.2 mLh^{-1}; p = 0.461).

Method (2) produced higher values for Vss than (1) with a mean difference of 343 mL (95% CI: 34.9, 651.0 mL; p = 0.034).

Method (2) produced higher values for estimated half-life than (1), with a mean difference of 2.04 hours (95% CI: 0.41, 3.68 h; p=0.022).

With respect to the time to reach a FVIII level of 0.01 IUmL^{-1} following administration, as shown in *Table 3*, method (2) produced higher values than (3) with a mean difference of 6.36 hours (95% CI: 1.96, 10.76 h; p=0.012).

The required prophylactic dose was calculated for dosing intervals of 48 and 72 hours. Differences were fairly large between method (1) and (2), which could be explained by longer half-life estimates by method (2) as compared to (1).

Table 3. Bayesian estimates of Time to 0.01IU/mL (1%) and calculated dose

	Time to 1%		Dose[a] (interval 48h)		Dose[a] (interval 72h)	
Patient	Method 2	Method 3	Method 1	Method 2	Method 1	Method 2
1	78	74	2646	768	22928	2860
2	94	83	534	475	2291	1453
3	88	76	942	728	4416	2374
4	80	81	509	595	2284	2184
5	62	61	920	531	7552	2155
6	98	91	314	290	1278	886
7	81	72	1197	802	6698	2887

[a] Calculated using a closed-form solution for 2 compartment PK.

References

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