Pharmacokinetic-Pharmacodynamic Modeling of Factor VIII Using Its Plasma Level and Global Hemostasis Biomarkers

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OBJECTIVES

The relationship between factor VIII (FVIII) prophylactic dosing and its corresponding plasma level is best interpreted within the context of its biological effects on platelet function (Hemodyne) and blood viscoelasticity (TEG). To establish appropriate pharmacokinetic-pharmacodynamic (PK-PD) models for FVIII, we conducted a pilot PK-PD study for FVIII plasma level and global hemostasis biomarkers (Hemodyne and TEG) throughout a 48 hour FVIII prophylaxis interval.

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METHODS

Ten non-bleeding severely FVIII deficient patients (FVIII <1%) were infused with a prophylactic FVIII dose (mean 32.1 IU/kg). Blood was collected over 48 h for FVIII clotting activity (FVIII:C), Hemodyne markers (platelet contractile force [PCF], clot elastic modulus [CEM]) and TEG markers (reaction-time [R], kinetics-time [K]). The PK parameters included volume of distribution (Vdss), total clearance (CL) and plasma half-life (t1/2). PK-PD modeling using linear and Emax models was performed using Scientist® Version 2.0 (Micromath Research, St. Louis, MO, USA).

RESULTS

Table 1. Mean SD PK Estimates

FVIII Dose (IU/kg)	32.1 (10.6)
Cmax (IU/dL)	88 (31.5)
CL (mL/h/kg)	3.1 (1.3)
Vdss (ml/kg)	39.6 (8.9)
T1/2 (h)	11.6 (4.1)

Table 2. Mean (SD) PD Estimates

	Eo	Slope	Emax	EC50 (IU/dL)
PCF (kdyne)	0.3 (0.3)	0.08 (0.04)	NA	NA
CEM (Kdyne/cm²)	0 (0)	0.32 (0.16)	NA	NA
R (min)	24.0 (8.4)	NA	-19.6 (12.5)	68.5 (28.4)
K (min)	7.3 (4.8)	NA	-6.8 (8.7)	67.2 (29)

CONCLUSIONS

- The PK of FVIII prophylaxis is consistent with previously published literature.
- Platelet function parameters CEM and PCF have linear PD effects and are thus FVIII dose-dependent
- The TEG parameters R and K follow a sigmodial Emax PD model
- Based on these data, dose prediction and tailoring of FVIII therapy can be performed to achieve desired laboratory endpoints
- Further study is needed to establish the clinic effects of such dose-tailoring

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