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Individualized factor IX dosing in two brothers: application of longitudinal pharmacokinetic modelling to optimize therapeutic benefit

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Haemophilia B occurs in approximately 1 in 25 000 male births, requiring regular replacement of factor IX in individuals with moderate to severe disease. Prophylactic dosing aims to minimize and prevent the frequency of joint bleeds to avoid haemophilic arthropathy, the leading cause of morbidity in patients with haemophilia B [1]. The efficacy of recombinant factor IX has been clearly demonstrated in the prophylaxis and treatment of haemorrhage in patients with haemophilia B [2]; however, wide inter-individual variability in the dose–response relationship for recombinant factor IX and in the dose–exposure relationship as children mature necessitates individualization in some children to achieve optimum activity levels [3].

For more than two decades, both pharmacokinetic (PK) and pharmacodynamic approaches have been used to successfully individualize therapeutics in paediatric and adult patients. This pharmacologic approach has been extended to guide the successful replacement of various clotting factors (i.e. antithrombin III, factor VIII) [4,5] in patients, including factor IX [6,7]. This same approach can be used to optimize disease management in patients with haemophilia B who are unresponsive to standard dosing regimens. Individualized dosing also offers the potential for considerable cost savings by utilizing the least amount of factor IX required to minimize haemorrhagic episodes [8]. To illustrate the utility of a PK-guided dosing approach, we present data for two brothers with haemophilia B where prophylactic recombinant factor IX (BeneFix®; Genetics Institute, Inc., Cambridge, MA) therapy was individualized and serially re-optimized using PK modelling and simulation.

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Authors contribution

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For each PK evaluation, factor IX activity levels were drawn immediately prior to and approximately 0.5, 1, 2, 4, 8, 10, 24, 48 and when possible 72 h following administration of a bolus injection. Per cent factor IX activity vs. time data (as reported by our clinical laboratory via a single stage assay) were curve fit using a peeling algorithm to obtain initial polyexponential parameter estimates, followed by a non-linear, weighted, least squares algorithm to obtain final parameter estimates. Goodness-of-fit criteria (e.g. Akaike Information Criteria, Schwartz Criteria, objective function, correlation matrix, coefficients of variation) were then applied to validate PK model selection and the resultant PK parameters used for subsequent dose simulation. All PK methods utilized standard mathematical techniques resident within Kinetica® software (Thermo Electron, Philadelphia, PA).

For the purposes of dose simulation, several assumptions were required: (i) no concentration-dependent changes occur in the calculated distribution and elimination rate constants, (ii) no changes in the terminal phase of the per cent activity vs. time curve would be observed if sampling were carried out beyond 72 h, (iii) a linear dose–exposure relationship exists between 2–250% factor IX activity, and (iv) the recombinant factor IX (BeneFix®) concentration/effect profile observed with PK modelling is representative of the disposition profile for subsequent administration and therefore suitable to use for dose simulations. Clinical pharmacodynamic targets for prophylactic treatment were defined by the Haematologist caring for these children (BW). With each PK evaluation, several dosing options were provided to the Haematologist to maintain factor IX troughs greater than 5%. This target was determined largely as a result of persistent bleeds in these patients at troughs ranging from 1–5%. Although not the focus of this report, dosing recommendations for the management of acute bleeding episodes were also simulated in these two patients.

In both cases, the postinfusion per cent factor IX activity vs. time data were best fit to a biexponential function ($r^2 > 0.98$), thus supporting the use of a two-compartment open model to characterize drug disposition. This report details changes in per cent activity half-lives and recommended dosing targets for two siblings over a 6-year period.

Patient 1 is a white male with severe haemophilia B receiving prophylactic recombinant factor IX (BeneFix®; Genetics Institute, Inc.). His initial PK evaluation was conducted at 2 years 9 months of age at a time when he was receiving approximately 110 U kg^{-1} three times a week. While maintained on this dose he experienced frequent forehead bleeds, one soft-tissue bleed and one joint bleed in both knees. To maintain a peak around 100% (to minimize costs and avoid overexposure) and a trough greater than 5% (determined at the discretion of the haematologist), the recommendation of 90 U kg^{-1} every 48 h was made (Table 1). Trough levels evaluated 4 months after this initial study and the initiation of this dosing regimen revealed factor IX activity levels of 15%, thereby validating both the accuracy and adequacy of the PK-guided individualized factor IX dosing regimen.

Patient 1 was re-evaluated at 5 years 6 months of age to determine whether his PK profile changed as a result of normal growth and development. In the time between PK evaluations he had few issues, with no joint bleeds, and only two soft-tissue bleeds over the prior year. This evaluation showed that both the initial and terminal half-lives had markedly decreased

indicating a higher weight-adjusted factor IX dose would be required to meet the desired PK target (Table 1). Subsequent to his second PK study, this patient experienced one joint bleed in addition to several soft-tissue bleeds attributed to sports injuries unrelated to his haemophilia. He was re-evaluated at 7 years of age, which revealed similar initial and terminal half-lives to the values at 5.5 years (Table 1).

His final PK profile was performed at 8 years 9 months of age. In the time since his last evaluation he experienced rare breakthrough bleeding episodes associated wholly with sports activity. This evaluation showed a noticeable increase in initial and terminal half-lives from his prior two PK profiles leading to an increase in measured activity levels throughout the sampling timeframe. Based on his 72 h factor IX activity result of 16%, his breakthrough bleeding was deemed unrelated to sub therapeutic factor IX activity levels.

In the time since his last PK profile evaluation (at 8 years 9 months) he has been continued on 6000 units/dose of recombinant factor IX twice weekly. Throughout this time he has had a total of five joint bleeds, all of which were associated with sports activities, and at 16 years of age he is currently well controlled on a dose of 90 units kg^{-1} twice weekly.

Following the success observed with Patient 1, early PK profiling for his brother was performed. Patient 2 is similarly a white male with severe haemophilia B receiving prophylactic recombinant factor IX (Bene-Fix®, Genetics Institute, Inc.). His initial PK evaluation was conducted at 1 year 4 months of age with therapeutic targets defined by his treating haematologist (BW).

The initial factor IX per cent activity profile at 1 year 4 months revealed a terminal half-life consistent with values reported in the literature (Table 2). Subsequent to the initiation of his new maintenance dose he had no joint bleeds, but did experience several soft tissue bleeds attributed largely to frequent falling while learning to walk.

At the time of his next evaluation (2 years 4 months of age) his PK study revealed an increase in his initial half-life and a decrease in the terminal half-life, resulting in a recommendation to decrease his weight-adjusted factor IX maintenance dose. In the time since this final PK evaluation he has been maintained on a dosing schedule of recombinant factor IX ranging between 90–102 units kg^{-1} twice weekly. Throughout this time he has experienced no joint bleeds, and at 12 years of age is currently maintained on a dose of 90 units kg^{-1} twice weekly.

The goal of these prospective PK analyses was to individualize prophylactic factor IX dosing for BeneFix® to achieve clinician targeted per cent activity levels in an attempt to minimize bleeding episodes. Apart from the clinical success we experienced we also observed changes in factor IX disposition over time in these children. These findings are consistent with those of Bjorkman *et al.*, who described linear changes in factor IX PK parameters with increasing age and body weight [3]. Similarly, the biexponential profile we observed in our profiles is corroborated by previous studies which demonstrate that factor IX concentrations decline in a biphasic pattern [9,10]. Given the complexity regarding factor IX disposition for the time-dependent activity of this protein, a simple PK approach (i.e. a one compartment model) frequently used in the course of clinical therapeutic drug monitoring

would not have been accurate or sufficient for the purpose of individualizing factor IX therapy for BeneFix®.

It is important to note that our laboratory reports factor IX per cent activity, as is standard in clinical haematology, and not factor IX concentrations. Thus, we exercised a degree of caution when interpreting the parameter estimates that were generated by traditional PK analysis. In contrast to classical plasma concentration vs. time data, where distribution volumes and clearance rates can be estimated, we restricted the interpretation of our data to that of two distinct rates of decline in per cent activity. Although speculative, this may represent an initial rate of decline in activity for protein that is in excess of that required to saturate the binding sites on the vascular endothelium and other tissue compartments, followed by subsequent decline in activity of protein that represents dissociation from these binding sites, re-equilibration with the central compartment and subsequent catabolism.

Despite the inherent complexity and assumptions made surrounding the modelling of factor IX activity, these two evaluations provide an example of how PK modelling and simulation can aid in dose selection and optimization of therapeutic outcomes of patients with factor IX deficiency using a specific recombinant factor IX concentrate. Additionally, when one considers the enormous cost of factor IX therapy, PK analysis is able to provide information on dose selection that makes the most financial sense [8].

References

1. Coppola A, di Capua M, de Simone C. Primary prophylaxis in children with haemophilia. Blood Transfus. 2008; 6:s4–11. [PubMed: 19105503]
2. White G, Shapiro A, Ragni M, et al. Clinical evaluation of recombinant factor IX. Semin Hematol. 1998; 35:33–8. [PubMed: 9565165]
3. Björkman S, Shapiro A, Berntorp E. Pharmacokinetics of recombinant factor IX in relation to age of the patient: implications for dosing in prophylaxis. Haemophilia. 2001; 7:133–9. [PubMed: 11260271]
4. Blowey DL, Kearns GL. Congenital nephrotic syndrome alters antithrombin-III disposition in children. Clin Pharmacol Ther. 1998; 63:76.
5. Shakhnovich V, Daniel J, Wicklund B, Kearns G, Neville K. Use of pharmacokinetic modelling to individualize FFP dosing in factor V deficiency. Haemophilia. 2013; 19:251–5. [PubMed: 23173558]
6. Abdel-Rahman, SM., Wicklund, BM., Kearns, GL. Individualizing Factor IX Dosing Using Pharmacodynamic Modeling of Factor IX for Dose Optimization; ASCPT Annual Meeting; Orlando, FL. March 6–10; 2001. Abstract
7. Shapiro AD, Korth-Bradley J, Poon MC. Use of pharmacokinetics in the coagulation factor treatment of patients with haemophilia. Haemophilia. 2005; 11:571–82. [PubMed: 16236106]
8. Carlsson M, Björkman S, Berntorp E. Multidose pharmacokinetics of factor IX: implications for dosing in prophylaxis. Haemophilia. 1998; 4:83–8. [PubMed: 9873843]
9. Björkman S, Carlsson M, Berntrop E. Pharmacokinetics of factor IX in patients with haemophilia B: methodological aspects and physiological interpretation. Eur J Clin Pharmacol. 1994; 46:325–32. [PubMed: 7957517]
10. Goudemand J, Peynet J, Chambost H, et al. A cross-over pharmacokinetic study of a double viral inactivated factor IX concentrate (15 nm filtration and SD) compared to a SD factor IX concentrate. Thromb Haemost. 1998; 80:919–24. [PubMed: 9869161]

Table 1

Individualized dosing assessment and strategy for Patient 1.

Age (year)	2.75	5.5	7.0	8.75
Weight (kg)	13.4	19.8	24.5	29.0
Clinical Status at the time of study	Numerous soft tissue and joint bleeds	Few soft-tissue, no joint bleeds	No severe bleeds	Increased break-through bleeding from sports injuries
Pre-dose activity level (%)	9	10	NP	25 *
t1/2-alpha (h)	5.5	2.9	2.3	6.4
t1/2-beta (h)	47.3	27	23.7	35.7
Prophylaxis options				
Trough ~5%	NP	1600 U q3d, or 3200 U q4d	1000 U q2d, or 2200 U q3d,or 4800 U q4d	1250 U q3d, or 2000 U q4d,
Trough ~10%	1200 U q3d	3200 U q3d	1700 U q2d, or 3900 U q3d	2500 U q3d, or 4000 U q4d
Trough ~15%	1200 U q2d	NP	NP	NP

DL, loading dose; DM, maintenance dose; h, hour; NP, not performed; q, every.

* reflects a 48 hour level.

Table 2

Individualized dosing assessment and strategy for Patient 2.

Age (year)	1.3	2.3
Weight (kg)	12.4	14.8
Clinical Status at the time of study	Awaiting port placement for prophylaxis	No significant bleeds
Pre-dose activity level (%)	<1	NP
t1/2-alpha (h)	3.5	5.1
t1/2-beta (h)	29.7	21.2
Prophylaxis option		
Trough ~5%	550 U q2d, or 1200 U q3d, or 2250 U q4d	500 U q2d, or 1200 U q3d, or 2800 U q4d
Trough ~10%	1100 U q2d, or 2350 U q3d, or 4500 U q4d	860 U q2d, or 2200 U q3d

DL, loading dose; DM, maintenance dose; h, hour; NP, not performed; q, every.