CASE REPORT

Pharmacokinetic-guided dosing of factor VIII concentrate in a patient with haemophilia during renal transplantation

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SUMMARY

A 29-year-old man with severe haemophilia A and end-stage renal disease underwent a renal transplantation. To prevent bleeding, patient was treated with replacement therapy using factor VIII (FVIII) concentrate, according to National guidelines. Bayesian analysis was performed by combining observed FVIII concentrations with a population pharmacokinetic (PK) model for patients with severe haemophilia A in a perioperative setting. Application of Bayesian analysis led to accurate prediction of observed concentrations after prescribing dosing advice. We believe that PK-guided dosing of factor concentrates is a valuable step towards further individualisation of treatment in patients with bleeding disorders, especially in those patients requiring precise targeting of coagulation factor levels due to high risk of either bleeding or thrombosis, as illustrated by this patient undergoing a major surgical procedure.

BACKGROUND

Haemophilia A is an X linked inherited deficiency of coagulation factor VIII (FVIII), characterised by bleeding in muscles and joints. Patients are classified according to residual coagulation factor concentrations, for example, severe (FVIII<0.01 IU/mL), moderate (FVIII: 0.01–0.05 IU/mL) and mild (FVIII: 0.06–0.40 IU/mL) disease.¹ Replacement therapy with factor concentrates is prescribed ‘on demand’ in case of acute bleeding or for surgical and dental procedures or ‘prophylactically’ to prevent spontaneous bleeding in patients with a severe bleeding phenotype.

Patients with haemophilia A are currently dosed with FVIII concentrate according to body weight,

clinical phenotype, residual FVIII levels, severity of bleeding or surgical bleeding risk and crude estimations of clearance.¹ In case of surgical procedures or bleeding, minimal FVIII target levels are maintained according to National guidelines to safeguard haemostasis.² FVIII clearance is influenced by various factors, such as age, body weight and von Willebrand factor (VWF). The latter prevents FVIII clearance by protecting it from proteolysis and cellular uptake in the circulation. The liver is primarily responsible for FVIII clearance by mechanisms of cellular clearance. Owing to high molecular weight of FVIII, clearance by the kidney does not play a role.^{3 4}

Previously, we demonstrated that novel dosing methods are necessary to minimise underdosing and overdosing in the perioperative period.⁵ In this study, 45% of trough and steady-state FVIII plasma concentrations within 24 hours after surgery were lower than specified target ranges, while 75% of these plasma concentrations were above target >6 days after hospitalisation.⁵ Moreover, we developed a perioperative population pharmacokinetic (PK) dosing model for (moderate) patients with severe haemophilia A to optimise dosing (table 1).⁶ In this case report, we applied Bayesian analysis using this model to individualise perioperative dosing. Important as this patient required precise targeting of coagulation factor levels due to a high risk of bleeding and thrombosis. Here, we show feasibility of individualised PK-guided iterative dosing.

CASE PRESENTATION

A 29-year-old man with severe haemophilia A presented with end-stage renal disease due to a

Table 1 Model equations describing the perioperative population PK model*

CL	$CL \left(\frac{\text{mL}}{\text{h}} \right) = 150 \times \left(\frac{\text{Body weight}}{68} \right)^{0.75} \times \left(\frac{\text{Age}}{40} \right)^{-0.17} \times 1.26^{\text{Blood group}} \times 0.93^{\text{Severity of surgical procedure}}$
V1	$V1 (\text{mL}) = 2810 \times \left(\frac{\text{Body weight}}{68} \right) \times \left(\frac{\text{Age}}{40} \right)^{-0.09}$
Q	$Q \left(\frac{\text{mL}}{\text{h}} \right) = 160 \times \left(\frac{\text{Body weight}}{68} \right)^{0.75}$
V2	$V2 (\text{mL}) = 1900 \times \left(\frac{\text{Body weight}}{68} \right)$

Body weight (kg); age (years); blood group equals one in case of blood group O and zero in case of blood group non-O; severity of surgical procedure equals one in case of a medium risk surgical procedure and zero in case of a low-risk surgical procedure.

*According to Hazendonk *et al*.⁶

CL, clearance; PK, pharmacokinetic; Q, intercompartmental clearance; V1, central volume of distribution; V2, peripheral volume of distribution.

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Table 2 Patient characteristics and laboratory measurements

Age (years)	29	
Body weight (kg)	93	
Blood group	0	
Prophylactic treatment	2000 IU FVIII (Helixate) three times/week	
Individual PK parameters*		
Clearance (mL/kg)	180	
Central volume of distribution (mL)	3260	
Intercompartmental clearance (mL/kg)	186	
Peripheral distribution volume (mL)	2750	
	Prior surgery	After surgery
GFR (mL/min)	<10	73
Creatinine ($\mu\text{mol/L}$)	1427	105
Urea (mmol/L)	50	6.9

*Derived from perioperative population PK model.⁶
FVIII, factor VIII; GFR, glomerular filtration rate; PK, pharmacokinetic.

proliferative familial IgA nephropathy and severe symptoms of nephrotic syndrome. Medical history also included a period of acute renal failure due to postinfectious glomerulonephritis, which was treated conservatively. Renal treatment consisted of peritoneal dialysis and prednisolone. Prophylactic treatment for haemophilia A consisted of 2000 IU FVIII concentrate three times a week. Further patient characteristics are depicted in table 2. Patient underwent a renal transplantation with perioperative iterative FVIII concentrate dosing guided by the application of Bayesian analysis using individual FVIII plasma concentrations in combination with information from the perioperative population PK model.

INVESTIGATIONS

Renal function tests prior to and after surgery are depicted in table 2. Peak and trough FVIII plasma concentrations were measured daily by a one-stage clotting factor assay, using FVIII-deficient plasma (Siemens Healthcare, Marburg, Germany) and reference plasma (Cryocheck, Precision Biologic, Kordia, Leiden, The Netherlands) on an automated coagulation analyser (Sysmex CA1500, Siemens, Breda, The Netherlands). PK analysis was performed using non-linear mixed-effects modelling (NONMEM (V7.2.0), Globomax LLC, Ellicott City,

Maryland, USA). Individual PK parameter estimates were obtained from Bayesian analysis after performance of an individual FVIII PK profile (figure 1). Application of Bayesian analysis using measured FVIII plasma concentrations resulted in iterative dose adjustments.

TREATMENT

During the perioperative period, patient was treated with FVIII concentrate by bolus infusions, with specific FVIII trough target plasma concentrations >0.65 IU/mL during the first 24 hours and between 0.50 and 0.80 IU/mL during the next 5 days in accordance to protocol defined by the treating haematologist, who adapted standard treatment due to high risk of the intervention.² As shown in figure 1, predicted trough FVIII plasma concentrations were in accordance with measured FVIII plasma concentrations. Moreover, trough FVIII plasma concentrations of >0.50 IU/mL were achieved during five consecutive days following surgery.

OUTCOME AND FOLLOW-UP

Perioperative haemostasis was evaluated as adequate by the surgical team and no postsurgical bleeding or thrombosis was observed. At 12 weeks postsurgical evaluation, renal graft was functioning well.

DISCUSSION

This is the first publication of a patient treated using PK-guided dosing during the total perioperative period based on a perioperative population PK model. We show that iterative adaptive dosing by Bayesian analysis is possible and feasible for major surgical interventions.

Renal transplant surgery is often complicated by adverse haematological events such as bleeding and also intravesical thrombosis, both with a risk of renal allograft rejection.⁷ One earlier report described a renal transplantation in a patient with mild haemophilia that was complicated by the occurrence of an intravesicular bleeding resulting in an allograft rejection.⁸ In another case report, FVIII plasma concentrations were kept >0.70 IU/mL for >2 weeks and afterwards >0.20 IU/mL with long-term successful transplantation of the allograft.⁹ To prevent adverse events, maintenance of predefined trough levels is important. We have shown that it is possible to guide FVIII dosing by iterative application of Bayesian analysis using a recently developed perioperative population PK model in a

Figure 1 An individual PK profile is constructed based on measurement of three FVIII plasma concentrations according to the prophylactic population PK model by Björkman *et al.* In the perioperative setting, FVIII was targeted at >0.65 IU/mL in the first 24 hours following surgery followed by target trough FVIII plasma concentrations of >0.50 IU/mL. Application of Bayesian analysis using a perioperative population PK model resulted in iterative FVIII concentrate dose adjustments. FVIII, factor VIII; PK, pharmacokinetic.

major surgical procedure prone for complications such as bleeding and thrombosis.

Strikingly, actual peak and trough FVIII plasma concentrations after surgery were somewhat higher than predicted by the model. Most probably this under prediction is caused by high postsurgical VWF levels due to inflicted endothelial damage due to the intensity of the surgical procedure. VWF prolongs FVIII presence in the circulation, due to the decrease in clearance by protection from proteolysis, resulting in higher FVIII plasma concentrations.^{4 10 11} In the ongoing prospective randomised controlled 'OPTI-CLOT' trial, which is described in more detail elsewhere,¹² we hope to gain more insight into the relationship between VWF levels and PK parameter estimates. It is expected that future incorporation of VWF into the population PK model will minimise discrepancies. A proposal for when and how

often to measure VWF can then be provided, which will further improve individualised treatment.

Bayesian analysis is already a routine practice for dosing of certain antibiotics, ciclosporin, and some chemotherapeutics. Therefore, we believe that implementation of this approach in the current routine practice of haemophilia will increase quality of care and help achieve individualisation of treatment.

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Contributors MHC and RAAM were responsible for protocol development. HCAMH was responsible for inclusion of the patient and implementation of the study protocol and analysis. RAAM was responsible for advice of iterative dose adjustments. MJHAK was responsible for replacement therapy. MHC supervised the study. HCAMH and MHC were the main authors of the manuscript. All authors substantially contributed to the writing and critically revised the manuscript, with approval of the final draft.

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Patient's perspective

As a patient with haemophilia and comorbidity, I have often experienced anxiety with regard to haemostatic complications around the various surgical procedures I have undergone. Now that I have experienced the advantages and minimal disadvantages of PK-guided dosing, and I realise that this methodology provides a real opportunity to improve suboptimal targeting of coagulation factor levels in the perioperative setting. My recent renal transplantation, which was associated with a high risk of bleeding and thrombosis, illustrates this nicely. Moreover, I realise that in general, minimisation of overdosing will not only decrease thrombotic risk but also minimise healthcare costs by potential decrease of overall consumption of factor concentrates. Inversely, minimisation of underdosing is important to decrease bleeding risk. To conclude, I gladly support this treatment innovation as it optimises quality of care and leads to individualisation of haemophilia treatment.

Learning points

- Individualised perioperative treatment of patients with haemophilia A is possible by application of a Bayesian approach using a recently developed FVIII population PK model, as predefined target ranges were adequately maintained.
- Future individualised PK-guided dosing of factor concentrates may minimise underdosing and overdosing, leading to improvement of quality of care.
- Especially in surgical procedures requiring strict maintenance of FVIII concentrations, PK-guided dosing may be of additional value.

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