CASE REPORT

Pharmacokinetic-guided dosing of factor VIII concentrate in a morbidly obese severe haemophilia A patient undergoing orthopaedic surgery

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SUMMARY

A 58-year-old morbidly obese male (body mass index: 38 kg/m²) with severe haemophilia A underwent total knee replacement surgery. Perioperatively, factor VIII (FVIII) levels were measured daily and maximum *a posteriori* (MAP) Bayesian estimation was used to calculate the individual pharmacokinetic (PK) parameters and doses required to obtain prescribed FVIII target levels. In the MAP Bayesian procedure, a population PK model was used in which PK parameters were normalised using body weight. In this specific case, ideal body weight was used to scale the PK parameters instead of actual body weight. Except for the preoperative FVIII level, adequate FVIII levels were achieved during the 10-day perioperative period. During follow-up visits, the knee prosthesis was reported to function adequately.

BACKGROUND

Haemophilia A is a congenital bleeding disorder, characterised by a deficiency of clotting factor VIII (FVIII), resulting in prolonged bleeding, after (minor) trauma or surgery.¹ Patients with haemophilia are categorised according to FVIII baseline levels: mild (between 0.05 and 0.40 IU/mL), moderate (0.01 to <0.05 IU/mL) or severe haemophilia (less than 0.01 IU/mL).² In patients with severe haemophilia, bleedings can occur spontaneously. For both severe and some moderate patients, FVIII prophylaxis is warranted to prevent bleeding in joints and muscles in order to avoid invalidating haemarthrosis and joint deterioration.³ These patients regularly administer FVIII concentrate doses to obtain target trough levels above 1% (0.01 IU/mL).⁴ In the prophylactic dosing situation, doses are generally adjusted when bleeding occurs, while pharmacokinetic (PK) profiling is still not standard of care. In the perioperative setting, physiological FVIII levels are required for a longer period of time. Therefore, in this setting, more frequent and higher dosing is necessary.

Generally, factor concentrates are dosed according to body weight and to target values, as stated by national guidelines.^{5–7} However, these doses and required target values are not evidence based. Moreover, they are based on empirical *in vivo* recovery data from non-obese patients. In an obese population, the *in vivo* recovery will be higher; the application of dosing according to actual body weight will lead to unwanted higher levels and, consequently, ‘overtreatment’ of these patients.⁸

Recently, a population PK model specifically for perioperative dosing of standard half-life FVIII concentrates in patients with severe and moderate haemophilia A was developed.⁹ In this model, PK parameters differed from those observed during non-surgical prophylaxis. Such a perioperative population PK model can be used to obtain maximum *a posteriori* (MAP) Bayesian estimates of individual PK parameters more accurately in the perioperative setting. However, this perioperative population PK model was developed using data from non-obese patients. Therefore, in patients with obesity, the feasibility of this model may be limited. In this report, we applied the non-obese population PK model to guide dosing in a morbidly obese patient (body mass index (BMI): >35 kg/m²) with haemophilia A undergoing total knee replacement surgery.

CASE PRESENTATION

A 58-year-old morbidly obese man (BMI: 38 kg/m²), with severe haemophilia A with arthropathy of right knee, underwent total knee prosthesis surgery. Prophylactically, the patient infused himself daily with 2000 IU FVIII concentrate (NovoEight). Patient’s medical history also included diabetes

Table 1 Patient and laboratory characteristics

Age (years)	58.3
Actual body weight (kg)	121*
Ideal body weight† (kg)	70.4
BMI‡ (kg/m ²)	38
Height (cm)	176.0
Inhibitors (historically)	None
Inhibitors prior to surgery	None
Baseline FVIII plasma level (IU/mL)	<0.01
Blood group	O ⁺
Creatinine (μmol/L)	73
MDRD (mL/min)	90
Glucose (mmol/L)	15.3
ALAT (U/L)	97
Prophylactic FVIII dosing	2000 IU daily

*The body weight during the assessment of the PK profile was 118 kg.

†Ideal body weight (IBW) was calculated using the following equation: IBW=0.9 * Height – 88, in which Height is specified in centimetre.¹⁶

‡BMI is calculated using the following equation: BMI=ABW/(Height²), where Height is specified in metre and ABW is actual body weight in kilogram.¹⁷

ALAT, alanine aminotransferase; BMI, body mass index; MDRD, modification of diet in renal disease.

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Figure 1 Pharmacokinetic (PK)-guided perioperative standard half-life factor VIII (FVIII) concentrate dosing. (A) PK profile obtained after 50 IU/kg FVIII concentrate bolus dose. The individual PK parameters obtained from this PK profile were used to calculate the initial FVIII dose prior to the surgical procedure. (B) Iterative maximum *a posteriori* Bayesian dosing performed at six different moments in the perioperative period. FVIII levels were predicted using the perioperative population PK model by Hazendonk *et al.*⁹ This perioperative population PK model for FVIII was used to obtain individual PK parameters estimates, from which FVIII doses were calculated in order to achieve prescribed perioperative FVIII target levels during surgery and thereafter. CL, clearance of the central compartment; Vss, volume of distribution in steady state.

mellitus type II and hypertension. No FVIII inhibitors were present historically and prior to surgery (table 1). The initial preoperative FVIII dose was based on individual PK, obtained after a test dose of 6000 IU FVIII concentrate 94 weeks before surgery. During the surgical procedure, the patient received in total 450 mL Ringer's lactate and 350 mL 0.9% sodium chloride via continuous infusion. Perioperative FVIII concentrate dosing was iteratively adjusted by daily monitoring of FVIII levels and, subsequently, MAP Bayesian PK analysis.

INVESTIGATIONS

FVIII levels were measured with a one-stage clotting assay using an automated haemostasis analyser (STA-Evolution Expert Series, STAGO, Mississauga, ON, Canada) with FVIII deficient plasma (HRF, Raleigh, North Carolina, USA). The reference FVIII plasma was obtained using an in-house protocol. As a test dose, the patient received a bolus dose of 50 IU/kg FVIII. Subsequently, eight blood samples were taken within a 48-hour period after FVIII concentrate administration to construct an individual PK profile. MAP Bayesian analysis was performed with NONMEM V.7.4.1 (ICON Development Solutions, Ellicott City, Maryland, USA) to obtain individual PK parameter estimates using the prophylactic population PK model by Björkman

*et al.*¹⁰ Consecutively, initial FVIII concentrate dosing was calculated prior to the surgical procedure. During the surgical procedure, FVIII concentrate was administered by both continuous (0–172 hours) and bolus (172–475 hours) infusion. FVIII levels were monitored daily. Dosing (dose amount and frequency of dosing) was adjusted iteratively on the basis of the individual PK parameter estimates obtained by the application of the MAP Bayesian analysis using the perioperative population FVIII PK model by Hazendonk *et al.*⁹

TREATMENT

For patients with obesity, it has been reported that *in vivo* recovery is higher than that of non-obese patients. Therefore, ideal body weight (70.4 kg) is regularly used instead of actual body weight (in this case 121 kg) to obtain individual PK parameter estimates and, hence, to calculate dosing, and frequency of FVIII concentrate dosing.¹¹ A presurgical individual PK profile provided the following PK parameter estimates (Clearance (CL)=163.2 mL/hour, volume of distribution in steady state (Vss)=4636 mL, $t_{1/2}$ = 20.8 hours) (figure 1A). Individual PK parameter estimates derived from the PK profile were used to calculate the initial FVIII loading dose (2750 IU) and initial rate of continuous FVIII infusion (200 IU/hour) to achieve a target level of >1.0 IU/mL.

As this target was not met prior to surgery (0.83 IU/mL), an additional FVIII bolus of 1000 IU was administered.

After the loading dose prior to surgery, subsequent doses were adjusted using the perioperative population PK model by Hazendonk *et al*⁹ (figure 1B). The FVIII plasma levels were predicted with the perioperative individual PK parameter estimates (day of surgery: CL=233.6 mL/hour, Vss=5519 mL), as derived using MAP Bayesian analysis. During the first 24 hours, patient received 10.292 IU FVIII concentrate in total via continuous and bolus infusions. Directly following initiation and until 24 hours after surgery, all FVIII levels were within target range, as defined by the treating physician (>1.0 IU/mL).⁵ After 24 hours, the target FVIII level was lowered to >0.80 IU/mL by the treating team and maintained for five consecutive days after which it was further reduced to >0.50 IU/mL. To achieve the lower FVIII target level after 24 hours, dose calculations were made on the basis of individual PK parameters from the day of surgery (CL=232.4 mL/hour, Vss=5518 mL). The continuous FVIII infusion (300 IU/hour) was discontinued for 3 hours on day 1 (24–48 hours) and, subsequently, lowered to 200 IU/hour. On day 6 (144–168 hours), the individual PK parameter estimates (day 6: CL=191.3 mL/hour, Vss=4857 mL) were decreased. To achieve the FVIII target level of >0.50 IU/mL on day 7, the continuous FVIII infusion (150 IU/hour) was discontinued for 5 hours on day 6 and, subsequently, continued with a lower rate (100 IU/hour).

OUTCOME AND FOLLOW-UP

By individualised dosing using the ideal body weight, target FVIII levels were obtained adequately after surgery. However, due to minimal bleeding from the operative scar, 5 days after surgery, the treating physician increased the FVIII target trough levels from >0.50 IU/mL to >0.80 IU/mL for a 3-day period on day 9 after surgery (figure 1B—day 9). Although the patient was discharged, a target FVIII trough level of >0.50 IU/mL was maintained for 14 days. Thereafter, regular prophylactic treatment was initiated. At follow-up visit, the knee prosthesis was functioning adequately.

DISCUSSION

In this report, we describe how MAP Bayesian analysis can be applied to individualise FVIII dosing for a morbidly obese patient with severe haemophilia A undergoing orthopaedic surgery. We demonstrated that the perioperative population PK model from Hazendonk *et al* can be applied in patients with obesity by using their ideal body weight, as observed FVIII levels were predicted adequately.

In literature, it has been shown that ideal body weight may be used for individualisation of FVIII concentrate dosing in patients with obesity (BMI from 30 to 40 kg/m²) and overtreatment using *in vivo* recovery can be minimised.⁸ In the referred study, however, it was also shown that in a single patient with extreme obesity (BMI=45.8 kg/m²) FVIII levels were below target when dosed on ideal body weight. In another report, it was suggested to calculate the dose using a capped BMI of 30 kg/m². Although adequate FVIII levels were obtained in a single-studied patient, this method neglects the biological and physiological principles of allometric scaling, which state that PK parameters correlate with a measure of body size.¹² In this report, it is shown that accurate predictions for the measured perioperative FVIII levels can be obtained by application of MAP Bayesian analysis. However, the initial desired FVIII target level was not achieved using the FVIII concentrate dose administered

prior to the surgical procedure. As the PK profile following the FVIII test dose was adequately described using the population PK model from Björkman *et al*, it is not expected that the underprediction of the initial FVIII dose has been caused by using the ideal body weight. Moreover, the body weight of the patient did not differ significantly between the assessment of the PK profile and the surgical period. Although during the surgical procedure, fluids were administered via continuous infusion that could have increased the extracellular volume and consequently the volume of distribution. Nevertheless, it is important to consider that adequate high FVIII levels are of great importance in an acute setting. As a result, FVIII levels should be checked before the start of surgery and corrected if necessary.

Although MAP Bayesian analysis has been applied previously to guide FVIII concentrate dosing for a patient with haemophilia A receiving a kidney graft,¹³ this is the first report on iterative PK-guided dosing of a morbidly obese patient undergoing orthopaedic surgery. Iterative PK-guided dosing allows for multiple adjustments of individual PK parameters in the perioperative period, as several studies have reported continuous changes in PK parameters. In figure 1B, individual PK parameter estimates

Patient's perspective

By undergoing the orthopaedic knee surgery, I hoped to have less pain and bleedings or none afterwards. Having undergone this surgery, this has become a reality and more than that, since I can bend my knee further than expected. Therefore, I don't need my crutches anymore, which allows me to walk my dog, go shopping and walking up the stairs again. Moreover, I feel more energetic than before the surgery, which helps me with the physical activities during physiotherapy and fitness exercises. Importantly, regaining these abilities allows me to do more with my family.

As the doses of FVIII were determined by the OPTICLOT research team, this gave me the confidence that I was being watched over carefully and that the FVIII levels were adequate during the surgical procedure. In my opinion, it can be recommended to have the doses of clotting factor calculated using the methods from the OPTICLOT research team as it is paramount to have adequate FVIII levels. However, the applied method can be further optimized to reach the desired target levels by also having a morning blood sample on the desired time from a trained clinical, that is able to draw blood properly from hemophilia patients. Hereby, I believe that more adequate FVIII levels can be obtained that allow to calculate the needed FVIII doses more precisely.

As a patient, I have had more surgeries in the past. However, this surgical procedure, in which the FVIII doses were individualized, gives me more confidence. Moreover, knowing that a research team looked carefully at the achieved FVIII levels gave me a sense of relief. Therefore, if I need to have surgery again, I would like to have my doses being calculated using the methods applied similar to this surgical procedure.

To further advance clinical hemophilia care, a quicker bedside FVIII sample test should become available. This would allow to check the FVIII levels and, subsequently, adapt the individualized FVIII dosing more frequently.

As a result, I can recommend this procedure to any hemophilia patient undergoing a surgical procedure. Consequently, this method may allow to decrease the clotting factor use which is beneficial for healthcare from a financial point of view.

are depicted according to perioperative day. Moreover, if the FVIII target levels are adapted by the treating physician due to clinical (risk of) bleeding, doses can be recalculated with this methodology.

While PK-guided dosing is increasingly applied to obtain a prophylactic dose regimen, this report shows that iterative Bayesian (PK-guided) dosing can also be applied in a surgical setting.^{14 15} Importantly, the initial FVIII bolus dose, calculated using ideal body weight, was underestimated, probably due to the infusion of electrolyte infusions. However, the calculated FVIII doses in the perioperative setting provided adequate target levels. Although this case report is limited by the description of a single patient, these data underline the possibility of optimising perioperative dosing using MAP Bayesian analysis with a specific perioperative population PK model. Therefore, this report shows the need for data from special populations, such as from patients with obesity and haemophilia, that allows to extend and enrich the present population PK models.

Learning points

- For morbidly obese patients, the use of ideal body weight seems adequate to individualise factor VIII (FVIII) concentrate dosing by the application of population pharmacokinetic (PK) modelling during surgery.
- Although the perioperative population PK model was not constructed using ideal body weight of the patient, the FVIII levels can be adequately predicted.
- Maximum *a posteriori* Bayesian estimation of FVIII doses can support alterations in FVIII target level necessary to adequately treat clinical complications.

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REFERENCES

- 1 Fijnvandraat K, Cnossen MH, Leebeek FW, *et al.* Diagnosis and management of haemophilia. *BMJ* 2012;344:e2707.
- 2 Blanchette VS, Key NS, Ljung LR, *et al.* Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost* 2014;12:1935–9.
- 3 Escobar M, Sallah S. Hemophilia A and hemophilia B: focus on arthropathy and variables affecting bleeding severity and prophylaxis. *J Thromb Haemost* 2013;11:1449–53.
- 4 Iorio A, Iserman E, Blanchette V, *et al.* Target plasma factor levels for personalized treatment in haemophilia: a Delphi consensus statement. *Haemophilia* 2017;23:e170–e179.
- 5 Leebeek FWG, Mauser-Bunschoten EP. New Dutch guidelines for diagnosis and treatment of haemophilia and allied disorders. *Ned Tijdschr Hematol* 2010;7:107–14.
- 6 Hay CR, Brown S, Collins PW, *et al.* The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol* 2006;133:591–605.
- 7 Srivastava A, Brewer AK, Mauser-Bunschoten EP, *et al.* Guidelines for the management of hemophilia. *Haemophilia* 2013;19:e1–e47.
- 8 Graham A, Jaworski K. Pharmacokinetic analysis of anti-hemophilic factor in the obese patient. *Haemophilia* 2014;20:226–9.
- 9 Hazendonk H, Fijnvandraat K, Lock J, *et al.* A population pharmacokinetic model for perioperative dosing of factor VIII in hemophilia A patients. *Haematologica* 2016;101:1159–69.
- 10 Björkman S, Oh M, Spotts G, *et al.* Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight. *Blood* 2012;119:612–8.
- 11 Henrard S, Speybroeck N, Hermans C. Impact of being underweight or overweight on factor VIII dosing in hemophilia A patients. *Haematologica* 2013;98:1481–6.
- 12 Boban A, Henrard S, Lambert C, *et al.* Continuous infusion of factor VIII concentrates in obese patients with severe haemophilia A: is weight-based dose-adjustment required? *Haemophilia* 2016;22:e62–e64.
- 13 Hazendonk HC, Kruip MJ, Mathôt RA, *et al.* Pharmacokinetic-guided dosing of factor VIII concentrate in a patient with haemophilia during renal transplantation. *BMJ Case Rep* 2016;2016:bcr2016217069.
- 14 Mangles S, Rea C, Madan B, *et al.* Real life experiences of a PK dosing study—Challenges and lessons learned. *Haemophilia* 2018;24:e145–e148.
- 15 Hazendonk H, van Moort I, Mathôt RAA, *et al.* Setting the stage for individualized therapy in hemophilia: What role can pharmacokinetics play? *Blood Rev* 2018;32:265–71.
- 16 Devine BJ. Gentamicin therapy. *Drug Intelligence and Clinical Pharmacy* 1974;8:650–5.
- 17 Garrow JS, Webster J. Quetelet's index (W/H²) as a measure of fatness. *Int J Obes* 1985;9:147–53.

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