"Body weight and fat mass index as strong predictors of factor VIII in vivo recovery in adults with hemophilia A"

Henrard, Séverine ; Speybroeck, Niko ; Hermans, Cédric

Abstract
Background: The treatment of hemophilia A requires infusions of factor VIII (FVIII) concentrates. The number of units to be given in order to obtain the target level is calculated using the formula: [body weight (BW) x desired FVIII increase]/2, which assumes that each unit infused per kg of BW increases the FVIII level by 2%. Objectives: The present observational study evaluated the dependence of FVIII recovery on different morphometrical variables: BW, fat mass index (FMI), body mass index, and the difference between actual and ideal BW. Patients and methods: FVIII recovery was measured in 46 non-actively bleeding hemophilia A patients, being treated with a recombinant FVIII concentrate. Regression trees were used to identify morphometrical predictors of recovery. Results: The median recovery was 2.08 for all patients, 2.63 for those with a BW >= 81.0 kg and 1.87 for others (P < 0.001). The recovery was significantly higher when FMI was >= 20% compared with FMI < 15% (median recove...
Body weight and fat mass index as strong predictors of factor VIII in vivo recovery in adults with hemophilia A

S. HENRARD,* † N. SPEYBROECK* and C. HERMANS†

Institute of Health and Society, Université catholique de Louvain, Brussels; and Haemostasis and Thrombosis Unit, Division of Adult Haematology, Cliniques universitaires Saint-Luc, Brussels, Belgium

To cite this article: Henrard S, Speybroeck N, Hermans C. Body weight and fat mass index as strong predictors of factor VIII in vivo recovery in adults with hemophilia A. J Thromb Haemost 2011; 9: 1784–90.

Summary. Background: The treatment of hemophilia A requires infusions of factor VIII (FVIII) concentrates. The number of units to be given in order to obtain the target level is calculated using the formula: [body weight (BW) × desired FVIII increase]/2, which assumes that each unit infused per kg of BW increases the FVIII level by 2%. Objectives: The present observational study evaluated the dependence of FVIII recovery on different morphometrical variables: BW, fat mass index (FMI), body mass index (BMI), and the difference between actual and ideal BW. Patients and methods: FVIII recovery was measured in 46 non-actively bleeding hemophilia A patients, being treated with a recombinant FVIII concentrate. Regression trees were used to identify morphometrical predictors of recovery. Results: The median recovery was 2.08 for all patients, 2.63 for those with a BW ≥ 81.0 kg and 1.87 for others (P < 0.001). The recovery was significantly higher when FMI was ≥ 20% compared with FMI < 15% (median recovery: 2.35 vs. 1.74; P = 0.007). Using regression trees, three groups were created: BW < 80.5 kg and FMI < 22.3%, BW < 80.5 kg and FMI ≥ 22.3% and BW ≥ 80.5 kg. Median recovery in these groups was 1.80, 2.16 and 2.63, respectively (P < 0.001). Conclusions: The dose calculation of FVIII should take into account both BW and FMI, and be adapted to underweight or overweight patients. Comparison of the average recovery after different FVIII concentrates should keep in mind morphometrical patient characteristics.

Keywords: factor VIII recovery, fat mass index, hemophilia A, recombinant factor VIII.

Correspondence: Cedric Hermans, Haemostasis and Thrombosis Unit, Haemophilia Clinic, Division of Haematology, St-Luc University Hospital, Avenue Hippocrate 10, BE-1200 Brussels, Belgium.
Tel.: +32 2 764 17 85; fax: +32 2 764 89 59.
E-mail: cedric.hermans@uclouvain.be

Received 21 March 2011, accepted 17 June 2011

Introduction

Hemophilia A is a hereditary hemorrhagic disease characterized by a partial or complete deficiency of circulating factor VIII (FVIII) [1]. For preventive or curative therapy of bleeding episodes, concentrates of FVIII are administered by intravenous (i.v.) infusions. Correct dosing of FVIII is crucial as underdosing puts patients at risk of hemorrhage, and overdosing results in a waste of expensive concentrates.

The number of FVIII units to be given in order to achieve a specific circulating FVIII level is calculated using the following formula: [body weight (BW) in kg × desired FVIII increase in %]/2. This formula is based on a FVIII recovery of 2 assuming that each unit of FVIII infused per kg of body weight will increase the circulating FVIII level by 2%.

This recovery value of 2 was validated in 1981 by Ingram [2] and was derived from three different approaches. The first approach used a formula relating the observed FVIII increase, i (IU dL⁻¹), to the patient’s weight, w (kg), and the administered dose, d (IU), using the formula (w × i)/d = k, where k was found to be 2 in patients followed at Oxford [3]. The two other approaches used different methods for dose calculation, the plasma volume being considered to be arbitrary 0.41 dL kg⁻¹ in the second approach and [0.24 × height (cm)] + [0.09 × weight (kg)]−17.1 in the third. Ingram showed that the mean value of the (w × i)/d index was close to 2. If a value of 2 was accepted for the constant k, the plasma volume was assumed to be equivalent to 0.5 (≈ 0.41)dL kg⁻¹. A value of 2 was found to be valid except for patients whose morphometrical characteristics markedly differed from the average.

To our knowledge, the real impact of the fat mass index (FMI), body mass index (BMI) or the difference between actual and ideal BW (IBW) on FVIII recovery has not yet been evaluated. The aim of the present study was to assess the inter-individual variability of FVIII recovery in a group of patients and study its dependence on several morphometrical variables (BW, FMI, BMI, and difference between BW and IBW). In addition, a review of FVIII recovery values after different recombinant FVIII concentrates, as reported in peer-reviewed literature, was conducted.
Patients and methods

Patients

The present study included 46 adult patients with hemophilia A who regularly attended the Haemophilia Comprehensive Centre of the Cliniques universitaires Saint-Luc in Brussels between November 2003 and April 2010. They all received a dose of FVIII as part of their prophylactic treatment or to prevent bleeding complications before invasive procedures. None of the patients was actively bleeding at time of enrolment. All patients were treated with a commercially available second- or third-generation concentrate of recombinant FVIII (Advate®, Kogenate® or Refacto®).

Baseline characteristics, including haemophilia severity, age, height, BW, as well as dose and type of coagulation factor (Advate®, Kogenate®, or Refacto®) were recorded at enrolment. Blood sampling was performed before FVIII infusion and repeated on the opposite arm 10 min after infusion. FVIII levels were measured using a one-stage assay. For patients treated with Refacto®, the appropriate standard was used. The FVIII recovery was calculated according to the following formula: [body weight (kg) × observed FVIII increase (%)]/administered dose (IU). FVIII recovery was expressed as a percentage increment in FVIII per unit of FVIII per kg infused. BMI was calculated according to the following formula: BW (kg)/height (m)². IBW was calculated using Lorentz’s formula: height (cm)–100–[(height (cm)–150)]/4. FMI was calculated by impedance (Omron® BF306 Body Fat Monitor; Omron Healthcare Europe, Hoofddorp, the Netherlands).

Statistical analysis

Variables were analyzed using means and standard deviations (SDs) when they were normally distributed, and medians (P25 and P75) when they were not normally distributed. Continuous variables were compared using the Kruskal-Wallis test, and categorical variables using Fisher’s exact test. The study subjects were divided into tertile groups according to BW and to differences between BW and IBW in order to compare FVIII recovery between groups. For BMI and FMI, group cut-offs were obtained from the literature. Regression tree analysis was used in order to analyze the relation between morphometrical determinants and FVIII recovery. Regression tree-based models are non-linear and non-parametric alternatives in comparison to linear models for regression problems. The technique of regression trees has been used in other medical contexts, but to our knowledge, not yet applied to the field of hemophilia. The one-standard error rule was used to select the best tree [4]. Additionally, a random forest provided a ranking based on the overall contribution of each morphometrical variable in the construction of the tree. Statistical analyzes were performed using R software version 2.12.0 (Free Software Foundation, Inc., Boston, MA, USA). A P-value < 0.05 was considered statistically significant.

Literature review

A literature search on published FVIII recovery values and their dependence on morphometrical variables was performed for five recombinant FVIII concentrates (Advate® (Baxter Bioscience, Deerfield, IL, USA), Kogenate® (Bayer HealthCare AG, Leverkusen, Germany), Kogenate FS® (Bayer HealthCare AG), Refacto® (Pfizer Inc/Wyeth, New York, NY, USA) and Recombinate® (Baxter Healthcare Corp., Hyland Immuno Division, Glendale, CA, USA)). All articles published in PubMed from 1966 to December 2010 were identified using a PubMed search with the names of the concentrates as keywords. All papers were then critically examined for FVIII recovery data in adult patients. Information pertaining to the recovery as reported in the package insert of each concentrate was also collected.

Results

Patient characteristics and FVIII recovery

In all, 46 patients were included in the study with a mean age of 40.4 ± 12.3 years. They suffered from severe, moderate or mild hemophilia A, and received a median FVIII dose of 2000 IU, with a minimum of 980 IU and a maximum of 4200 IU (Table 1). Half of the patients received Advate®

Table 1 Baseline and clinical patient characteristics (n = 46)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD or median [P25; P75]</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII recovery, IU dL⁻¹/IU kg⁻¹</td>
<td>2.08 [1.70; 2.52]</td>
<td></td>
</tr>
<tr>
<td>FVIII dose, IU</td>
<td>2000 [1985; 3000]</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>40.4 ± 12.3</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>177.1 ± 7.0</td>
<td></td>
</tr>
<tr>
<td>BW, kg</td>
<td>77.6 ± 17.8</td>
<td></td>
</tr>
<tr>
<td>IBW difference, kg</td>
<td>7.3 ± 15.4</td>
<td></td>
</tr>
<tr>
<td>BMI, kg m⁻²</td>
<td>24.7 [20.7; 27.0]</td>
<td></td>
</tr>
<tr>
<td>FMI, %</td>
<td>22.5 ± 9.2</td>
<td></td>
</tr>
<tr>
<td>&lt; 15.0</td>
<td>19.6 (9)</td>
<td></td>
</tr>
<tr>
<td>15.0–19.9</td>
<td>23.9 (11)</td>
<td></td>
</tr>
<tr>
<td>≥ 20.0</td>
<td>56.5 (26)</td>
<td></td>
</tr>
<tr>
<td>FVIII level, %</td>
<td>5%–25% (mild)</td>
<td>21.7 (10)</td>
</tr>
<tr>
<td>&lt; 1% (severe)</td>
<td>21.7 (10)</td>
<td></td>
</tr>
<tr>
<td>1%–4% (moderate)</td>
<td>56.6 (26)</td>
<td></td>
</tr>
</tbody>
</table>

© 2011 International Society on Thrombosis and Haemostasis
Table 2 Baseline characteristics of patients in function of the factor VIII (FVIII) concentrate used

<table>
<thead>
<tr>
<th>Coagulation factor</th>
<th>Advate® (n = 23)</th>
<th>Kogenate® (n = 16)</th>
<th>ReFacto® (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII recovery, IU dL⁻¹/IU kg⁻¹</td>
<td>Median [P₂₅; P₇₅]</td>
<td>Median [P₂₅; P₇₅]</td>
<td>Median [P₂₅; P₇₅]</td>
</tr>
<tr>
<td>BW, kg</td>
<td>72.0 [61.5; 80.0]</td>
<td>81.0 [69.3; 90.4]</td>
<td>81.0 [79.5; 94.0]</td>
</tr>
<tr>
<td>IBW difference, kg</td>
<td>0.3 [–7.9; 10.6]</td>
<td>7.8 [–0.3; 20.3]</td>
<td>13.0 [11.3; 16.6]</td>
</tr>
<tr>
<td>BMI, kg m⁻²</td>
<td>22.4 [19.8; 26.1]</td>
<td>24.6 [22.3; 28.7]</td>
<td>26.8 [26.0; 27.5]</td>
</tr>
<tr>
<td>FMI, %</td>
<td>16.6 [14.2; 25.8]</td>
<td>25.4 [17.1; 32.2]</td>
<td>24.2 [20.0; 27.3]</td>
</tr>
</tbody>
</table>

BW, body weight; IBW, ideal body weight; IBW difference, difference between BW and IBW; BMI, body mass index; FMI, fat mass index.

*(P-value < 0.05).

(n = 23/46, 50.0%), one-third Kogenate® (n = 16/46, 34.8%) and the remaining seven ReFacto® (15.2%) (Table 2). The mean BW was 77.6 ± 17.8 kg. Twenty patients had a BMI ≥ 25 kg m⁻² (43.4%) and 26 a FMI ≥ 20.0% (56.5%) (Table 1). BMI was significantly higher in the ReFacto® group compared with the Advate® group (Kruskal–Wallis P = 0.044). The difference between BW and IBW was significantly higher in the ReFacto® group compared with the Advate® group (Kruskal–Wallis P = 0.040). Median FVIII recovery was 2.08 IU dL⁻¹/IU kg⁻¹. No significant difference with respect to FVIII recovery, BW or FMI was observed between the various concentrates. Median recovery was 2.2 in severe hemophiliacs (n = 10), 2.0 in moderate hemophiliacs (n = 26) and 2.2 in mild hemophiliacs (n = 10). The recovery was not significantly different when patients were categorized according to their hemophilia severity (Kruskal–Wallis P = 0.232).

**FVIII recovery and morphometrical predictors (univariate analysis)**

Patients were divided into tertile groups according to their BW: low (< 70.0 kg, n = 14), medium (70.0–80.9 kg, n = 15) and high (≥ 81.0 kg, n = 17). Median FVIII recovery was 1.98, 1.86 and 2.63, respectively. FVIII recovery was significantly higher in the high BW group compared with the low and medium BW groups (Kruskal–Wallis P < 0.001). A box plot illustrates median FVIII recovery in the different BW groups (Fig. 1A).

In order to evaluate the impact of differences between BW and IBW, three groups were created using tertiles: patients with categorized according to their hemophilia severity (Kruskal–Wallis P = 0.232).

**Fig. 1.** Box plot of factor VIII (FVIII) recovery according to body weight (BW). (A) difference between BW and ideal body weight (IBW) (B), fat mass index (FMI) (C) and body mass index (BMI) (D).

© 2011 International Society on Thrombosis and Haemostasis
a BW difference lower than 0.25 kg (median FVIII recovery: 1.89, \( n = 15 \)), those with a BW difference between 0.25 and 11.99 kg (median FVIII recovery: 2.12, \( n = 15 \)) and those with a BW difference higher than or equal to 12.00 kg (median FVIII recovery: 2.47, \( n = 16 \)). The FVIII recovery was significantly higher in the last group as compared with the first (Kruskal–Wallis \( P = 0.032 \)) (Fig. 1B).

Patients were divided into three groups according to their FMI: FMI < 15.0\% (\( n = 9 \)), between 15.0\% and 19.9\% (\( n = 11 \)), and \( \geq 20.0\% \) (\( n = 26 \)). Median FVIII recovery for these groups was 1.74, 1.89 and 2.35, respectively. FVIII recovery was significantly higher in the FMI \( \geq 20\% \) group compared with the FMI < 15.0\% group (Kruskal–Wallis \( P = 0.007 \)) (Fig. 1C).

In a similar way, patients were divided into three groups according to their BMI: BMI between 18.5 and 24.9 kg m\(^{-2}\) (normal patients (\( n = 26 \)); median FVIII recovery = 1.88), between 25.0 and 29.9 kg m\(^{-2}\) (overweight patients (\( n = 14 \)); median FVIII recovery = 2.30) and higher than or equal to 30.0 kg m\(^{-2}\) (obese patients (\( n = 6 \)); median FVIII recovery = 2.70) (Fig. 1D). FVIII recovery was significantly different between the normal and obese BMI groups (Kruskal–Wallis \( P = 0.010 \)).

**Morphometrical predictors of FVIII recovery (multivariate analysis)**

A regression tree analysis was used to divide the patient population so as to create homogenous patient groups with respect to FVIII recovery (Fig. 2). Potential morphometrical predictors of FVIII recovery used in the analysis were BW, difference between BW and IBW, BMI, FMI, height and patient age. BW was found to be the strongest predictor of FVIII recovery. Patients with BW \( \geq 80.5 \) kg presented higher FVIII recovery compared with patients with a BW < 80.5 kg (mean FVIII recovery: 2.62 vs. 1.90, respectively). In the last group, FVIII recovery was superior in patients with a higher FMI compared with those with a lower FMI (mean FVIII recovery: 2.15 vs. 1.78, respectively).

A box plot (Fig. 3) of FVIII recovery in the three groups based on a regression tree showed that FVIII recovery was significantly higher in patients of group 3 compared with group 1 (Kruskal–Wallis \( P < 0.001 \)). Median FVIII recovery (\( P_{25} \); \( P_{75} \)) was 1.80 (1.63; 1.97) in group 1, 2.16 (1.83; 2.32) in group 2 and 2.63 (2.23; 2.90) in group 3.

Although BMI and patient height did not appear as the main splitters in the final tree, they were identified as important predictors of FVIII recovery as shown by their discriminatory power ranking (Table 3). Age and difference between BW and IBW only had a minor influence.

In group 1, formed on the basis of regression trees, 80.0\% (\( n = 16/20 \)) of patients were found to be undertreated (FVIII recovery < 2) compared with 33.3\% (\( n = 3/9 \)) in group 2 and 11.8\% (\( n = 2/17 \)) in group 3. The proportion of undertreated patients was significantly different between the groups (Fisher's exact test, \( P < 0.001 \)).

**Literature review of FVIII recovery values for Advate®, Kogenate®, Kogenate FS®, ReFacto® and Recombinate®**

In the 16 identified studies that reported FVIII recovery in adults treated with recombinant FVIII (Advate®, Kogenate®, Kogenate FS®, ReFacto® or Recombinate®), information about BW was not consistently available [5–10] (Table 4). Several studies [5,6,8–15] including both adults and children
showed a lower FVIII recovery (< 2) in children [16,17]. In studies stating BW and age among adult patients, Di Paola et al. [18] reported a mean FVIII recovery of 2.35 ± 0.50 for Advate® and 2.23 ± 0.33 for ReFacto® in patients with a mean BW of 80.4 ± 14.7 kg (min–max: 63.8–123.5 kg); Kessler et al. [19] found a mean FVIII recovery of 2.43 ± 0.38 in adults with a mean BW of 76 kg (min–max: 57–112 kg); and Santoro et al. [20] showed a mean FVIII recovery of 2.50 ± 0.31 in adults with a mean BW of 69.5 ± 13.0 kg (min–max: 42–90 kg). As shown in Table 4, all studies reported a mean FVIII recovery higher than 2 except for two Asian studies. Yoshioka et al. [15] reported a mean FVIII recovery of 1.73 ± 0.40 in Japanese patients with a mean BW of 56.1 ± 10.2 kg, and Shi et al. [14] found a mean FVIII recovery of 1.9 ± 0.9 in Chinese patients with a mean BW of 58.7 ± 16.3 kg.

Discussion

In 1981, Ingram [2] compared three ways to calculate the FVIII dose to be administrated to hemophilia A patients. The first approach used the empirical formula relating observed increments (target–baseline FVIII levels or i IU dL−1) to patient weight (w kg) and dose given (d IU) using the expression (w × i)/d = k, where k represented FVIII recovery and was found to be equal to 2, considered as the target. The second method was based on patient plasma volumes calculated using BW as 0.41 dL kg−1. The third approach used patient plasma volumes calculated using both height and weight, where plasma volume (dL) was computed as [0.24 × height (cm)] + [0.09 × weight (kg)]−17.1. Accepting a value of 2 for the constant k is equivalent to considering a plasma volume of 0.5. The authors concluded that the first formula was superior to the two others,
and only in cases where the patient’s body build departed markedly from the average would it be necessary to consider both height and BW for plasma volume calculation.

Since this landmark report, only a few studies have evaluated the dependence of recovery on patient BW [21]. Given that plasma volume is not proportional to BW [22,23], FVIII recovery is not an independent parameter, but varies according to individual morphometrical variables. The physiology of plasma volume, published data and the present study results support the concept that in vivo FVIII recovery increases in tandem with BW. Recently, Collins et al. [23] suggested that in clinical practice, patients were appropriately dosed when IBW was used instead of actual BW. To our knowledge, no other authors have investigated the influence of morphometrical indicators, such as FMI or the difference between BW and IBW.

Not surprisingly, FVIII recovery was found to increase steadily with BW, as supported by a median FVIII recovery ranging from 1.87 among patients with BW < 81.0 kg to 2.63 in patients with a BW ≥ 81.0 kg. Additionally, FVIII recovery increased in line with the difference between BW and IBW: patients exhibiting a BW difference between 0.25 and 11.99 kg were found to have a median FVIII recovery of 2.12. Moreover, patients with a FMI ≥ 20.0% were shown to be over treated as they achieved higher than expected FVIII levels. In contrast, patients with a FMI < 15.0% were undertreated. FVIII recovery was also higher in obese patients compared with normal BMI patients. The regression tree method showed that FVIII recovery depended on both BW and FMI. Therefore, an assumed rise of 2%/IU of factor VIII/kg is not applicable to groups 1 and 3.

In previous studies reporting FVIII recovery in adults treated with Advate®, Kogenate®, Kogenate FS®, ReFacto®, or Recombinate®, patient BW was not always available, meaning that recovery values need to be interpreted with great caution and cannot be compared. When BW and patient age data were available (only adults), all studies exhibited a mean FVIII recovery higher than 2; however, many of these patients were overweight or obese, with the exception of the two Asian studies [14,15] where mean patient BW was expectedly lower.

Since Ingram’s 1982 study [2], FVIII recovery of 2 has been used in all recommendations dealing with replacement therapy in hemophilic patients when either advising a target FVIII level or giving a FVIII dose in units per kg BW. It is now apparent that a 2%/IU rise in FVIII/kg is not applicable to all hemophilia A patients irrespective of BW and FMI. Given these considerations, FVIII dosing for the treatment of bleeding episodes or prevention of bleeding complications before invasive procedures should be individualized rather than using fixed and arbitrary dosing in certain patient cases [24].

Approximately half of our patients were overweight or obese, based on both BMI and FMI, with 20 (43.5%) having a BMI ≥ 25 kg m⁻² and 26 (56.5%) having a BMI ≥ 20%. Individually adapting the FVIII dose is increasingly relevant as a result of the growing number of obese hemophiliacs [25,26].

A possible limitation of the present study is that the recovery values were calculated on a single blood sample taken 10 min after the end of the infusion of the concentrate. One cannot rule out that the peak FVIII level was delayed in some patients. It had indeed been reported that the peak FVIII level is often found 10–15 min after the end of infusion, even if later peak values, after 1–2 h, have been observed [27]. Underestimation of the recovery values, which cannot be excluded in some patients, would be small and without significant impact on the interpretations of the results of the present study.

In conclusion, FVIII dosing should take into account patient BW and FMI, and it must be individually adapted to underweight or overweight patients. However, a FVIII recovery value of 2 can be used for normal BW patients with a FMI in the range of 15%–20%. A comparison of the average recovery reported with different FVIII concentrates should take into consideration the morphometrical characteristics of the studied patient population. Because of the influence of morphometrical variables, only findings from cross-over studies performed in the same patients appear to be valid to compare the kinetic properties of different FVIII concentrates.

Disclosure of Conflict of Interest

The authors state that they have no conflict of interest.

References


© 2011 International Society on Thrombosis and Haemostasis