von Willebrand factor/factor VIII concentrate (Haemate® P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery

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Summary. Background: While plasma-derived concentrates containing large amounts of von Willebrand factor (VWF) are effective in treating von Willebrand disease (VWD), optimal dosing remains to be fully characterized. Objectives: To determine the feasibility of dosing Haemate P® VWF/factor VIII (FVIII) concentrate based on pharmacokinetics (PK) in the management of surgical subjects with VWD. Methods: VWD subjects scheduled for elective surgery were enrolled in a prospective multicenter open-label cohort study. A pre-operative loading dose of VWF/FVIII concentrate based upon prior individual subject PK analysis was administered followed by postoperative therapeutic/maintenance infusions. Results: Twenty-eight subjects with types 1, 2A or 3 VWD and one with type 2 M were enrolled. Median in vitro recovery of VWF ristocetin cofactor (VWF:RCo) was 1.9 IU dL⁻¹ (IU kg⁻¹)⁻¹ with an interquartile range (IQR) of 1.6–2.5 IU dL⁻¹ (IU kg⁻¹)⁻¹. Median response, half-life and clearance were 74.0% (IQR, 55.5–100%), 15.6 h (IQR, 9.0–28.4 h) and 3.26 mL kg⁻¹ h⁻¹ (IQR, 2.29–5.21 mL kg⁻¹ h⁻¹), respectively. A PK-guided median VWF:RCo loading dose of 62.4 IU kg⁻¹ (IQR, 50.1–87.0 IU kg⁻¹) was administered. Postoperative mean trough VWF:RCo levels of 62–73 IU dL⁻¹ were sufficient to prevent bleeding. Investigators rated hemostasis excellent or good in 96.3% of subjects on the day of surgery and 100% on the next day and on day 14. A subject with multiple risk factors developed pulmonary embolism, which resolved without sequelae. Conclusions: Haemate P® provided effective and safe hemostasis in VWD subjects undergoing elective surgery. Selection of Haemate® P loading dose on the basis of VWF PK proved feasible.

Keywords: factor VIII, hereditary diseases, postoperative hemorrhage, prospective studies, surgical hemostasis, von Willebrand factor.

Introduction

Virus-inactivated, plasma-derived concentrates containing von Willebrand factor (VWF) and factor VIII (FVIII) have become a standard of treatment for von Willebrand disease (VWD). A heterogenous disease, VWD is subdivided into three main types according to quantitative (types 1 and 3) or qualitative (types 2A, 2B, 2 M and 2 N) abnormalities [1]. Patients with VWD are subject to impaired hemostasis via two mechanisms: (i) defective adhesion and aggregation of platelets to damaged subendothelium in primary hemostasis and (ii) decreased FVIII levels resulting from shortened FVIII half-life as a result of deficiency of VWF.

While most cases of type 1 VWD can be treated with the synthetic vasopressin analog desmopressin (DDAVP), patients with type 3 VWD and the majority of those with type 2 require concentrates containing large amounts of VWF because insufficient functional endogenous VWF is released by DDAVP. Some type 1 patients may also require VWF/FVIII concentrates if they are not responsive to DDAVP, need prolonged hemostatic cover as a result of major surgery, or present with contraindications to DDAVP, such as cardiovascular disease.

Plasma-derived virus-inactivated VWF/FVIII concentrates have been available since the 1980s and have been used extensively and effectively to treat VWD [2,3]. However, optimal dosing intensity and duration still need to be more...
fully delineated in specific clinical situations such as surgery and recurrent bleeding [2–4]. In addition, the pharmacokinetics (PK) of the VWF/FVIII concentrates in the various types of VWD remains to be more completely characterized.

As VWF/FVIII concentrates were originally developed to treat individuals with hemophilia A, their potency was labeled according to the FVIII coagulant activity (FVIII:C) content. Consequently, at the outset and for many years thereafter dosing for VWD was based on units of FVIII:C. However, the ratio of FVIII to VWF differs between concentrates, and hence dosing based on FVIII can lead to undesirable variability in attained levels of VWF. Some concentrates are now labeled with content of both FVIII:C and VWF ristocetin cofactor activity (VWF:RCo), and in several reports reliance on the VWF:RCo activity of the concentrate for replacement therapy in VWD patients has been advocated [5–7].

Introduced in 1981, Haemate® P (CSL Behring, Marburg, Germany; also distributed as Humate-P® in North America) has established itself as the gold standard of VWF/FVIII concentrates in the management of VWD [3]. Haemate P® is derived from plasma and contains approximately 2.4 IU VWF:RCo for each IU of FVIII:C, the highest ratio among a panel of 12 VWF/FVIII concentrates tested in a comparative study [8]. In addition, Haemate P® is one of the concentrates with the best preserved multimer structure. The largest multimers of VWF are most effective in promoting the formation of the platelet plug [9–11]. The average content of high molecular weight VWF multimers (bands ≥ 11) in this concentrate is 84.1% of the corresponding bands in normal human plasma, the highest percentage initially among six and subsequently 12 concentrates tested in comparative studies [8,12,13]. In addition to its clinical efficacy, Haemate® P has also demonstrated an excellent safety record over the past 25 years of clinical use [14–19].

In a number of retrospective studies, surveys and case reports the successful peri-operative use of Haemate® P has been described [16,17,20–26]. Recently, a prospective study in subjects undergoing emergency surgery has been reported [19], as well as a small prospective series of five type 2 VWD subjects undergoing elective surgery [26].

This investigation involving elective surgery in VWD subjects of various types was designed to assess the feasibility of basing dosing decisions on pre-operative PK analysis. This is the first prospective clinical study of Haemate® P to determine the loading dose of VWF on the basis of VWF PK.

Methods

Study design

In this prospective multicenter open-label cohort study of 29 subjects with VWD undergoing elective surgery, dosing of Haemate® P based on PK was evaluated at 12 centers between October 2001 and May 2003. Eleven additional participating centers did not enroll any subjects. Independent ethics committees of all centers approved the study, and written informed consent was obtained from all subjects.

The specific aim of the study was to assess the effectiveness of the VWF/FVIII concentrate for bleeding prophylaxis in elective surgery when the loading dose of concentrate is based on pre-operative PK determinations of individual subject in vivo recovery (IVR) of VWF. The pre-operative PK analysis encompassed both VWF and FVIII, and the analytical results were used to compute the loading dose for surgery. Subjects were followed for 14 days after surgery, and therapeutic/maintenance VWF/FVIII doses and administration intervals were selected by the investigator based on clinical and laboratory findings of the individual subject.

Subject selection

Candidates for study entry must have presented with a clinical and laboratory diagnosis of VWD and a history of abnormal bleeding. Both males and females > 5 years old with hereditary VWD were eligible. Enrollment was restricted to subjects scheduled for elective surgery requiring a hospital stay of at least 24 h. Exclusion criteria were acquired VWD, known antibodies to FVIII or VWF, platelet type VWD, and exposure to DDAVP, FVIII inhibitor bypass activity (FEIBA), cryoprecipitate or blood or plasma derivatives containing FVIII or VWF within 10 days prior to PK infusion or surgery.

Study medications

Five Haemate® P lots were used for PK and peri-operative infusions. During the study, subjects were allowed to receive standard antithrombotic prophylaxis, cyclo-oxygenase-2 (COX-2) inhibitors, aminocaproic acid, tranexamic acid and fibrin glue. FEIBA, cryoprecipitate and non-COX-2 agents with antiplatelet actions, for example dextran, non-steroidal anti-inflammatory drugs and preparations containing acetylsalicylic acid were not allowed.

Pharmacokinetic determinations

At least 2 weeks but not more than 1 month prior to a planned surgical intervention, subjects received a single i.v. concentrate infusion with a median of 79 IU kg⁻¹ VWF:RCo (approximately 32 IU kg⁻¹ FVIII:C). Plasma samples drawn at 0, 0.25, 0.5, 1, 2, 4, 8, 24 and 48 h after the end of infusion were assayed for VWF:RCo, VWF antigen (VWF:Ag) and FVIII:C at the local study center laboratories using the standard methods at each center and also at a central coagulation laboratory (Ulrich Budde, Hamburg, Germany). Collagen binding capacity (VWF:CB) and multimer analysis were performed at the central laboratory site. VWF:CB, an assay that detects primarily higher molecular weight multimeric forms of VWF, was performed with a non-commercial enzyme-linked immunosorbent assay (ELISA) employing collagen suspension (Horm®; Nycomed AG, Munich, Germany). VWF multimers were evaluated using luminographic detection in agarose gels [27].
IVR and response were determined for VWF:RCo, VWF:Ag, FVIII:C and VWF:CB. IVR is expressed in units of IU dL⁻¹ (IU kg⁻¹)⁻¹ and calculated as IVR = ΔCₘ₃ₒₓ/(dose/bw), where ΔCₘ₃ₒₓ = maximum plasma concentration increment in 2 h (IU dL⁻¹), dose = IU administered and bw = kg body weight. The definition of response was the observed as a percentage of expected peak activity, namely, response = ΔCₘ₃ₒₓ/(dose/pv) × 100%, where pv = plasma volume in dL.

For PK analysis, a two-compartment model was adopted with bolus input and first-order output, and a parameter was included to account for endogenous background levels. The elimination half-lives of VWF:RCo and VWF:Ag were calculated from the slope of the decay curve during the terminal phase. The area under the curve (AUC), mean residence time (MRT), volume of distribution at steady state (Vss) and clearance were calculated for VWF:RCo and VWF:Ag.

**Peri-operative infusions**

General recommendations for target levels of VWF:RCo and FVIII:C to be attained after the loading dose and therapeutic/maintenance infusions were provided to the investigators (Fig. 1). The loading dose required to achieve a target VWF:RCo concentration increment (ΔVWF:RCo) in IU dL⁻¹ was calculated based on individual subject PK results as dose = ΔVWF:RCo/bw/IVRobserved.

The initial loading infusion was administered 1–2 h before the start of the elective procedure. Postoperative doses were given at the discretion of the investigator. It was recommended that required postoperative infusions be administered at least once every 24 h.

**Hemostatic endpoints**

Assessment of hemostatic effectiveness was based on laboratory assays, bleeding time, transfusion requirements and rating of hemostasis by the investigator. Blood samples to determine VWF:RCo, VWF:AG and FVIII:C values were collected before and after the loading infusion as well as before and after the first, second and third therapeutic/maintenance infusions. IVR and response were calculated for these three variables, and the time courses of their levels were monitored. Bleeding time was determined using the Ivy method [28] with the Simplate device (Organon Teknika, Durham, NC, USA) before and 30 min after the loading infusion. Follow-up was for 14 days postoperatively or until the end of treatment.

Hemostatic efficacy was rated daily by the treating physician on a four-point scale of excellent, good, moderate, or none. A rating of excellent was assigned when clinical hemostasis was within normal limits. Hemostasis was rated good in the case of slight oozing, moderate for moderate, controllable bleeding and none in the case of severe hemorrhage that was difficult to control.

**Safety monitoring**

Subjects were monitored for adverse events (AEs) from the time of informed consent until postoperative day 14 or until the end of treatment with the VWF/FVIII concentrate if treatment extended beyond day 14. The incidence of AEs possibly related to study treatment was calculated as the total number of such AEs divided by the number of infusions.

**Statistical analysis**

Data were summarized by calculation of the median and interquartile range (IQR) and in some instances the mean and SD. The correlation between VWF:RCo and VWF:CB in individual subjects was evaluated using Spearman’s coefficients. Differences between VWD types were assessed by one-way analysis of variance after confirmation of normality using the Kolmogorov-Smirnov test and of homoscedasticity using the Levene test. Minor and major surgery data were compared using the exact Mann–Whitney U-test. Linear mixed-effects regression for repeated measures was used to model the relationship between log₁₀-transformed IVRₚ₉₆/VWF:RCo and administered dose of VWF/FVIII concentrate in the study population [29]. Exact two-sided 95% confidence intervals (CI) around binary proportions were constructed using the Blyth–Still–Casella method [30]. For proportions of 100%, an exact one-sided lower 95% confidence limit was calculated. Data were analyzed using SAS 8.2 (SAS Institute Inc., Cary, NC, USA), WinNonLin Professional 3.2 (Pharsight Corp., Mountain View, CA, USA), spss 11.5 (SPSS Inc., Chicago, IL, USA) and StatXact 6.3 (Cytel Software Corp., Cambridge, MA, USA) statistical software. All authors critically reviewed

![Fig. 1. Recommended von Willebrand factor ristocetin cofactor and factor VIII coagulant activity targets.](image-url)
Results

All 29 enrolled subjects received a PK infusion. One subject was excluded from the PK analysis as a result of a protocol deviation, namely, treatment with VWF/FVIII concentrate 4 days prior to the PK infusion. Another subject was lost to follow-up after the PK phase of the study. During the peri-operative phase, 28 subjects received the individually calculated loading doses, and 27 subsequently underwent a surgical procedure. It was determined that one subject no longer required a scheduled polypectomy.

Baseline subject demographics are detailed in Table 1. Subjects underwent 11 minor and 16 major surgical procedures (Table 2). Median duration of surgery was 45.0 min (IQR, 25.0–85.0 min). Twenty subjects (69%) received tranexamic acid during the study in accordance with clinical practice at the individual study centers.

Pharmacokinetic profiles

Median infusion speed was 6.0 mL min⁻¹ (IQR, 4.0–11.6 mL min⁻¹). The 48-h time courses of VWF:RCo, VWF:Ag and FVIII:C after a median VWF/FVIII concentrate dose of 79 IU kg⁻¹ are shown in Fig. 2. The baseline levels of VWF:RCo in samples assayed by the participating centers were <10 IU dL⁻¹ (Table 3). The median peak value (160 IU dL⁻¹; IQR, 139–199 IU dL⁻¹) was reached 15 min after PK infusion, and the median level remained at 140–150 IU dL⁻¹ until 2 h postinfusion. By 8 h, median levels had decreased to 82 IU dL⁻¹ (IQR, 69–105 IU dL⁻¹), further declining to 42 IU dL⁻¹ (IQR, 29–58 IU dL⁻¹) by 24 h. The temporal pattern of change in VWF:Ag was similar, although median levels were consistently higher than those of VWF:RCo. This observation was expected as measured VWF:Ag levels include both functional and non-functional VWF, whereas VWF:RCo assays measure functional VWF.

The median baseline level of FVIII:C was 36.0 IU dL⁻¹ (IQR, 14.0–46.0 IU dL⁻¹). The 48-h profile of FVIII:C differed from that of VWF in that median levels peaked at a lower level (116 IU dL⁻¹; IQR, 81.5–130 IU dL⁻¹) and diminished more slowly, remaining at 92.0 IU dL⁻¹ (IQR, 73.5–108 IU dL⁻¹) by 24 h (Fig. 2). By 48 h, the median FVIII:C level had declined to 64.0 IU dL⁻¹ (IQR, 42.0–82.5 IU dL⁻¹).

Table 2 Surgery

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedure</th>
<th>n (VWD Type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor (n = 11)</td>
<td>Hand surgery</td>
<td>3 (1, 2A, 2A)</td>
</tr>
<tr>
<td></td>
<td>Arthroscopic synovectomy or meniscus resection</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td></td>
<td>Extraction of less than four teeth</td>
<td>4 (1, 1, 2A, 2A)</td>
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<tr>
<td></td>
<td>Hemorrhoid resection</td>
<td>1 (2 M)</td>
</tr>
<tr>
<td></td>
<td>Circumcision</td>
<td>1 (2A)</td>
</tr>
<tr>
<td>Major (n = 16)</td>
<td>Arthroscopic removal of osteosynthesis material</td>
<td>2 (2A, 3)</td>
</tr>
<tr>
<td></td>
<td>Total knee replacement</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td></td>
<td>Hysterectomy</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td></td>
<td>Hysterectomy + adnexectomy</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>Adnexectomy</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>Extraction of greater than or equal to four teeth</td>
<td>4 (2A, 2A, 3, 3)</td>
</tr>
<tr>
<td></td>
<td>Laparoscopic cholesystectomy</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td></td>
<td>Removal of basalioma</td>
<td>1 (2A)</td>
</tr>
<tr>
<td></td>
<td>Mandibular osteotomy</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Figure 3 displays a representative distribution of VWF multimers during the 48-h period after VWF/FVIII administration in a subject with type 3 VWD. At baseline, no bands are present. After VWF/FVIII infusion, a series of bands appear that conform to the pattern of normal plasma. Of special note are the highest molecular weight multimers localized at the top of the gels. By 24 h after administration the largest multimers are disproportionately reduced compared with the lower molecular weight multimer species.

VWF:CB is an assay for VWF that detects primarily higher molecular weight multimeric forms of VWF [31]. The highest median VWF:CB value of 147 IU dL⁻¹ (IQR, 81–189 IU dL⁻¹) occurred at 30 min post-PK infusion. VWF activity measured by VWF:CB assay diminished more rapidly than that by VWF:RCo assay. By 24 h postinfusion, the median value had decreased to 26 IU dL⁻¹ (IQR, 19–45 IU dL⁻¹). VWF:CB and VWF:RCo measurements of individuals were highly correlated, as evidenced by a median subject-specific Spearman’s correlation coefficient of 0.94 (IQR, 0.89–0.98).

The median IVR of VWF:RCo was 1.9 IU dL⁻¹ (IU kg⁻¹)⁻¹ and response 74 IU dL⁻¹ (Table 4). The median VWF:RCo terminal half-life was 15.6 h, as indicated in Table 5. There were no significant differences between VWD types in either VWF:RCo half-life (P = 0.23) or IVR (P = 0.43). IVR and response of VWF:Ag and FVIII:C are shown in Table 4.

Table 1 Baseline subject data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>26</td>
</tr>
<tr>
<td>Oriental</td>
<td>3</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>5–16</td>
<td>2</td>
</tr>
<tr>
<td>17–64</td>
<td>22</td>
</tr>
<tr>
<td>≥65</td>
<td>5</td>
</tr>
<tr>
<td>Type of von Willebrand disease</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2A</td>
<td>10</td>
</tr>
<tr>
<td>2 M</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>11</td>
</tr>
<tr>
<td>Major</td>
<td>16</td>
</tr>
</tbody>
</table>
Dosing

The median VWF:RCo loading dose was 62.4 IU kg\(^{-1}\) (IQR, 50.1–87.0). VWF:RCo loading doses were similar for minor and major surgery (Fig. 4). Loading doses also did not differ among the VWD types (\(P = 0.41\)). The pre-operative loading dose of VWF:RCo and FVIII:C was based on individual IVR of the subjects. While recommendations were given in the study protocol (Fig. 1), selection of desired target levels for subjects was at the discretion of the investigators who specified a median of 100 IU dL\(^{-1}\) (IQR, 100–115 IU dL\(^{-1}\)) for VWF:RCo and a median of 98 IU dL\(^{-1}\) (IQR, 82–100 IU dL\(^{-1}\)) for FVIII:C. The recommended target level of FVIII:C in the protocol was > 80 IU dL\(^{-1}\). The median deviation of FVIII:C levels from the investigator-specified target plasma levels (3.3 IU dL\(^{-1}\); IQR, −16.7 to 19.3 IU dL\(^{-1}\)) was smaller than that for VWF:RCo (21.5 IU dL\(^{-1}\); IQR, 10.8–35.9 IU dL\(^{-1}\)).

Postloading therapeutic/maintenance VWF/FVIII dosage and frequency and treatment duration were at the discretion of the investigator. For the 25 subjects with available data, the median number of therapeutic/maintenance VWF/FVIII concentrate treatment days was 6 days (IQR, 3–9 days). The first postloading dose was lower by a median of 19.4 IU kg\(^{-1}\) than the loading dose (\(P = 0.0004\)). Thereafter, as shown in Fig. 4, median VWF:RCo postloading doses were similar in the successive follow-up intervals up to > 6 days.

The total postloading therapeutic/maintenance dose in subjects undergoing minor surgery (120 IU kg\(^{-1}\); IQR, 91.2–269 IU kg\(^{-1}\)) was less than half as great as that of the major surgery groups.

Table 3  Baseline von Willebrand factor (VWF) and factor FVIII (FVIII) concentrations

<table>
<thead>
<tr>
<th>von Willebrand disease type</th>
<th>Median % (IQR)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VWF:RCo</td>
</tr>
<tr>
<td>1</td>
<td>17.0 (9.0–32.0)</td>
</tr>
<tr>
<td>2A</td>
<td>34.2 (20.4–59.0)</td>
</tr>
<tr>
<td>2 M</td>
<td>19.0 (19.0–19.0)</td>
</tr>
<tr>
<td>3</td>
<td>3.0 (1.0–4.4)</td>
</tr>
<tr>
<td>All</td>
<td>18.0 (6.7–32.0)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; VWF:RCo, von Willebrand factor ristocetin cofactor; VWF:Ag, von Willebrand factor antigen; FVIII:C, factor VIII coagulant activity.

*Except as otherwise indicated.
The pre- to postinfusion increments in VWF:RCo plasma levels achieved after the loading and subsequent therapeutic/maintenance doses were uniformly greater than those that occurred in FVIII:C levels (Fig. 6). Mean VWF:RCo levels were in the 62–73 IU dL$^{-1}$ range before and 166–170 IU dL$^{-1}$ after the first three therapeutic/maintenance infusions (Fig. 6). Mean FVIII:C levels were between 114–136 IU dL$^{-1}$ before and 158–180 IU dL$^{-1}$ after the first three therapeutic/maintenance infusions (Fig. 6). Pre-infusion mean FVIII:C levels before each therapeutic/maintenance dose progressively increased, in contrast to those of VWF:RCo which remained stable (Fig. 6).

During the peri-operative phase of the study, the IVR of VWF:RCo remained comparable to that determined in the PK phase. The median IVR of VWF:RCo was 1.9 IU dL$^{-1}$ (IU kg$^{-1}$)$^{-1}$ after the loading dose, as well as the first and third infusions, and 2.2 IU dL$^{-1}$ (IU kg$^{-1}$)$^{-1}$ after the second infusion. IVR results were similar in minor and major surgery. The log$_{10}$-transformed IVR$_{\text{VWF:RCo}}$ did not vary in relation to the doses administered, as indicated by a slope estimate of 0.000142 kg IU$^{-1}$ (CI, 0.00375 to 0.004031 kg IU$^{-1}$). Dose linearity of the VWF/FVIII concentrate was observed over a wide range of doses (from 15 to 151 IU kg$^{-1}$).

**Plasma levels**

On the day of surgery, a hemostatic efficacy rating of excellent was recorded by the treating physician for 81.5% (CI, 63.6–92.4%) of the subjects, good for 14.8% (CI, 5.2–32.0%) and moderate for 3.7% (CI, 0.2–17.5%). On postoperative day 1, 92.6% (CI, 77.6–98.7%) of subjects received a rating of excellent and 7.4% (CI, 1.3–22.4%) good. At the final evaluation on day 14, hemostatic efficacy was rated excellent in all subjects (100%; CI, 89.0–100%). In no subject was a hemostatic efficacy rating of none assigned by the treating physician at any time. Ratings by subjects after hospital discharge were predominantly excellent or good.

Eighteen of the 20 subjects (90%) who underwent a bleeding time evaluation before and 30 min after the loading dose showed a shortening in bleeding time. In nine subjects the bleeding time was completely corrected, for example, the abnormally prolonged pre-infusion value was normalized, and reflected a smaller number of infusions and longer interval between infusions rather than a difference in the size of the doses. Thus, the median number of postloading VWF/FVIII concentrate infusions was three (IQR, 2–7) for minor surgery and seven (IQR, 4.5–11.5) for major surgery ($P = 0.041$).

During the first two postoperative days, the median between-dose interval in the minor surgery group (24 h) was 50% longer ($P = 0.014$) than that of subjects who underwent major surgery (16 h), as indicated in Fig. 5. In contrast, median doses were similar between major and minor surgery (Fig. 4).
bleeding time improvement in an additional four subjects exceeded 30%.

One subject required a red blood cell transfusion. This subject who underwent bilateral total knee replacement exhibited a low pre-operative hematocrit but no obvious postoperative bleeding and received three units of packed red cells.

Adverse events

Five adverse events (AEs) in five subjects during the perioperative phase of the study were classified as possibly related to the study treatment: pulmonary embolism, thrombophlebitis of the leg, vomiting, rash, and an alanine aminotransferase (ALT) increase. Only the pulmonary embolism was judged to be serious and moderate in severity. The other four AEs were mild. No possibly related AEs occurred during the PK phase of the study. There were a total of 236 study infusions, and the incidence rate of possibly related AEs per infusion was 2.1%, or 17% per subject treated. No inhibitor antibodies to either VWF or FVIII were detected.

The pulmonary embolism developed 10 days after bilateral knee replacement in an 81-year-old female subject with type 1 VWD. Several thromboembolic risk factors were present in this subject: advanced age, recent major orthopedic surgery and thrombocytosis (769 · 10^9 L^-1); she did not receive any antithrombotic prophylaxis treatment. The embolism was detected by scintigraphy after the development of dyspnea and resolved under heparin treatment 6 days later without

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VWF dosing

**Discussion**

Haemate® P was the first virus-inactivated concentrate available for treatment of VWD, and while it has been extensively and successfully used for a quarter of a century, additional clinical trials are warranted to investigate optimal dosing strategies. This prospective study of subjects undergoing elective surgery provides further evidence that Haemate P® is highly effective in preventing excessive bleeding in patients with VWD undergoing major or minor surgery. On the day of surgery, hemostasis was rated as excellent or good in 96% of cases. On the first postsurgical day, 100% of cases were rated excellent or good. This study also demonstrates the clinical utility of a pre-operative PK analysis to determine dosing.

Determination of optimal dose size and frequency has been a major concern in the use of VWF/FVIII concentrates to treat VWD [4]. It should be recognized that the present study was designed to assess the feasibility of PK-guided dosing and not minimal effective dose, dosage frequency or duration. This study demonstrates for the first time that the IVR is constant over a wide range of doses and that initial PK determinations can provide a reliable basis for serial dosing decisions. Successful hemostasis was accomplished with a median VWF:RCo loading dose of 62.4 IU kg⁻¹ in subjects with various types of VWD undergoing minor and major surgery. By comparison, a median loading dose of 82.3 IU kg⁻¹ was utilized in a recent prospective study of Haemate® P among subjects undergoing emergency surgery [19]. In a small prospective study of Haemate® P use in type 2 VWD subjects undergoing elective surgery, the mean loading dose was 90 IU kg⁻¹ VWF:RCo [26]. In that study, the investigators concluded based on PK that lower doses of VWF/FVIII could be effective and proposed recommendations for both loading and maintenance dosing. The findings in the present study support the proposal that reduced loading doses can be effective.

Postoperative doses of VWF:RCo were lower than the loading dose (Fig. 4). A similar observation was also described for the Haemate® P study of emergency surgery [19]. By contrast, in a retrospective Canadian study of 97 patients, no difference was found between loading and postoperative doses [17]. In that study the median dose used to treat peri-operative events was 69 IU kg⁻¹ VWF:RCo.

In this study, the size of therapeutic/maintenance doses did not differ between minor and major surgery. However, postloading infusions were greater in number and during the first two postoperative days the between-infusion intervals were shorter for major surgery. The treatment recommendations called for levels of VWF:RCo above 50 IU dL⁻¹ during the postoperative period, and this objective was met. During the study, the median VWF:RCo IVR was 1.9 IU dL⁻¹ (IU kg⁻¹)⁻¹. In other studies on Haemate® P, IVR of 1.35 IU dL⁻¹ (IU kg⁻¹)⁻¹ [17], 1.5 IU dL⁻¹ (IU kg⁻¹)⁻¹ [32], 1.7 IU dL⁻¹ (IU kg⁻¹)⁻¹ [19,26] and 2.1 IU dL⁻¹ (IU kg⁻¹)⁻¹ [16] were reported. The IVR was consistent over doses ranging from 15 to 151 IU kg⁻¹. The median terminal half-life of VWF:RCo determined in this study was 15.6 h, in line with values reported in several smaller previous studies of 11.3 [16], 11.3–13.9 [33] and 12 h [26].

A possible alternative approach for dosing may be based on clearance determinations. For instance in a type 3 patient with a clearance of 3–4 mL kg⁻¹ h⁻¹, a daily maintenance dose of 54–72 IU kg⁻¹ will maintain plasma levels of around 75 IU dL⁻¹. In order to minimize peak-to-trough differences, it is recommended that the daily maintenance dose be split into 2–3 fractions (e.g. 3 × 24 kg⁻¹ or 2 × 36 IU kg⁻¹).

This study was not designed to explore differences between VWD types. Nevertheless, in the present study population composed predominantly of types 1, 2A and 3 VWD, type-specific differences in results were not observed. These findings suggest that the VWF/FVIII concentrate regimen adopted in this study may be successfully applied to a wide range of VWD patients undergoing elective surgery and that the clinical phenotype rather than the specific type of VWD should be a determining factor in dosing strategies.

The only serious AE possibly related to study treatment was the occurrence of a pulmonary embolism in a subject with several well-recognized risk factors for thromboembolic events. While thromboembolic events have only rarely been reported in VWD patients receiving VWF/FVIII concentrates, deep vein thrombosis and pulmonary embolism events have occurred in patients with VWD receiving repeated VWF/FVIII infusions.
after surgery [7,34,35]. Constitutively high plasma FVIII levels have been reported to be associated with increased risk of venous thrombosis [36–39]. It remains to be established whether acute therapy-related FVIII elevations might augment thrombotic risk. Two studies have suggested that the increased risk is independent of acute phase reactions [40,41]. In a global questionnaire survey with responses from 160 treatment centers, the reported incidence of venous thromboembolism among VWD patients receiving VWF:FVIII concentrates was low (1 case per 1806 treatment-years) [35]. Plasma FVIII levels progressively increase over the course of VWF:FVIII concentrate treatment because VWF stabilizes not only the exogenously administered FVIII but also the endogenous FVIII pool. In the octogenarian who developed a non-fatal pulmonary embolism after bilateral knee replacement, an FVIII peak of 450 IU dL\(^{-1}\) was reached on the day before diagnosis of the embolism. The type of surgery performed and other factors increased the thromboembolic risk of this subject. Knee replacement surgery is associated with an increased risk of deep vein thrombosis and pulmonary embolism [42]. Laboratory testing also revealed postoperative thrombocytosis. Her advanced age and blood group A also contributed to the risk of thrombosis [43]. Finally, the patient had received no antithrombotic prophylaxis.

The threshold levels of FVIII above which significant risk exists for thromboembolic events have not been clearly defined. A recent study suggested that for patients without additional risk factors a level of 270 IU dL\(^{-1}\) might be an appropriate upper limit [44]. Other studies have suggested increased thrombotic risk at lower levels of FVIII (150–175 IU dL\(^{-1}\)) [36,37]. A challenge in treating VWD patients with concentrate is to maintain VWF levels high enough to offer protection against hemorrhage while minimizing exposure to very high FVIII levels. Available concentrates differ in their ratios of VWF to FVIII against hemorrhage while minimizing exposure to very high FVIII levels. Available concentrates differ in their ratios of VWF to FVIII and hence in their potential utility for attaining desired circulating levels of VWF and FVIII in situations requiring repeated infusions. The ratio of VWF to FVIII in Haemate® P is 2.4, which is higher than that of other available VWF:FVIII concentrates [7,13,45,46]. Increased awareness of ratios should be facilitated by recent regulatory requirements that both VWF:RCo and FVIII:C content must be included on the label [4].

Although thromboembolic events appear to be rare in patients with VWD treated with VWF:FVIII concentrates, particular caution should be exercised in patients with thromboembolic risk factors. It has been recommended that FVIII:C be assayed every 12 h on the day a VWF:FVIII dose is administered and every 24 h thereafter [47]. Also, for patients at higher risk prophylactic low-molecular weight heparin regimens have been advocated such as those routinely employed in non-VWD patients undergoing similar procedures [47].

This study demonstrates the feasibility of selecting the loading dose based on PK profiles of VWD patients undergoing elective surgery. It also provides data on dosing that can assist in formulating improved dosing guidelines for surgical patients with VWD. Moreover, the results underscore the appropriateness of monitoring both VWF and FVIII levels in the peri-operative period. Because of the potential hazards of very high FVIII levels and the availability of rapid standardized FVIII assays, it has been recommended that plasma FVIII:C levels be used to adjust peri-operative dose size and interval [13,22]. Also, antithrombotic prophylaxis should be considered in patients with bleeding diathesis having multiple risk factors for thrombosis.

An obstacle to routine VWF-based dosing decisions is the lack of standardized functional tests for VWF because the currently available assays for VWF:RCo are labor-intensive and variable [6]. Ongoing work to standardize VWF assays promises to enhance their value for clinical decision-making.

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Disclosure of Conflict of Interests

S. Haertel was employed by CSL Behring. The other authors state that they have no conflict of interest.

Appendix

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