

Haemate[®] P/Humate-P[®] for the treatment of von Willebrand disease: considerations for use and clinical experience

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Summary. von Willebrand disease (VWD) is a heterogeneous bleeding disorder with symptoms in affected patients ranging from mild effects to potentially devastating haemorrhagic events. Desmopressin (DDAVP) and von Willebrand factor/factor VIII (VWF/FVIII) concentrates are the principal treatments. Haemate[®] P/Humate-P[®] is an intermediate-purity VWF/FVIII concentrate with extensive clinical experience in VWD. This concentrate has been shown to correct haemostatic defects of VWD, with efficacy ratings of good/excellent in nearly all patients treated for bleeding or surgical events. Haemate P/Humate-P has a high content of the high molecular weight (HMW) VWF multimer fraction, which has been shown to be very effective in achieving haemostasis. The HMW VWF multimer pattern in Haemate P/Humate-P is more similar to that of normal human plasma (94% for Haemate P/Humate-P vs. 100% for normal human plasma) than that of other VWF/FVIII concentrates and

correlates with functional VWF activities including ristocetin cofactor activity (VWF:RCo) and collagen-binding activity. The recommended dosing of Haemate P/Humate-P is based preferentially on VWF:RCo activity, which is approximately twice that of FVIII:C (2.4:1). Haemate P/Humate-P has been shown to be safe; no serious adverse events or cases of thrombosis have been observed in clinical trials and no documented cases of viral transmission in nearly three decades of clinical use. While DDAVP is effective in a large proportion of VWD patients, it may not provide adequate haemostasis in all situations. In such cases, Haemate P/Humate-P is an effective replacement concentrate for all types of VWD in both adult and paediatric patients.

Keywords: factor concentrates, factor VIII, high molecular weight multimers, therapy, von Willebrand disease, von Willebrand factor

Introduction

As the most common inherited bleeding disorder, von Willebrand disease (VWD) affects approximately 1% of the worldwide population and is caused by quantitative or qualitative defects in von Willebrand factor (VWF), a glycoprotein involved in both primary and secondary haemostasis [1–3]. Symptoms range from infrequent mild bleeding to severe haemorrhagic events. Several VWD subtypes have been identified based on the specific VWF defect as well as the phenotype. The deficiency in VWF is

expressed by measures of VWF activity including ristocetin cofactor activity (VWF:RCo), a measure of VWF binding to platelets, and collagen-binding activity (VWF:CB), a measure of VWF binding to subendothelial collagen at sites of vascular injury. Patients may also have secondary low plasma levels of factor VIII (FVIII) coagulant activity (FVIII:C), as VWF is the primary carrier of FVIII in the circulation. Males and females are equally affected by this heterogeneous disorder and a high proportion of individuals, mainly of the mild forms, remain undiagnosed. Patients with VWD have poorer health-related quality of life compared with that of the general population [4].

In VWD patients who require treatment, desmopressin (DDAVP) and plasma-derived VWF/FVIII concentrates are the primary therapies for spontaneous acute bleeding episodes and for preventing bleeding during invasive or surgical procedures [5].

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Adjunctive therapies (e.g. antifibrinolytic amino acids, tranexamic acid, oestrogens, fibrin glues) may be useful in localized bleeds, but controlled studies generally have not shown an additional benefit for them. DDAVP is not effective in all types of VWD and may be contraindicated in patients with certain co-morbidities including atherosclerosis, heart failure or other conditions requiring diuretic treatment, as well as in very young children (<3 years old) or in patients older than 65–70 years of age [6]. In such cases, plasma-derived VWF/FVIII concentrates are the current standard for controlling acute bleeding episodes or as prophylaxis for invasive or surgical procedures. The commercially available concentrates differ in their purification and pathogen removal and inactivation techniques as well as in VWF multimer content and activity, which may affect therapeutic safety and efficacy. Clinical experience with Haemate P/Humate-P (CSL Behring), a VWF/FVIII concentrate with extensive experience in the treatment of patients with VWD, is summarized in this report.

Clinical pharmacology

Haemate P/Humate-P is a lyophilized, pasteurized, VWF/FVIII complex (human) that contains the high molecular-weight (HMW) multimers of VWF [7,8]. The ratio of VWF:RCo to FVIII:C in the concentrate is approximately 2.4:1 [9]. A comparative gel electrophoresis study of 12 VWF/FVIII concentrates demonstrated that the HMW VWF multimer pattern in Haemate P/Humate-P (94%) was similar to that in normal human plasma (100%), whereas other concentrates showed a deficit in this multimer fraction (e.g. 79% in Innobrand, and from 4% to 36% in the other 10 products examined) [9,10]. High molecular-weight multimers of VWF play an important role in early haemostasis and thrombus formation, particularly in vascular lesions under high shear stress conditions [11]. This multimer fraction binds more efficiently to subendothelial collagen structures than the smaller VWF multimers and provides high activity in the subsequent platelet adhesion and aggregation steps of haemostasis [12].

Results of comparative studies of VWF/FVIII concentrates also demonstrate that VWF specific activities (i.e. VWF:RCo/VWF:Ag and VWF:CB/VWF:Ag) were the highest for Haemate P/Humate-P (Fig. 1) [13,14]. These findings were based on an official European method for determining VWF potency in concentrates (i.e. VWF:RCo) and an additional physiological functional assay to determine collagen-binding ability (VWF:CB).

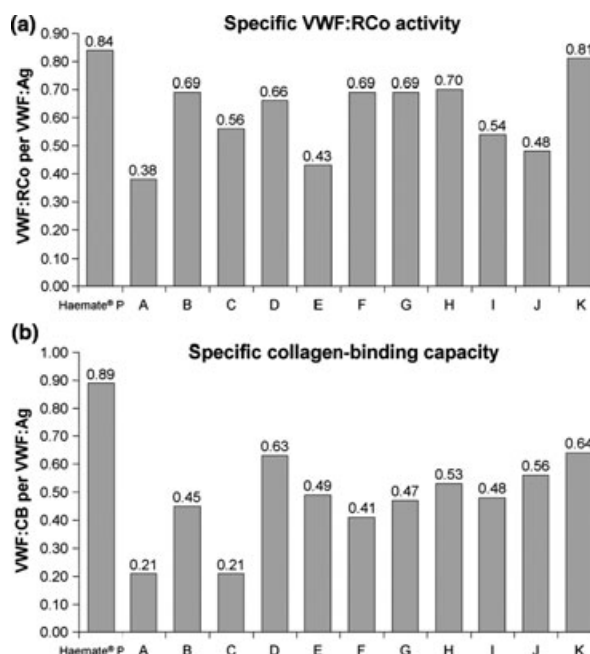


Fig. 1. A comparison of potencies among 12 von Willebrand factor (VWF)/factor VIII (FVIII) concentrates for VWF functional activities related to: (a) specific ristocetin cofactor activity (VWF:RCo/VWF:Ag) and (b) specific collagen type 1 binding activity (VWF:CB/VWF:Ag). The specific VWF activities correlate with the high molecular weight VWF multimer content of the concentrates. The high functional activities shown for Haemate P/Humate-P suggest that it would have good physiological activity clinically. Products A to K: Immunate STIM Plus (Baxter); Haemoctin SDH (Biotest Pharma); Octanate[®] (Octapharma); Profilate (Grifols); Alphanate[®] (Grifols); Green Eight (Greencross); Fanhdi[®] (Grifols); Factor 8Y (BPL); Emoclot DI[®] (Kedrion); Factane[®] (LFB); Innobrand (LFB). Reprinted by permission from Thieme Medical Publishers [14]. Budde U, Metzner HJ, Müller HG. Comparative analysis and classification of von Willebrand factor/factor VIII concentrates: impact on treatment of patients with von Willebrand disease. *Semin Thromb Hemost* 2006; 32: 626–35.

Furthermore, functional VWF activities were shown to correlate with the high content of HMW VWF multimers in Haemate P/Humate-P [7,10,14]. Results from other studies support the high *in vitro* VWF functional activities and HMW VWF multimer content of the concentrate [13,15]. Taken together, these data confirm the clinical utility of Haemate P/Humate-P in treating patients with VWD.

In patients with all subtypes of VWD, bleeding time decreased following administration of Haemate P/Humate-P [16–20]. The reduction in bleeding correlated with the multimeric composition of Haemate P/Humate-P being similar to that of normal plasma [16–18,20,21]. A single infusion pharmacokinetic study of Haemate P/Humate-P in eight VWD patients (types 1, 2, 2A, and 3) in the non-bleeding state found that the median half-life of VWF:RCo

Table 1. Dosing recommendations for Haemate P/Humate-P for the treatment of paediatric and adult patients with von Willebrand disease (VWD) [7].

VWD classification	Haemorrhage	Dosage (IU/kg VWF:RCo)
Type 1		
Mild: if desmopressin is inappropriate (baseline VWF:RCo activity typically >30%)	Major: (e.g. severe or refractory epistaxis, GI bleeding, CNS trauma, or traumatic haemorrhage)	Loading dose: 40–60 IU/kg. Maintenance dose: 40–50 IU/kg every 8–12 h for 3 days to keep nadir VWF:RCo level >50%; then 40–50 IU/kg daily for total of ≤7 days.
Moderate or Severe: if desmopressin is inappropriate (baseline VWF:RCo activity typically <30%)	Minor: (e.g. epistaxis, oral bleeding, menorrhagia)	40–50 IU/kg for 1 or 2 doses.
	Major: (e.g. severe or refractory epistaxis, GI bleeding, CNS trauma, haemarthrosis, or traumatic haemorrhage)	Loading dose: 50–75 IU/kg Maintenance dose: 40–60 IU/kg every 8–12 h for 3 days to keep nadir VWF:RCo level >50%; then 40–60 IU/kg daily for total of ≤7 days. Monitor and maintain FVIII:C plasma level according to the guideline for haemophilia A therapy.
Type 2 (all variants) if desmopressin is inappropriate and	Minor: (clinical indications above)	40–50 IU/kg for 1 or 2 doses.
Type 3	Major: (clinical indications above)	Loading dose: 60–80 IU/kg Maintenance dose: 40–60 IU/kg every 8–12 h for 3 days to keep nadir VWF:RCo level >50%; then 40–60 IU/kg daily for total of ≤7 days. Monitor and maintain FVIII:C plasma level according to the guideline for haemophilia A therapy.

CNS, central nervous system; GI, gastrointestinal; VWF:RCo, von Willebrand factor:ristocetin cofactor activity.

was 10.3 h and the median *in vivo* recovery of VWF:RCo was 1.89 (IU dL⁻¹)/(IU kg⁻¹) [7]. In addition, observed improvements in VWF multimer pattern were sustained for 22–26 h post-infusion in most cases.

Clinical efficacy

The clinical efficacy of Haemate P/Humate-P has been established in several clinical trials [8,16,17,20,22–29]. Dosing of the VWF/FVIII concentrate in most studies was based on FVIII:C potency. However, because the primary goal in VWD therapy is replacement of the deficient or dysfunctional VWF protein, haemostatic potency relative to VWF activity may be a more appropriate method for calculating dosages of VWF/FVIII concentrates. Dosing recommendations for Haemate P/Humate-P for the treatment of haemorrhage in paediatric and adult VWD patients are shown in Table 1.

More recent studies have evaluated Haemate P/Humate-P treatment using VWF:RCo unit dosing,

which addresses the primary deficiency in haemostasis in a majority of patients with VWD. A retrospective review conducted in Canada of data from 97 VWD patients with emergency authorizations for Haemate P/Humate-P treatment provides insight into the efficacy of this concentrate using VWF:RCo unit dosing [25]. These data were collected using a standardized form and included 437 events (bleeding episodes, surgeries) in the 97 patients. As dosing was based on FVIII:C units as per the German package insert, doses for the retrospective analysis were converted to VWF:RCo units based on an analysis of the 25 lots of Haemate P/Humate-P used to treat patients. The average ratio of VWF:RCo to FVIII:C in the concentrate was 2.6 IU (range 2.00–3.12 IU). Results showed an overall efficacy rating for Haemate P/Humate-P of excellent (complete cessation of bleeding) or good (partial, but adequate control of bleeding) in 97% of events (Table 2). The median Haemate P/Humate-P doses per infusion by event types were as follows: 69.1 IU VWF:RCo/kg for surgical events; 55.3 IU VWF:RCo/kg for bleeding;

Table 2. Efficacy ratings of excellent or good with Haemate P/Humate-P treatment using VWF:RCo dosing for 437 bleeding events in 97 patients with von Willebrand disease (VWD). Adapted from [25].

	VWD type					Total (<i>n</i> = 97)
	1 (<i>n</i> = 32)	2A (<i>n</i> = 5)	2B (<i>n</i> = 18)	3 (<i>n</i> = 28)	Other* (<i>n</i> = 14)	
Surgeries	26/26	6/6	13/14	21/21	6/6	72/73 (99)
Bleeding episodes	32/32	17/17	60/60	198/208	25/27	332/344 (97)
Prophylaxis	–	–	–	20/20	–	20/20 (100)

*Types 2N, 2M and acquired VWD.

Values in parentheses are percentages.

and 41.6 IU VWF:RCo/kg for prophylaxis. Most infusions were administered within the first 7 days after an event, with approximately 55% of surgical and 35% of bleeding patients requiring treatment after the first day.

An analysis of Haemate P/Humate-P use in paediatric patients included in the Canadian data indicated that it is highly effective in this population [25]. Efficacy ratings of excellent or good were achieved in 100% of infants (1 month to <2 years; *n* = 17), 95% of children (2 years to <12 years; *n* = 164), and 94% of adolescents (12 years to <16 years; *n* = 81). These findings confirm an earlier study in children (45 with bleeding; 64 undergoing invasive or surgical procedures) with various types of VWD in which Haemate P/Humate-P successfully stopped post-traumatic bleeding and was effective for bleeding prophylaxis for surgery, including children whose bleeding was not controlled by DDAVP [20]. Haemate P/Humate-P also corrected functional activity parameters of VWD (VWF:Ag, VWF:RCo, FVIII:C).

Several other studies have evaluated use of Haemate P/Humate-P in VWD patients undergoing surgery, both elective and urgent procedures. A retrospective review of 26 patients (median age 41.5 years) with type 1 (*n* = 19) or type 2B (*n* = 7) VWD who underwent 43 surgical or invasive procedures found that perioperative prophylaxis with Haemate P/Humate-P according to recommended guidelines successfully controlled bleeding [26]. Mean total dosage of Haemate P/Humate-P varied by procedure: 38.4 IU VWF:RCo kg⁻¹ for dental extractions; 87.3 IU VWF:RCo kg⁻¹ for invasive procedures; 120.8 IU VWF:RCo kg⁻¹ for minor surgery; and 284.1 IU VWF:RCo kg⁻¹ for major surgery. Only one patient with severe periodontal disease experienced bleeding 3 days after multiple dental extractions and received two additional doses of Haemate P/Humate-P to control bleeding. Another series in patients with predominantly type 1 and type 3 VWD suggested that a continuous infusion of Haemate P/Humate-P (average dose 24.3 VWF:RCo U kg⁻¹ day⁻¹) provided

effective prophylaxis for surgical procedures and achieved target levels of FVIII:C and VWF:RCo with approximately half the expected dose as that recommended for intermittent bolus administration [30].

The VWF:RCo component is more important than the FVIII:C component for prevention of perioperative bleeding in most patients with type 2 VWD, whose FVIII and VWF antigen levels are near the normal range, but with a marked reduction in HMW VWF multimer level and VWF activity. On the other hand, replacement of both FVIII:C and VWF:RCo are important in other VWD subtypes. Following the dosing recommendations for VWF/FVIII concentrates based on pharmacokinetic studies in patients with type 3 VWD [8,18] resulted in over-treatment of type 2 patients undergoing bleeding prophylaxis for surgery with Haemate P/Humate-P [8]. A combined pharmacokinetic and efficacy study in five type 2 patients determined the *in vivo* responses of VWF parameters and FVIII and assessed bleeding prophylaxis during elective major surgery with Haemate P/Humate-P using a lower dosing regimen – loading dose of 40–50 IU kg⁻¹ FVIII:C (88–110 IU kg⁻¹ VWF:RCo) followed by 15–20 IU kg⁻¹ FVIII:C (33–44 IU kg⁻¹ VWF:RCo) every 12 h (half-life of VWF parameters was approximately 12 h) for several days [8]. The reduced dose regimen corrected bleeding times to normal at levels of FVIII:C and VWF:RCo between 1 U mL⁻¹ and 2 U mL⁻¹ in VWD patients, as compared with levels of between 0.6 U mL⁻¹ and 1.5 U mL⁻¹ in healthy controls. The correction of haemostatic defects was associated with improved VWF multimer pattern (Fig. 2). The investigators recommended a further reduction in the dose of Haemate P/Humate-P for major surgery to 60–80 IU kg⁻¹ VWF:RCo for a loading dose, followed by 30–40 IU kg⁻¹ VWF:RCo every 12 h for 5–7 days. Others have shown that a pharmacokinetic-guided approach to VWF:RCo dosing of Haemate P/Humate-P in patients with VWD undergoing elective surgery is feasible to achieve reliable target plasma FVIII:C and VWF:RCo levels for effective haemostasis [27].

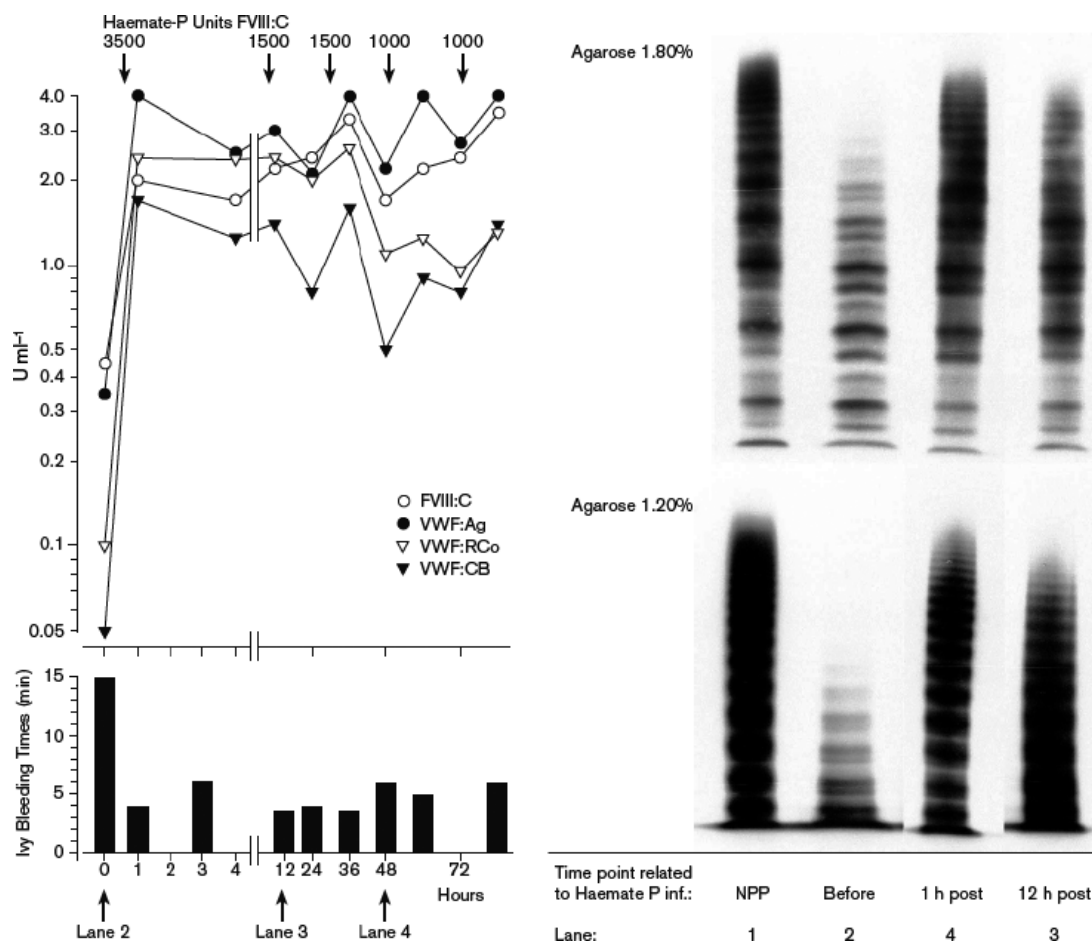


Fig. 2. A female with type 2B VWD received one pre-operative Haemate P/Humate-P loading dose (50 IU kg^{-1} FVIII:C; 110 IU kg^{-1} VWF:RCo) followed by doses of $15\text{--}20 \text{ U kg}^{-1}$ FVIII:C ($33\text{--}44 \text{ U kg}^{-1}$ VWF:RCo) twice daily for several days after major surgery (splenectomy). Treatment corrected the strongly prolonged Ivy bleeding times and the VWF parameters to normal (left), and corrected the VWF multimer pattern as visualized by luminescence technique according to Budde *et al.* [35] (right). FVIII, factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor; FVIII:C, FVIII coagulant activity; VWF:RCo, VWF ristocetin cofactor activity. Reprinted with permission from Lippincott, Williams and Wilkins [8]. Michiels JJ, Berneman ZN, van der Planken M, Schroyens W, Budde U, van Vliet HHDM. Bleeding prophylaxis for major surgery in patients with type 2 von Willebrand disease with an intermediate purity factor VIII-von Willebrand factor concentrate (Haemate-P). *Blood Coagul Fibrinolysis* 2004; 15: 323–30.

Calculation of Haemate P/Humate-P doses based on VWF:RCo activity for patients with various VWD subtypes undergoing urgent surgery or having urgent bleeding episodes resulted in efficacy (achievement of haemostasis) in virtually all patients (98% and 100% excellent/good ratings, respectively) [28,29]. In a study of 33 patients (median age 31 years) with 53 urgent bleeding events, the median loading dose of Haemate P/Humate-P was 67 IU kg^{-1} VWF:RCo and the median daily maintenance dose per infusion was 74 IU kg^{-1} VWF:RCo, with a median treatment duration of 2 days [28]. In another study of 39 patients (median age 43 years) with 42 surgical treatment events, median Haemate P/Humate-P doses were 82.3 IU kg^{-1} VWF:RCo for loading and

52.8 IU kg^{-1} VWF:RCo for maintenance, with a median duration of three treatment days [29]. In neither study did the type of VWD significantly influence the daily utilization of Haemate P/Humate-P.

A small study ($n = 8$) of patients with type 2A VWD found that Haemate P/Humate-P was superior to Alphanate (Grifols) in restoring haemostasis, as assessed by the increase in VWF:RCo activity $\text{unit}^{-1} \text{ kg}^{-1}$ [31]. FVIII levels normalized with both treatments in all patients, whereas VWF:RCo was restored to the normal range in all eight patients after treatment with Haemate P/Humate-P compared with in four of eight patients after treatment with Alphanate. The authors noted that VWF/FVIII con-

concentrates with a higher VWF:RCo than FVIII:C content allow lower doses of concentrate to be administered when dosing is based on the VWF:RCo content [31].

Safety

A safety consideration for products derived from pooled human plasma is the risk of transmission of pathogens and subsequent disease. Haemate P/Humate-P is a purified product that undergoes a pasteurization process to inactivate both lipid-enveloped and non-enveloped viruses [7]. *In vitro* experiments have demonstrated that human immunodeficiency virus (HIV), herpes simplex virus-1, bovine viral diarrhoea virus, cytomegalovirus (CMV) and polio viruses are inactivated to undetectable levels. *In vivo* studies in chimpanzees demonstrated the low risk of transmission of hepatitis in that no animal injected with the pasteurized product became seropositive, whereas those injected with hepatitis B-infected cryoprecipitate or a non-pasteurized antihemophilic factor VIII/VWF complex product developed markers of hepatitis B. Evidence from clinical trials confirms the low risk of pathogen transmission with Haemate P/Humate-P in patients with VWD or haemophilia [22,32,33]. In two studies, patients remained seronegative for hepatitis B surface antigen and did not show clinical signs of or develop hepatitis infection after treatment with Haemate P/Humate-P [22,32]. Patients did not develop markers for, or signs of, other viral infections including hepatitis A, CMV, Epstein-Barr or HIV [22]. Other studies also demonstrated that patients were seronegative for HIV-1 and HIV-2 antibodies for periods ranging from 4 months to 9 years following initial treatment with Haemate P/Humate-P [33,34]. Furthermore, there are statements that there have been no documented cases of viral transmission in patients receiving this concentrate in over 25 years of clinical use in Europe and over 17 years of use in the USA (data on file, CSL Behring).

Haemate P/Humate-P has a favourable safety profile. No serious adverse events related to the drug have been reported in clinical trials [16,20,22,23,25,26,28,29]. Allergic symptoms including mild allergic reaction were reported $\leq 6\%$ of patients, while other unexpected adverse events included chills, phlebitis, vasodilatation, paraesthesia, peripheral oedema, extremity pain and pseudothrombocytopenia in a few patients [7,29]. No cases of thrombosis were observed in clinical trials. Nonetheless, as thromboembolic events may occur

in patients with VWD who have other thrombotic risk factors, care should be exercised with administration of VWF/FVIII concentrates to patients at high thrombotic risk.

Conclusion

von Willebrand disease is a heterogeneous inherited bleeding disorder for which the haemostatic defects are not uniform across types. DDAVP and VWF/FVIII concentrates are the principal treatments. The HMW VWF multimer pattern in Haemate P/Humate-P is more similar to that of normal human plasma (94% vs. 100%) than that of other VWF/FVIII concentrates and correlates with high functional VWF activities including VWF:RCo and VWF:CB. Administration of Haemate P/Humate-P in patients with different VWD subtypes results in effective haemostasis in both adult and paediatric patients. The ratio of VWF:RCo to FVIII activity is approximately 2.4:1. Dosing of Haemate P/Humate-P in VWD patients should be based preferentially on VWF:RCo content, reflecting the primary treatment goal of correcting VWF activity. In addition, dosing based on FVIII activity may result in over-treatment of some patients, particularly those with type 2 VWD in whom the VWF:RCo component of VWF/FVIII concentrates is more important for preventing peri-operative bleeding and normalizing bleeding times than is the FVIII:C component. Administration of Haemate P/Humate-P has been shown to be safe based on study data and extensive clinical experience. Although derived from pooled human plasma, purification and pasteurization effectively reduce pathogen risk of Haemate P/Humate-P such that no cases of viral transmission have been documented in many years of use including during the devastating era of HIV infection among haemophiliacs. Additional studies are assessing dosing based on VWF:RCo activity as well as a pharmacokinetic guided approach to dosing.

Conflict of interest

The author is a recipient of research grants from Novo Nordisk, CSL Behring and Baxter.

References

- 1 Castaman G, Federici AB, Rodeghiero F, Mannucci PM. Von Willebrand disease in the year 2003: towards the complete identification of gene defects for correct diagnosis and treatment. *Haematologica* 2003; 88: 94–108.

- 2 Werner EJ, Broxson EH, Tucker EL, Giroux DS, Shults T, Abshire TC. Prevalence of von Willebrand disease in children: a multiethnic study. *J Pediatr* 1993; 123: 893–8.
- 3 Sadler JE, Mannucci PM, Berntorp E *et al.* Impact, diagnosis and treatment of von Willebrand disease. *Thromb Haemost* 2000; 84: 160–74.
- 4 Barr RD, Sek J, Horsman J *et al.* Health status and health-related quality of life associated with von Willebrand disease. *Am J Hematol* 2003; 73: 108–14.
- 5 Battle J, Noya MS, Giangrande P, López-Fernández MF. Advances in the therapy of von Willebrand disease. *Haemophilia* 2002; 8: 301–7.
- 6 Pasi KJ, Collins PW, Keeling DM *et al.* Management of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2004; 10: 218–31.
- 7 CSL Behring GmbH. *Humate-P[®] antihemophilic factor/von Willebrand factor complex (human): prescribing information*, CSL Behring GmbH, revised October 2007, http://www.humate-p.com/pdf/HumateP_PI.pdf, accessed 28 April 2008.
- 8 Michiels JJ, Berneman ZN, van der Planken M, Schroyens W, Budde U, van Vliet HHD. Bleeding prophylaxis for major surgery in patients with type 2 von Willebrand disease with an intermediate purity factor VIII-von Willebrand factor concentrate (Haemate-P). *Blood Coagul Fibrinolysis* 2004; 15: 323–30.
- 9 Walter O, Budde U, Muysers C, Metzner HJ, Suiter TM. Determination of high molecular weight von Willebrand factor multimers and their impact on specific VWF activities in VWF/FVIII-concentrates. *J Thromb Haemost* 2003; 1(Suppl. 1): abstract 1673.
- 10 Suiter T, Budde U, Metzner HJ, Muysers C, Walter O. Comparison of von Willebrand factor activities measured by ristocetin cofactor assay and two different VWF-collagen-binding assays in VWF/FVIII-concentrates. *J Thromb Haemost* 2003; 1(Suppl. 1): abstract 1667.
- 11 Furlan M. von Willebrand factor: molecular size and functional activity. *Ann Hematol* 1996; 72: 341–8.
- 12 Ruggeri ZM. Structure of von Willebrand factor and its function in platelet adhesion and thrombus formation. *Best Pract Res Clin Haematol* 2001; 14: 257–79.
- 13 Lethagen S, Carlson M, Hillarp A. A comparative in vitro evaluation of six von Willebrand factor concentrates. *Haemophilia* 2004; 10: 243–9.
- 14 Budde U, Metzner HJ, Müller HG. Comparative analysis and classification of von Willebrand factor/factor VIII concentrates: impact on treatment of patients with von Willebrand disease. *Semin Thromb Hemost* 2006; 32: 626–35.
- 15 Metzner HJ, Hermentin P, Cuesta-Linker T, Langner S, Müller HG, Friedebold J. Characterization of factor VIII/von Willebrand factor concentrates using a modified method of von Willebrand factor multimer analysis. *Haemophilia* 1998; 4(Suppl. 3): 25–32.
- 16 Berntorp E, Nilsson IM. Use of a high-purity factor VIII concentrate (Hemate-P) in von Willebrand's disease. *Vox Sang* 1989; 56: 212–7.
- 17 Scharrer I, Vigh T, Aygören-Pürsün E. Experience with Haemate P in von Willebrand's disease in adults. *Haemostasis* 1994; 24: 298–303.
- 18 Fukui H, Nishino M, Terada S *et al.* Hemostatic effect of a heat-treated factor VIII concentrate (Haemate-P) in von Willebrand's disease. *Blut* 1988; 56: 171–8.
- 19 Rose E, Forster A, Aledort LM. Correction of prolonged bleeding time in von Willebrand's disease with Humate-P. *Transfusion* 1990; 30: 381.
- 20 Kreuz W, Mentzer D, Becker S, Scharrer I, Kornhuber B. Haemate P in children with von Willebrand's disease. *Haemostasis* 1994; 24: 304–10.
- 21 Berntorp E. Plasma product treatment in various types of von Willebrand's disease. *Haemostasis* 1994; 24: 289–97.
- 22 Schimpf K, Mannucci PM, Kreuz W *et al.* Absence of hepatitis after treatment with a pasteurized factor VIII concentrate in patients with hemophilia and no previous transfusions. *N Engl J Med* 1987; 316: 918–22.
- 23 Köhler M, Hellstern P, Wenzel E. The use of heat-treated factor VIII-concentrates in von Willebrand's disease. *Blut* 1985; 50: 25–27.
- 24 Dobrkovska A, Krzensk U, Chediak JR. Pharmacokinetics, efficacy and safety of Humate-P in von Willebrand disease. *Haemophilia* 1998; 4(Suppl. 3): 33–39.
- 25 Lillicrap D, Poon M-C, Walker I, Xie F, Schwartz BA. Association of Hemophilia Clinic Directors of Canada: Efficacy and safety of the factor VIII/von Willebrand factor concentrate Haemate-P/Humate-P: ristocetin cofactor unit dosing in patients with von Willebrand disease. *Thromb Haemost* 2002; 87: 224–30.
- 26 Franchini M, Rossetti G, Tagliaferri A *et al.* Efficacy and safety of factor VIII/von Willebrand factor concentrate (Haemate-P) in preventing bleeding during surgery or invasive procedures in patients with von Willebrand's disease. *Haematologica* 2003; 88: 1279–83.
- 27 Lethagen S, Kyrle PA, Castaman G, Haertel S, Mannucci PM for the Haemate P Surgical Study Group. von Willebrand factor/factor VIII concentrate (Haemate[®]P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. *J Thromb Haemost* 2007; 5: 1420–30.
- 28 Gill JC, Ewenstein BM, Thompson AR, Mueller-Velten G, Schwartz BA for the Humate-P Study Group. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy. *Haemophilia* 2003; 9: 688–95.
- 29 Thompson AR, Gill JC, Ewenstein BM, Mueller-Velten G, Schwartz BA for the Humate-P Study Group. Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/

- VWF concentrate (Humate-P). *Haemophilia* 2004; **10**: 42–51.
- 30 Lubetsky A, Schulman S, Varon D *et al.* Safety and efficacy of continuous infusion of a combined factor VIII–von Willebrand factor (vWF) concentrate (Haemate-P) in patients with von Willebrand disease. *Thromb Haemost* 1999; **81**: 229–33.
- 31 Morley N, Makris M, Hampton K. The use of two plasma derived factor VIII concentrates in type 2A von Willebrand's disease (VWD). *J Thromb Haemost* 2003; **1**(Suppl. 1): abstract P0112.
- 32 Heimbürger N, Karges HE, Mauler R, Nováková-Banet A, Hilfenhaus J, Wiedmann E. Factor VIII concentrate: hepatitis-safe preparation, virus inactivation and clinical experience. *Proc 4th Inter Symp Hemophilia Treatment*, Tokyo. 1984; 107–15.
- 33 Schimpf K, Brackmann HH, Kreuz W *et al.* Absence of anti-human immunodeficiency virus types 1 and 2 seroconversion after the treatment of hemophilia A or von Willebrand's disease with pasteurized factor VIII concentrate. *N Engl J Med* 1989; **321**: 1148–52.
- 34 Mösseler J, Schimpf K, Auerswald G, Bayer H, Schneider J, Hunsmann G. Inability of pasteurised factor VIII preparations to induce antibodies to HTLV-III after long-term treatment. *Lancet* 1985; **1**: 1111.
- 35 Budde U, Drewke E, Mainusch K, Schneppenheim R. Laboratory diagnosis of congenital von Willebrand disease. *Semin Thromb Hemost* 2002; **28**: 173–89.