The management of patients with congenital von Willebrand disease during surgery or other invasive procedures: focus on antihemophilic factor/von Willebrand factor complex

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Abstract: Von Willebrand disease, the most common hereditary bleeding disorder, arises from quantitative or qualitative defect of von Willebrand factor (VWF). The aim of the treatment is to correct the dual defect of hemostasis caused by the abnormal/reduced VWF and the concomitant deficiency of factor VIII (FVIII). The synthetic vasopressin analogue desmopressin is the mainstay of therapy in about 80% of patients, while nearly 20% are unresponsive and must be treated with FVIII/VWF concentrates. This latter therapeutic option will be focused in the review, with particular consideration to the management of surgery and invasive procedures in these patients.

Keywords: von Willebrand disease, therapy FVIII/VWF concentrates, bleeding

Introduction

Von Willebrand disease (VWD) is the most common genetic bleeding disorder with a prevalence of approximately 1%–2% confirmed in different population studies (Rodeghiero et al 1987). The severity of the bleeding tendency is usually proportional to the degree of the VWF defect, although the large majority of cases diagnosed appear to have a mild disease (Castaman et al 2003).

In this review, we summarize the most important clinical, diagnostic, laboratory and therapeutic features of VWD. In particular, we focus on the use of factor VIII (FVIII)/von Willebrand factor (VWF) concentrates for the management of surgical or other invasive procedures in VWD patients.

Structure and function of von Willebrand factor

VWF is synthesized by endothelial cells and megakaryocytes. The gene coding for VWF has been cloned and located at chromosome 12p13.2. It is a large gene composed of about 178 kilobases and containing 52 exons. The primary product of the VWF gene is a 2813 amino acid protein made of a signal peptide of 22 amino acids (also called pre-peptide), a large pro-peptide of 741 amino acids and a mature VWF molecule containing 2050 amino acids. Different protein regions, corresponding to four types of repeated domains (D1, D2, D', D3, A1, A2, A3, D4, B, C1, C2) of cDNA, are responsible for the different binding functions of the molecule. VWF is the result of ordered intra-cellular processing, leading to the storage and/or secretion of a heterogeneous array of multimeric multi-domain glycoproteins, referred to as VWF (Ruggeri 2001).

VWF has two major functions in hemostasis. First, it is essential for platelet-subendothelium adhesion and platelet-to-platelet interactions as well as platelet

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aggregation in vessels in which rapid blood flow results in elevated shear stress. Adhesion is promoted by the interaction of a region of the A1 domain of VWF with GpIbα on platelet membrane. It is thought that high shear stress activates the A1 domain of the collagen-bound VWF by stretching VWF multimers into their filamentous form. Furthermore GPIbα and VWF are also necessary for platelet-to-platelet interactions. Aggregation of platelets within the growing haemostatic plug is promoted by the interaction with a second receptor on platelets, GPIIb-IIIa which, once activated, binds to VWF and fibrinogen, recruiting more platelets into a stable plug. Both these binding activities of VWF are highly expressed in the largest VWF multimers (Ruggeri 2001).

Second, VWF is the specific carrier of FVIII in plasma. VWF protects FVIII from proteolytic degradation, prolonging its half-life in circulation and efficiently localizing it at the site of vascular injury. Each VWF monomer has one binding domain, located in the first 272 amino acids of the mature subunit (D' domain) which can bind one FVIII molecule; in vivo, however only 1%–2% of available monomers are occupied by FVIII. Therefore, any change in plasma VWF level is usually associated with a concordant change in FVIII plasma concentration (Vlot et al 1998).

Classification and diagnosis of von Willebrand disease

Inherited VWD has been subdivided in three types (Franchini et al 2007). Type 1 and 3 VWD reflect, respectively, the partial or virtually complete deficiency of VWF while type 2 VWD reflects a qualitative deficiency of VWF. Type 1 is the most common form of VWD, accounting for approximately 80% of all cases, and is transmitted as an autosomal dominant trait with incomplete penetrance. Type 1 disease is characterized by a mild to moderate reduction in von Willebrand factor antigen (VWF:Ag) and ristocetin cofactor (VWF:RCo) plasma levels. The VWF is functionally normal, as is the range of plasma VWF multimers, and the plasma level of factor VIII (FVIII) is reduced in proportion to the VWF level. These patients manifest a spectrum of mucocutaneous bleeding symptoms, the severity of which usually correlates with the level of their VWF deficiency (Federici 2004).

Type 2 VWD is divided in four subtypes: type 2A, 2B, 2M and 2N. Type 2A von Willebrand disease is the most frequent subtype among type 2 VWD. It is inherited mainly with an autosomal dominant pattern, but a recessive modality of transmission is also described. The hallmark of type 2A disease is a low VWF:RCo to VWF:Ag ratio (<0.7), with absent high molecular weight VWF multimers and impaired ristocetin-induced platelet agglutination (RIPA). Like type 2A, the inheritance pattern of type 2B is mainly autosomal dominant, but cases with apparently recessive patterns have also been described. Typical laboratory characteristics of type 2B include a mild thrombocytopenia, low to normal FVIII, low to normal VWF:Ag, low VWF:RCo, heightened RIPA and absence of large multimers from plasma. Type 2M VWD disease includes variants in which binding to platelets is impaired but the VWF multimeric distribution is normal. Laboratory results generally are similar to those in type 2A, but there is the presence of a normal plasma multimeric pattern. Finally, type 2N von Willebrand disease is characterized by normal levels of VWF:Ag and VWF:RCo and normal multimeric structure, but low plasma FVIII levels due to the decreased plasma half-life of FVIII, which cannot bind to VWF as a consequence of an intrinsic abnormality of VWF. It therefore resembles haemophilia A, but its inheritance pattern is not X-linked but autosomal recessive (Laffan et al 2004).

Type 3 VWD is inherited by an autosomal recessive trait and is characterized by undetectable levels of VWF in plasma and platelets and by very low plasma levels (1%–5%) of FVIII. As a consequence, patients with type 3 VWD experience a severe bleeding tendency characterized not only by mucocutaneous hemorrhages but also by hemarthroses and hematomas as observed in severe hemophilia (Federici et al 2002).

The classification of VWD is reported in Table 1.

Treatment of von Willebrand disease

The aim of therapy for VWD is correct the dual defect of hemostasis, ie, the abnormal platelet adhesion and the abnormal coagulation due to low FVIII levels (Mannucci 2001). There are two treatments of choice in VWD, ie, desmopressin (DDAVP) and transfusional therapy with blood products (Mannucci 2004). Other non-transfusional therapies, like antifibrinolytic agents, have been successfully used alone or in association with standard treatment for patients with VWD, particularly for oral and other moderate mucous membrane bleeding.

DDAVP is most effective in patients with type 1 VWD. In these patients FVIII, VWF and BT are usually corrected within 30 min after administration and remain normal for 6–8 h. However, most patients initially responsive to DDAVP, become less responsive to therapy when treated repeatedly (phenomenon called tachyphylaxis). In other VWD subtypes, responsiveness to DDAVP is variable. In type 2A, FVIII

Table 1 Classification of von Willebrand disease

VWD type	Transmission	Pathogenic mechanism	Laboratory parameters					
			VWF:Ag	VWF:RCo	FVIII:C	VWF:RCo/ VWF:Ag	RIPA	Multimers
Type 1	AD	Partial quantitative deficiency of VWF	↓	↓	N/↓	>0.7	↓	Uniform ↓ of all multimers
Type 2	AD, AR	Qualitative defects of VWF						
2A		Decreased platelet-dependent VWF function	↓↓	↓	N/↓	<0.7	↓	Lack of HMWM
2B		Increased platelet-dependent VWF function	↓↓	↓	N/↓	<0.7	↑	Lack of HMWM
2M		Decreased platelet-dependent VWF function	↓	↓	N/↓	<0.7	↓	Normal or supranormal
2N		Decreased VWF affinity for FVIII	N	N	↓	>0.7	N	Normal
Type 3	AR	Complete deficiency of VWF	↓↓↓	↓↓↓	↓↓↓	–	↓↓↓	Undetectable

Abbreviations: N, normal; AD, autosomal dominant; AR, autosomal recessive; FVIII, factor VIII; FVIII:C, factor VIII coagulant; GP, glycoprotein; HMWM, high molecular weight multimers; RIPA, ristocetin-induced platelet agglutination; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor.

levels are usually increased by DDAVP but BT is shortened in only a minority of cases. DDAVP is contraindicated in type 2B because of the transient appearance of thrombocytopenia. Type 2M shows a variable pattern of response and the decision to use desmopressin should be made based on the results of a test infusion. In type 2N, relatively high levels of FVIII are observed following DDAVP, but released FVIII circulates for a shorter time period in patient plasma because the stabilizing effect of VWF is impaired. Finally, patients with type 3 VWD are usually unresponsive to DDAVP (Mannucci 2000).

For those VWD patients in whom DDAVP is either ineffective or contraindicated, VWF and FVIII levels can be restored by the infusion of virus-inactivaed plasma-derived concentrates of these proteins. Several intermediate and high-purity FVIII-VWF products are commercially available (see Table 2) and many reports in the literature have documented their efficacy in the treatment of bleeding episodes or as prophylaxis of hemorrhages during surgical or invasive procedures in VWD patients.

A retrospective survey on the use of Haemate P reported 97 patients with all types of VWD who were treated for 73 surgical operations, 344 bleeding events and 93 other events including invasive procedures. The efficacy was rated as excellent or good in 99% of surgical operations, 97% of bleeding episodes and 86% of other events (Dobrkovska et al 1998). The same intermediate-purity FVIII/VWF concentrate was utilized in a large retrospective study organized by the Canadian Hemophilia Centers. Patients were treated for 437 events, including bleeding episodes and surgical procedures. The rates of excellent-to-good responses were 97% overall, 99% in surgical procedures, 97% in bleeding episodes and 86% in other cases (Lillicrap et al 2002). Other two prospective studies supported the safety and efficacy of Hemate P for the treatment of urgent bleeding and urgent surgical events (Gill JC et al 2003; Thompson et al 2004). We have previously reported the experience of three Italian hemophilia centers on 26 VWD patients who underwent 43 surgical or invasive procedures (14 major surgery, 11 minor surgery, 11 dental extractions and 7 invasive diagnostic procedures) under coverage with Haemate P (Franchini et al 2003). The mean daily dose of concentrate given was 39.3 (range 25–52.5) IU VWF:RCo/kg for major surgery, 28.7 (range 21.4–34.8) IU VWF:RCo/kg for minor

Table 2 FVIII/VWF concentrates registered in Italy for the treatment of von Willebrand disease

Product	Manufacturer	Purification	Viral inactivation	FVIII activity (U/mg protein)	VWF:RCo/FVIII (ratio)
Alphanate	Grifols	Affinity chromatography	S/D + 72 h at 80 °C	>100	1.6
Fanhdi	Grifols	Affinity chromatography	S/D + 72 h at 80 °C	>100	1.6
Haemate P	CSL Behring	Multiple precipitation	Pasteurization 10 h at 60 °C	40 ± 6	2.5
Immunate	Baxter	Ion exchange chromatography	D/VH 10 h at 60 °C + 1 h at 80 °C	100 ± 50	1.1

Abbreviations: VWF, von Willebrand factor; RCo, ristocetin cofactor; Ag, antigen; FVIII, factor VIII; S/D, solvent/detergent; D/VH, detergent/vapor heat.

Table 3 Literature results on the use of FVIII/VWF during surgical or invasive procedures

Author, year	Product	Pts	VWD types	Type of interventions	Dose range	Efficacy (%)
Nitu-Whalley, 2001	Haemate P/BPL 8Y	38	26 type 1, 6 type 2, 3 type 3	10 major, 35 minor, 18 oral surgeries	14–77 IU FVIII:C/kg/d	82
Lillicrap, 2002	Haemate P	73	26 type 1, 20 type 2, 21 type 3, 6 NI	73 surgery	11.9–222.8 IU VWF: RCo/kg	99
Franchini, 2003	Haemate P	26	19 type 1, 7 type 2	14 major, 11 minor, 11 oral surgeries, 7 IP	21.4–52.5 IU VWF: RCo/kg/d	98
Thompson, 2004	Haemate P	39	16 type 1, 9 type 2, 8 type 3, 6 NI	25 major, 17 minor surgeries	32.5–216.8 IU VWF: RCo/kg	100
Federici, 2007	Haemate P	56	19 type 1, 27 type 2, 10 type 3	17 major, 28 minor, 19 oral surgeries, 9 IP	27–146 IU VWF: RCo/kg/d	97
Lethagen, 2007	Haemate P	29	10 type 1, 11 type 2, 8 type 3	16 major, 11 minor	50.1–87.0 IU VWF: RCo/kg	96.3
Federici, 2002	Fanhdi	14	5 type 1, 7 type 2, 2 type 3	7 major, 5 minor, 2 oral surgeries	17–92 IU FVIII:C/kg/d	93
Mannucci, 2002	Alphanate	39	6 type 1, 19 type 2, 14 type 3	71 surgical or invasive procedures	20–76 IU VWF: RCo/kg	96
Goudemand, 1998	VHP	54	NI	23 major, 31 minor surgeries	51–55 IU VWF:RCo/kg	100
Borel-Derlon, 2007	Wilfactin	44	5 type 1, 25 type 2, 14 type 3	43 major or minor, 14 oral surgeries, 51 IP	11.1–100 IU VWF:RCo/kg	100

Abbreviations: Pts, patients; VWD, von Willebrand disease; VWF, von Willebrand factor; FVIII:C, factor VIII coagulant activity; NI, not indicated; VWF:RCo, von Willebrand factor ristocetin cofactor; IP, invasive procedures; d, day.

surgery, 24.0 (range 23.5–25) IU VWF:RCo/kg for dental extractions and 32.3 (range 27.3–37) IU VWF:RCo/kg for invasive procedures. The mean days of treatment were 9.7 (range 5–23) for major surgery, 4.2 (range 2–7) for minor surgery, 1.6 (range 1–5) for dental extractions and 2.7 (range 1–5) for invasive procedures. As only a bleeding episode was recorded without drug-related adverse events, we concluded that Haemate P was safe and effective in preventing excessive bleeding after major and minor surgery or invasive procedures in VWD patients.

An Italian retrospective multicenter cohort study (Federici et al 2007) evaluated the response to Haemate P in 100 VWD patients treated for bleeding, surgeries or prophylaxis and recorded a 97% of excellent/good clinical response in the 56 patients who underwent 73 surgical or invasive procedures. Finally, a prospective multicenter trial on 29 subjects with VWD undergoing elective surgery found that Haemate P, whose preoperative loading dose was based on a pharmacokinetic study, provided an excellent or good hemostasis in 96.3% of subjects on the day of surgery and 100% on the next days (Lethagen et al 2007).

The highly purified, doubly virus-inactivated FVIII/VWF concentrate Fanhdi has been reported to be efficacious in the management of VWD in a retrospective clinical study (Federici et al 2002). In 22 patients 12 bleeding episodes and invasive procedures were treated with Fanhdi. There was 92% excellent or good efficacy and no adverse events.

The results of a large international prospective study by the Alphanate study Group were published in 2002 and included 39 patients receiving prophylactic treatment for 71 surgical or invasive diagnostic procedures. A good clinical response with this FVIII/VWF concentrate was observed in 71% of patients (Mannucci et al 2002). It was also demonstrated that surgery could be safely undertaken even when Alphanate did not correct the bleeding time.

Goudemand and colleagues (Goudemand et al 1998) reported the French clinical experience on the use of the very high purity VHP VWF concentrate in 75 VWD patients treated on 99 occasions either to control spontaneous bleeding or to prevent hemorrhagic risk associated with surgery. Successful treatment of 31 minor and 23 major surgical procedures was reported.

Finally a single center ten year retrospective review conducted in United Kingdom identified 38 patients who received various FVIII/VWF concentrates for 68 elective surgical events (Nitu-Whalley et al 2001). The effectiveness of hemostasis was judged excellent in 56 (82%) surgical events. Table 3 summarizes the literature results.

On the whole, the literature results document that 20–50 IU/kg of FVIII/VWF concentrates given once daily until healing is complete are hemostatically effective in preventing bleeding in the majority of surgical or invasive procedures. Thus, for major procedures, FVIII and VWF:RCo levels should be raised to 80–100 UI/dL at the time of surgery and maintained above 50 IU/dL for at least 7–14 days. For minor procedures, FVIII

and VWF:RCo levels above 50 IU/dL at the time of surgery are advisable, followed by levels above 30 IU/dL for at least 5–7 days. Finally, dental extractions or invasive procedures may be managed with a single concentrate infusion aimed to reach VWF:RCo/FVIII levels of about 50 IU/dL.

However, the accumulation of FVIII that is exogenously infused together with that endogenously synthesized and stabilized by the infused VWF may result in very high FVIII concentrations (>150 IU/dL) when several infusions are given for severe bleeding episodes or to cover major surgery. There is some concern that sustained high concentrations of FVIII may increase the risk of postoperative deep vein thrombosis, as suggested by recent observations (Kyrle et al 2000). Therefore we suggest, when repeated injections of FVIII/VWF concentrates are administered, to monitor daily FVIII plasma levels.

Some authors have proposed the use of VWF:RCo units to calculate the dose of FVIII/VWF concentrate to administer and to monitor the response to treatment. Although this practice would better tailor the therapy of VWD patients avoiding the high post-infusion FVIII levels, it is not standardized and validated by prospective studies. Moreover, this test can be performed only by specialized coagulation laboratories (Ewenstein 2001).

In order to avoid high post-infusion FVIII plasma levels, a high-purity VWF concentrate with low FVIII content (Wilfactin, LFB) has been recently developed and its efficacy tested in a prospective study on 50 VWD patients (Borel-Derlon et al 2007). The hemostatic outcome was judged excellent or good in all the 108 surgical or invasive procedures performed and no adverse thrombotic complications were recorded.

Conclusions

FVIII/VWF concentrates play a valuable role in the management of patients with VWD who are unresponsive to DDAVP. Literature data testify that these products have an excellent level of safety and efficacy. However, further clinical trials are needed to improve the dosing and monitoring of these products in VWD patients during surgical or invasive procedures.

References

Borel-Derlon A, Federici AB, Roussel-Robert V, et al. 2007. Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients. *J Thromb Haemost*, 5:1115–24.

Castaman G, Federici AB, Rodeghiero F, et al. 2003. von Willebrand's disease in the year 2003: towards the complete identification of gene defects for correct diagnosis and treatment. *Haematologica*, 88:94–108.

Dobrkovska A, Krzensk U, Chediak JR. 1998. Pharmacokinetics, efficacy and safety of Humate-P in von Willebrand disease. *Haemophilia*, 4 (Suppl 3):33–9.

Ewenstein BM. 2001. Use of ristocetin cofactor activity in the management of von Willebrand disease. *Haemophilia*, 7(Suppl. 1):10–15.

Federici AB, Baudo F, Caracciolo C, et al. 2002. Clinical efficacy of highly purified, doubly virus-inactivated factor VIII/von Willebrand factor concentrate (Fanhdi) in the treatment of von Willebrand disease: a retrospective clinical study. *Haemophilia*, 8:761–7.

Federici AB. 2004. Clinical diagnosis of von Willebrand disease. *Haemophilia*, 10(Suppl 4):169–76.

Federici AB, Castaman G, Mannucci PM. Italian Association of Hemophilia Centers (AICE). 2002. Guidelines for the diagnosis and management of von Willebrand disease in Italy. *Haemophilia*, 8:607–21.

Federici AB, Castaman G, Franchini M, et al. 2007. Clinical use of Haemate P in inherited von Willebrand disease: a cohort study on 100 Italian patients. *Haematologica*, 92:944–51.

Franchini M, Rossetti G, Tagliaferri A, et al. 2003. 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*, 88:1279–83.

Franchini M, Lippi G. 2007. The role of von Willebrand factor in hemorrhagic and thrombotic disorders. *Crit Rev Clin Lab Sci*, 44:115–49.

Gill JC, Ewenstein BM, Thompson AR, et al. 2003. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/von Willebrand factor concentrate (Humate-P): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy. *Haemophilia*, 9:688–95.

Goudemand J, Negrier C, Ounnoughene N, et al. 1998. Clinical management of patients with von Willebrand's disease with a VHP vWF concentrate: the French experience. *Haemophilia*, 4 Suppl 3:48–52.

Kyrle PA, Minar E, Hirschl M, et al. 2000. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med*, 343:457–62.

Laffan M, Brown SA, Collins PW, et al. 2004. The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. *Haemophilia*, 10:199–217.

Lethagen S, Kyrle PA, Castaman G, et al. 2007. Von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. *J Thromb Haemost*, 5:1420–30.

Lillicrap D, Poon M-C, Walker I, et al. 2002. 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*, 87:224–30.

Mannucci PM. 2000. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first twenty years. *Haemophilia*, 6(Suppl 1):60–7.

Mannnucci PM. 2001. How I treat patients with von Willebrand disease. *Blood*, 97:1915–9.

Mannucci PM, Chediak J, Hanna W, et al. 2002. Treatment of von Willebrand disease with a high-purity factor VIII/von Willebrand factor concentrate: a prospective, multicenter study. *Blood*, 99:450–6.

Mannucci PM. 2004. Treatment of von Willebrand's Disease. *N Engl J Med*, 351:683–94.

Rodeghiero F, Castaman G, Dini E. 1987. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood*, 69:454–9.

Nitu-Whalley IC, Griffioen A, Harrington C, Lee CA. 2001. Retrospective review of the management of elective surgery with desmopressin and clotting factor concentrates in patients with von Willebrand disease. *Am J Hematol*, 66:280–4.

Thompson AR, Gill JC, Ewenstein BM, et al. 2004. Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/von Willebrand factor concentrate (Humate-P). *Haemophilia*, 10:42–51.

Vlot AJ, Koppelman SJ, Bouma BN, et al. 1998. Factor VIII and von Willebrand Factor. *Thromb Haemost*, 79:456–65.

Ruggeri ZM. 2001. Structure of von Willebrand factor and its function in platelet adhesion and thrombus formation. *Best Pract Res Clinical Haematol*, 14:257–9.