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Managing Patients with von Willebrand Disease Type 1, 2 and 3 with Desmopressin and von Willebrand Factor-Factor VIII Concentrate in Surgical Settings

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Key Words
Bleeding severity · Desmopressin · Pharmacokinetic studies · Trauma · von Willebrand factor/factor VIII concentrates

Abstract
Guidelines and recommendations for the acute and prophylactic treatment of bleeding in von Willebrand disease (VWD) patients with von Willebrand factor (VWF)/factor VIII (FVIII) concentrates should be based on the analysis of the content of VWF/FVIII concentrates and on pharmacokinetic studies in patients with different severity of VWD (type 1, type 2 or type 3). The VW/FVIII concentrates should be assessed using the parameters FVIII:coagulant activity (C), VWF:ristocetin cofactor activity (RCo), VWF:collagen binding and VWF multimeric patterns for the presence of large multimers to determine their predicted efficacy and safety in prospective management studies. As the bleeding tendency is moderate in VWD type 2 and severe in type 3 and because the FVIII:C levels are subnormal in type 2 but very low in type 3 VWD patients, new guidelines using VWF:RCo unit dosing for the acute and prophylactic treatment of bleeding episodes are proposed. Such guidelines should be stratified for the severity of bleeding, the type of surgery (minor or major) and also for the bleeding score in either VWD type 1, 2 or 3.

Introduction

Patients with von Willebrand disease (VWD) have an increased bleeding tendency following surgery or other invasive procedures. It is generally agreed that the low von Willebrand factor (VWF) level is most important for mucous membrane bleeds, whereas decreased factor VIII (FVIII) is more important for soft tissue and joint bleeds [1–3]. VWF levels should be normalized in the peri-operative and early postoperative period, especially when there is a risk for mucous membrane bleeds. FVIII should be normalized in connection with major surgery, both during the surgical procedure and ~7–10 days postoperatively [4].

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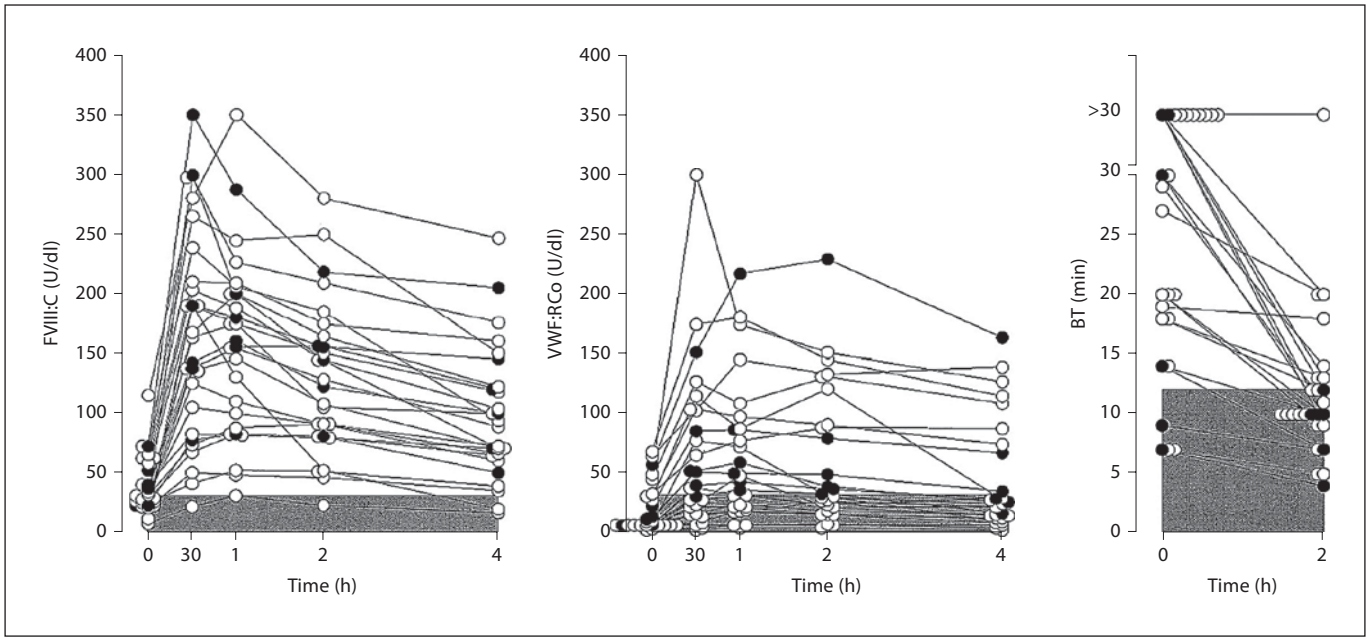


Fig. 1. Response to DDAVP in 26 patients diagnosed with VWD type 1 according to SSC ISTH criteria [8]. The responses of FVIII: C to DDAVP are good in 9 cases, but restrictive or even poor or non-responsive in more than half of these patients with VWD type 1, indicating that various degrees of severity of either autosomal recessive or dominant type 1 VWD patients are lumped when the SSC ISTH classification is applied [11, 12]. Among VWD type 1 patients, there is a group of mild VWD type 1 with a good response of VWF:RCo and complete correction of VWF parameters and BT after DDAVP [11, 12]. There is another well-recognized group of severe type 1 VWD patients with no or very poor responses of VWF:RCo and no correction of BT after DDAVP indicating the need of VWF/FVIII concentrate to manage and prevent bleeding during minor and major surgery or trauma [12].

Factor levels can be raised either by stimulating the endogenous release of FVIII and VWF with desmopressin (DDAVP, 1-desamino-8-D-arginine vasopressin), or by substituting the deficient factors with a coagulation factor concentrate containing VWF and FVIII.

Desmopressin: DDAVP

DDAVP is a widely used hemostatic drug [5]. It is a synthetic analogue of the natural hormone vasopressin, but it has no pressor activity, being in contrast to vasopressin. The effect is virtually immediate, usually with 2- to 4-fold increases in the plasma concentrations of FVIII, VWF and tissue plasminogen activator [6]. Most patients with VWD type 1 respond adequately to DDAVP (fig. 1; table 1). Some patients with type 2 may respond sufficiently, but most type 2 patients will have an insufficient response due to functional abnormalities in the VWF. In the classical form of type 2B, DDAVP causes platelet aggregation and thrombocytopenia, and should be avoided [7]. Type 3 patients do not respond to DDAVP. The response rate in type 1 and 2 is dependent on the severity of the disorder. Thus, even if the majority of type 1 patients may respond well, only a minority of those with severe type 1 will be responders [8]. The European multicenter study Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand disease (MCMDM-1VWD; www.shef.ac.uk/euvwd/) recently demonstrated that there is a clear correlation between mutations in the VWF gene and the response to DDAVP in type 1 VWD.

All patients should be given a test dose to ensure that the response is sufficient for clinical use. DDAVP can be used to treat major bleeds or to prevent bleeding in connection with surgery or other invasive procedures, if VWF:ristocetin cofactor activity (RCo) and FVIII:coagulant activity (C) reach normal levels after DDAVP. If response is lower or the duration is short, a VWF/FVIII concentrate should be considered [8–16].

In case of surgery, DDAVP (0.3 μg/kg) may be given intravenously about 30–60 min before surgery, or subcu-

Table 1. Response to DDAVP in patients with recessive VWD type 3, type 1 and type 2; mild VWD type 1 with normal VWF multimers (MM) and variable penetrance of bleeding, and autosomal dominant VWD type 1 and 2 [8, 16]

VWD classification	Mutation location	Response to DDAVP of FVIII:C, VWF and BT				
		FVIII:C	VWF:Ag	VWF:RCo	VWF:CB	BT correction
VWD type 1, normal MM	variable	good	good	good	good	yes
VWD type 1, abnormal MM						
1 m, sm, smf	D4, B1–B3, C1–C2	good	good/restricted	good/restricted	good/restricted	yes
Dominant VWD, abnormal MM						
1/2E	D3	good	transient	transient	transient	transient
1/Vicenza	D3	short	short/transient	short/transient	short/transient	transient
2M	A1	good	good/transient	poor	good/transient	transient
2A group II	A2	good	good	short/transient	short/transient	transient
2A group I	A2	good	restricted	poor	poor	no
2B	A1	good	good	poor	poor	no
2D	CK	partial	partial	poor	poor	no
Recessive VWD 3						
	double null (n) null/missense (m)	no	no	no	no	no
Severe 1 Secretion defect	double m/m or n/m	partial	poor	no	no	no
Severe 2C, 2D	D1 D2, CK double n/m or m/m	partial	partial	poor	poor	no
2N	D′–D3	poor/short	good	good	good	normal BT

taneously about 1–2 h preoperatively. The intranasal spray may be used in connection with minor procedures, and should be taken 1–2 h in advance in a dose of 300 μg (150 μg in patients weighing <30 kg) [8–16].

DDAVP dosing can be repeated at 12- or 24-hour intervals if necessary, but repeated dosing for several days should be avoided. If repeated, once-daily dosing of DDAVP over several days is required, tachyphylaxis and antidiuretic effects must be considered. It may be necessary to switch to a VWF/FVIII concentrate in some cases. A single dose of DDAVP is often sufficient for minor surgery. In connection with tooth extractions and other procedures involving mucous membranes, concomitant treatment with an antifibrinolytic agent, e.g. tranexamic acid, may be of benefit.

General Recommendations for the Evaluation of Prospective Studies [8–16]

Recessive VWD type 3 and severe type 1 patients with no response of VWF parameters and FVIII to DDAVP are candidates for prophylactic treatment of hemophilic bleeding in joints or soft tissues with low-dose VWF/FVIII substitution 2–3 times a week.

VWD type 2A, 2C and 2D patients with poor response of functional VWF parameters to DDAVP are candidates for VWF/FVIII concentrate substitution to prevent bleeding during minor and major surgery and/or trauma, and to treat spontaneous serious bleeding manifestations.

VWD type 2E, 2M and 2A group II patients with short or restricted good responses of functional VWF parameters to normal with correction of PFA-100 and Ivy bleeding time (BT) for a few to several hours are candidates for DDAVP treatment of minor bleeds or prevention of bleeding during minor surgery, but should receive additional VWF/FVIII substitution therapy for maintained correction of functional VWF parameters during and after major surgery or trauma.

VWD patients with good responses to DDAVP of FVIII:C and all VWF parameters to normal values, including correction of PFA-100 and Ivy BT for >6–12 h after DDAVP treatment, are candidates for DDAVP for the prevention of excessive bleeding associated with minor and major surgery or trauma.

Table 2. Protocol and study design for the evaluation of PK and clinical efficacy of VWF/FVIII concentrate in patients with VWD non-responsive to DDAVP to be treated for acute bleeding or to prevent surgery- or trauma-induced bleeding [15]

Blood sample	Before	After substitution of VWF/FVIII concentrate				
		1 h	3 h	6 h	12 h	24 h
Ivy BT assay	+	+	–	+	–	+
PFA-100	+	+	+	+	+	+
RIPA	+	+	+	+	+	+
FVIII:C	+	+	+	+	+	+
VWF:Ag	+	+	+	+	+	+
VWF:RCo	+	+	+	+	+	+
VWF:CB	+	+	+	+	+	+
VWF:MM	+	+	+	+	+	+

MM = Multimer; RIPA = ristocetin-induced platelet aggregation.

VWF/FVIII Concentrate

Patients who are unresponsive to DDAVP, i.e. severe type 1 patients, the majority of those with type 2, and all type 3 patients, require concentrates containing large amounts of VWF in case of bleeds or surgery. Some type 1 patients may also require VWF concentrates if they need prolonged treatment, or if they have contraindications to DDAVP, such as cardiovascular disease. Physicians treating VWD patients must be aware of the large differences between different VWF/FVIII concentrates.

Proper recommendations for prospective outcome studies to evaluate the pharmacokinetics (PK) and dynamics combined with clinical efficacy of VWF/FVIII concentrates in VWD patients are required (table 2) [15].

The in vitro characteristics of a VWF/FVIII concentrate should be labeled by its content of FVIII:C, VWF: antigen (Ag), VWF:RCo; VWF:collagen binding (CB; collagen type 1, 95%, and type 3, 5%) and the presence of large VWF multimers compared to normal control plasma [17–19]. The in vivo responses of VWF parameters to VWF/FVIII concentrates have to be evaluated according to the protocol proposed by the Scientific Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH) for studies on ex vivo biological effects of virus-inactivated concentrates in VWD patients [13–17]. Ideally, in each VWD patient who needs the recommended infusion of VWF/FVIII concentrate using both FVIII:C and VWF:RCo dosing (in IU/kg body weight) to treat or prevent spontaneous or surgery-induced bleeding, PK should be evaluated prospectively after the first loading dose during daytime, evening, night and at the weekend by the responsible hematologist in the hospital for future reference when the same concentrate is used (table 2). Each dose of VWF/FVIII concentrate has to be administered by intravenous infusion over a period of 15–30 min. Blood samples before and after the first loading dose have to be taken for FVIII:C and VWF parameters before infusion and 1 (not earlier), 3, 6, 12 and 24 h after infusion combined with assessment of BT or PFA-100 closure times at the discretion of the responsible physician (table 2) [15]. In case two or more VWF/FVIII infusions are needed during one treatment interval, subsequent blood samples should be taken before and 1 h after infusion.

For each lot of a VWF/FVIII concentrate, FVIII:C, VWF:Ag, VWF:RCo, VWF:CB and the presence of large VWF multimers in low- and medium-resolution SDS-agarose gels should be determined [16–19]. Blood sampling before and 1, 3, 6 and 12 h after infusion and before and after each following infusion is required for clinical outcome and efficacy studies. For the prophylactic treatment of bleeding during elective surgery, real field PK study of VWF/FVIII concentrates for 12 h starting from the administration of the first loading dose using VWF:RCo dosing per kg body weight (60 or 80 VWF:RCo U kg^{-1}) is mandatory [15].

Lethagen et al. [18] compared the in vitro characteristics of six von Willebrand concentrates (fig. 2 left). The content of high-molecular-weight (HMW) multimers (presence of large multimers) was normal, with a ratio of VWF:RCo/VWF:Ag >0.7 in Haemate-P (CS Behring, Marburg, Germany), Innobrand (CAF, Brussels, Germany) and Facteur Willebrand (LFB, Lille, France), being moderately reduced in Koate and 8Y and significantly reduced in Immunate. Budde et al. [19] compared 12 VWF/FVIII concentrates to investigate content and activities of FVIII:C and VWF parameters as well as the content of HMW VWF multimers. Compared to controls, HMW multimers were present in 93.6% for Haemate-P, 79.2% for Innobrand and <36% for the remaining VW/FVIII concentrates. VWF:RCo per unit FVIII:C was 2.88 for Haemate-P, 2.28 for Green Eight, 2.20 for Innobrand and 0.82 for Alphanate. Conversely, the FVIII/VWF:RCo ratio was 0.35 for Haemate-P, 0.44 for Green Eight, 0.45 for Innobrand and 1.2 for Alphanate. The ratio of VWF:RCo/VWF:Ag was 0.94 for Haemate-P, 0.81 for Innobrand and 0.43 for Alphanate, which simply reflects the presence or absence of large VWF multimers in the con-

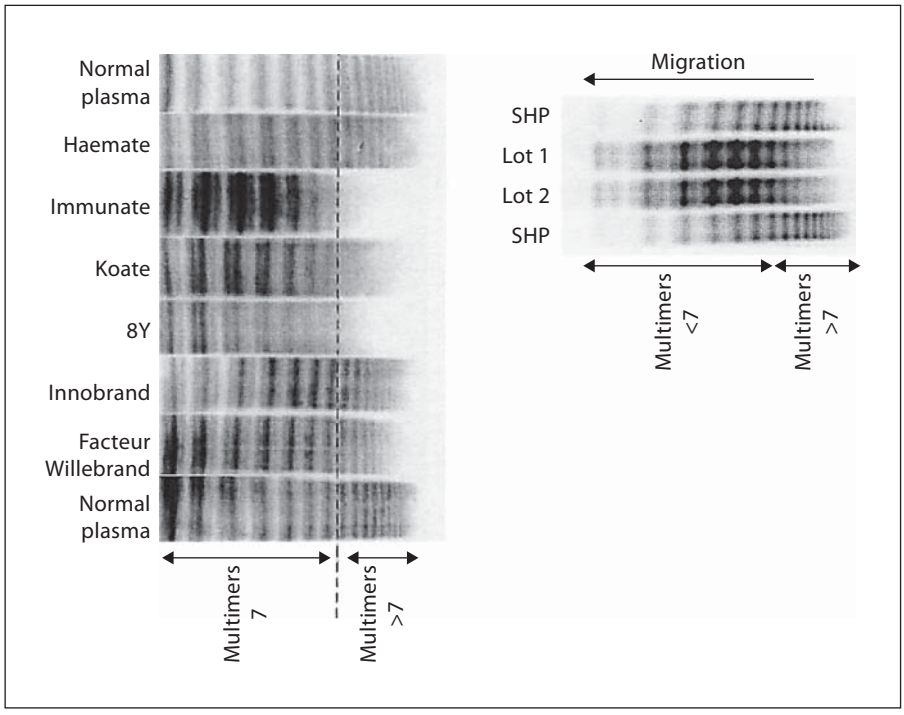


Fig. 2. Multimeric composition of VWF in the available VWF/FVIII concentrates (left) [18] and in Wilate (right) [21] compared to normal plasma. SHP = Standard human plasma; lots 1/2 = Wilate.

centrate. The ratio of VWF:CB/VWF:Ag was 0.89 for Haemate-P, 0.64 for Innobrand and 0.49 for Alphanate [19]. Since the ratio of VWF:RCo/VWF:Ag for Immunate is <0.50, it is no longer used for the prevention and treatment of bleeding in VWD patients. In the treatment of VWD patients, one should be aware that endogenous FVIII:C will bind to the amount of VWF:Ag infused, a main determinant for a much higher recovery and longer half-life of FVIII:C, indicating rather complex PK of the VWF-FVIII concentrates infused in VWD patients. Consequently, substitution of a VWF/FVIII concentrate with a low ratio of VWF:RCo/VWF:Ag (<0.70) and/or a high ratio of FVIII:C/VWF:RCo (>1) for several days after surgery or trauma are to be preferred in order to prevent unusually high FVIII:C levels, a major risk factor for postoperative deep vein thrombosis (fig. 3) [20].

The French PK study evaluated Wilfactin 100 VWF:RCo/kg^{-1} in 8 VWD type 3 patients. The calculated incremental recoveries of VWF:RCo (2.1%) and VWF:Ag (1.8%), the half-lives of VWF:RCo (12.4 h) and VWF:Ag (15.9 h), and the VWF:RCo and VWF:Ag curves were equal in terms of bioequivalence and PK. The FVIII:C levels increased slowly, with peak levels at 12–24 h of about 50%, which is 3 times lower compared to VWF peak levels after infusion of Wilfactin (fig. 4) [17]. As a consequence of this discrepancy, Innobrand, a mixture

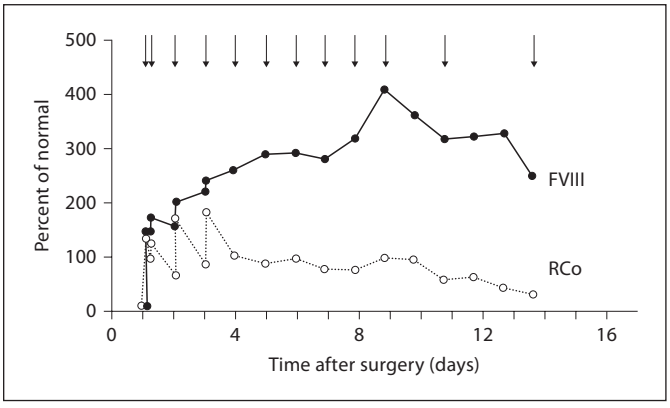


Fig. 3. Representative example of the effect of VWF/FVIII concentrate with a high FVIII-VWF:RCo ratio on plasma FVIII:C and VWF:RCo levels during long-term daily treatment for up to 8 days after major surgery. At levels of normal VWF:RCo maintained at ~1 IU/ml (100%), FVIII:C rose to levels >3 IU/ml (300%) [20].

of FVIII/purified VWF with a ratio of FVIII/VWF:RCo of 0.40 which resembles Haemate-P, was introduced. The European PK study compared Wilfactin and human factor VIII concentrate (Haemate-P or Innobrand) in 17 VWD patients (2 VWD type 1, 9 type 2A/B and 6 type 3

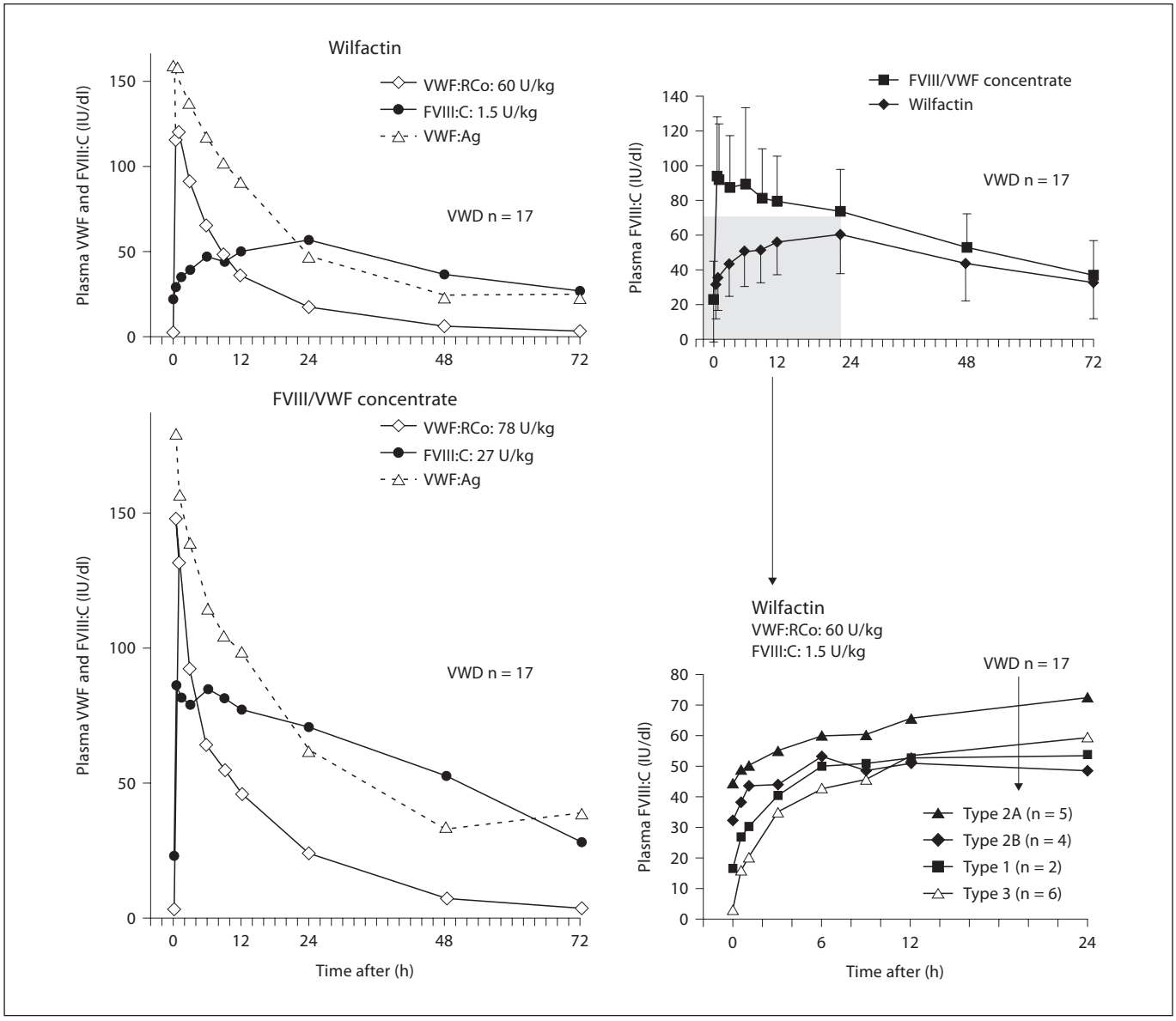
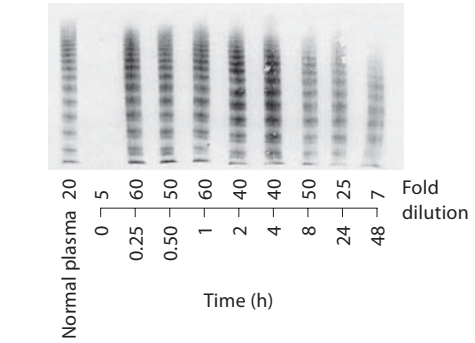
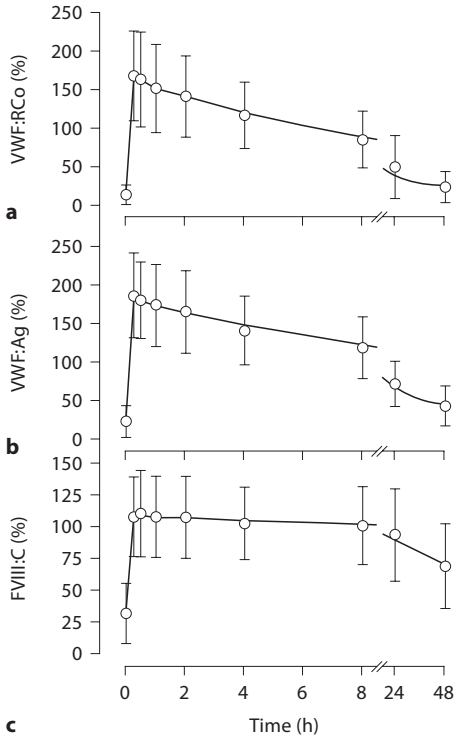


Fig. 4. Direct comparison of the in vivo responses of one loading dose of Wilfactin and VWF-FVIII concentrate (Haemate-P or Innobrand) in 17 patients with VWD: Wilfactin (upper left) and VWF/FVIII concentrate (Haemate-P or Innobrand, lower left) [17]. Direct comparison of FVIII:C response to Wilfactin versus VWF/FVIII (Haemate-P or Innobrand, upper right) and responses of FVIII:C subdivided in VWD type 1, type 2A, type 2B and type 3 [17].

patients) [17]. The administration of Wilfactin or VWF/FVIII concentrate resulted in a transient shortening of Ivy or Simplate BT in 71 and 82% of the patients, respectively. The shortening of BT was maximal 1–3 h after infusion and was lost after 24 h. The measured VWF content of Wilfactin versus Haemate-P/Innobrand as well as the calculated incremental recoveries of VWF:RCo (1.9 vs. 1.9) and VWF:Ag (2.2 vs. 2.2%), and the half-lives of VWF:RCo (11.7 vs. 12.8 h) and VWF:Ag (14.8 vs. 17.8 h, respectively) were bioequivalent in terms of efficacy. This confirms that the PK profile of VWF does not depend on the amount of FVIII in the concentrate or in the VWD type 2 patient. This is true for the comparison of Wilfactin and Haemate-P containing the large VWF multimers



VWF Multimers before and after Haemate-P infusion
Loading dose VWF:RCo 79 IU/kg (FVIII:C 32 IU/kg) in a case of type 3 VWD



In vivo recovery and PK of Haemate-P loading dose,
VWF:RCo 79 IU/kg (FVIII:C 32 IU/kg) in 29 patients with severe VWD

PK	VWF:RCo	VWF:CB	VWF:Ag	FVIII:C
Baseline IU/ml	<0.10	<0.10	0.18	0.36
Peak IU/ml	1.60	1.47	1.90	1.16
After 24 h, IU/ml	0.42	0.26	±1.00	0.92
Recovery, %	1.9	–	2.1	2.4
Half life, h	15.6	–	20.6	>48

Fig. 5. VWF response curves, multimers and PK of Haemate-P after one loading dose in 29 patients with severe VWD: 10 type 1, 10 type 2A, 1 type 2M and 8 type 3 VWD patients [23].

as reflected by the normal VWF:RCo/VWF:Ag ratios. As shown in the French and European VWD studies, the pattern of FVIII:C kinetics was typically very different after infusion of a VWF/FVIII concentrate (Haemate-P or Innobrand) compared to a purified VWF concentrate (Wilfactin; fig. 4). The human VWF/FVIII concentrates Haemate-P (FVIII:C/VWF:RCo ratio 0.34) and Innobrand (FVIII:C/VWF:RCo ratio 0.40) was followed by the predicted incremental recoveries resulting in a two times higher concentration of VWF parameters compared to FVIII:C immediately after the loading dose (fig. 4). In contrast, after infusion of Wilfactin containing a very small amount of FVIII:C (FVIII:C/VWF:RCo ratio <0.04), the maximal FVIII:C levels were progressively attained between 12 and 24 h after infusion, reaching subnormal to low normal levels (fig. 4) [17]. This delayed increase is due to the progressive stabilization of endogenous FVIII by its binding to the purified VWF:Ag in the

Table 3. Efficacy of VWF/FVIII concentrate replacement regarding surgery and major bleeding events

Source	VWF/FVIII concentrate	Patients/surgical procedures	Type of study loading dose VWF:RCo	Outcome
Michiels et al. 2004 [22]	Haemate-P	5/surgery	prospective 60–80 U kg^{-1}	excellent/good 100%
Dobrkovska et al. 1998 [24]	Humate-P	97/surgery	retrospective 80 U kg^{-1}	excellent/good 99%
Lillicrap et al. 2002 [25]	Humate-P	73/bleeding, 344 events surgical procedures	prospective 55/69 U kg^{-1}	excellent/good 99%
Goudemand et al. 2005 [17]	Wilfactin Haemate-P	direct comparison	prospective 60/100 U kg^{-1}	PK study figure 4
Mannucci et al. 2002 [26]	Alphanate	39/71 surgical or invasive procedures	prospective 60 U kg^{-1}	good clinical response thrombosis risk, figure 3
Franchini et al. 2003 [27]	Haemate-P	26/43 procedures	retrospective 35/61 U kg^{-1}	excellent/good 98%
Thompson et al. 2004 [28]	Humate-P	39/42 surgical procedures	prospective 82 U kg^{-1}	excellent/good 100%
Borel-Derlon et al. (2007) [29]	Wilfactin	50/139 non-surgical bleeds	prospective 50/60 U kg^{-1}	excellent/good 88%
Federici et al. (2007) [30]	Haemate-P	56/73 surgical procedures	retrospective	excellent/good 97%
Lethagen et al. (2007) [23]	Haemate-P	29/27 surgical procedures	prospective 62 U kg^{-1}	excellent/good 96.3% PK data figure 5

concentrate infused. Depending on the FVIII:C levels before treatment, type 2A and 2B had significantly higher FVIII:C levels during the first 12 h after infusion of Wilfactin compared to VWD type 3 (fig. 4, lower left). This will predict equal efficacy and safety in the acute and prophylactic treatment of bleeding in VWD type 2 with subnormal or low normal FVIII:C levels. Comparing the FVIII:C levels after infusion of Wilfactin (endogenous FVIII:C) and Haemate-P or Innobrand (exogenous and endogenous FVIII:C), the curves of FVIII:C reached equal levels 24–48 h after infusion, and subsequent decay did not differ until 72 h after infusion (fig. 4) [17]. This has important implications for the treatment of acute bleeding episodes and may also have an impact on the efficacy of long-term prophylaxis of joint bleeds in VWD type 3. The much higher levels of FVIII:C following each infusion lasting 2–3 days with Haemate-P or Innobrand compared to Wilfactin surely will have consequences with regard to dosing of each of the products for the acute and prophylactic treatment of bleeding in severe VWD type 3 and 1 patients.

Using the VWF/FVIII concentrate Wilate, large VWF multimers were absent (fig. 2, right) [19]. The VWF:RCo/FVIII:C ratio in 15 Wilate batches was 0.84 [21] (FVIII/VWF:RCo ratio 1.1) compared to a VWF:RCo/FVIII:C ratio of 2.2 (FVIII/VWF:Ag ratio 0.45) in Haemate-P [22].

Two prospective studies on one of the most used VWF/FVIII concentrates (Haemate-P) showed that preoperative PK assessment in each individual VWD patient was useful to determine the loading dose for minor or major surgery (fig. 5) [22, 23]. In the first small prospective study of Haemate-P used in VWD type 2 patients undergoing elective major surgery, the mean loading dose was 90 IU/kg VWF:RCo. From that PK study, it was concluded that a lower loading dose could be effective and recommendations for both loading dose (60 IU/kg VWF:RCo for major and 40 IU/kg VWF:RCo for minor surgery) and for maintenance dosing were proposed depending on the severity of VWD and the type of surgery. The second prospective study demonstrated for the first time that the initial in vivo recovery of VWF parameters and FVIII:C is constant

over a wide range of doses and that PK determinations can provide a reliable basis for serial dosing decisions. In this prospective study, 29 patients with severe VWD received a loading dose of 79 IU/kg 2 weeks prior to major surgery (fig. 5). From the in vivo recovery and PK in figure 5, a loading dose of 60–65 IU/kg was calculated as appropriate for successful hemostasis in these 29 VWD patients during subsequent elective surgery. On the day of surgery, hemostasis was indeed rated as excellent or good in 96%, being 100% on the first postoperative day [23].

There may be considerable differences in the relative concentration of VWF and FVIII and of the functional activity of VWF in the available VWF/FVIII concentrates (table 3) [18, 19, 21]. The dosing of a concentrate is dependent on the patients' own basal level, and the nature and severity of the bleeding or the procedure. Successful hemostasis will be attained with a median VWF:RCo loading dose of 40–60 IU kg^{-1} in subjects with various types of VWD undergoing minor and major surgery, respectively [14–16, 21–30]. The median in vivo recovery of VWF:RCo was 1.9 IU·dl^{-1}·(IU·kg^{-1}) after the loading dose [15, 20]. Median half-lives of VWF:RCo and VWF:Ag may range from 10 to 25 h. Postoperative mean trough VWF:RCo levels of 60–80 IU dl^{-1} were sufficient to prevent bleeding in several studies.

VWF concentrate administration is usually repeated every 12–24 h postoperatively. A VWF concentrate can also be administered as a continuous infusion. Levels of VWF:RCo and FVIII:C should be monitored when treatment is protracted. During extended substitution with a purified VWF or VWF/FVIII concentrate, monitoring of FVIII:C and VWF parameters is mandatory aiming to keep peak FVIII:C levels in the upper range of normal and VWF:RCo levels just above the lower range of normal (>0.60 IU/ml). Long-lasting FVIII:C levels >1.5–2.0 IU/ml should be avoided due to the risk of thrombosis (fig. 3).

Antifibrinolytic Agents

Tranexamic acid is probably the most widely used antifibrinolytic agent in VWD. More adverse effects hamper the alternative antifibrinoloytic, ε-aminocaproic acid. Tranexamic acid can be used either alone for minor procedures or in combination with DDAVP or a VWF concentrate, when mucous membranes are involved.

Conclusion

Surgical procedures can be safely performed in VWD patients receiving sufficient hemostatic treatment. DDAVP can be used for selected responders. When choosing a VWF concentrate, the relative content of FVIII and VWF, and the functional capacity of VWF must be considered. A PK test may help to tailor the postoperative and maintenance dose of a VWF concentrate.

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