Importance of Pharmacokinetics in the Treatment of von Willebrand Disease

a report by
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von Willebrand disease (vWD) and haemophilia A are the most frequent bleeding disorders in the general population, occurring in 66–100 people per million worldwide.[1] vWD is caused by both qualitative and quantitative defects in von Willebrand factor (vWF) resulting in a dual defect in haemostasis, i.e. the abnormal platelet adhesion due to reduced and/or dysfunctional vWF (primary haemostasis) and the abnormal coagulation due to low levels of factor VIII (FVIII) (secondary haemostasis). vWF serves as a bridge between platelets and subendothelium and is essential for the cohesion of platelets. Thus, vWF has a primary function in the formation of thrombi in blood coagulation. In addition, vWF binds to circulating FVIII and acts as a chaperone, protecting FVIII from proteolytic degradation. In the absence of or after a decrease in vWF, the half-life of FVIII in the circulation is reduced significantly.[2] However, the absence of vWF does not affect FVIII synthesis.

Classification of von Willebrand Disease

Since vWD is caused by both qualitative and quantitative mutations in vWF, the disease is classified according to the degree of qualitative and quantitative involvement (see *Table 1*).[3] Patients with type 1 vWD present with a decrease in the production of vWF and most remain mildly symptomatic. Type 2 vWD is the result of a vWF-dependent platelet function.[4,5] Type 3 vWD is the least common subtype and results from absent or profound reductions in plasma vWF and the absence of vWF in platelets and endothelial cells. In general, type 3 vWD is diagnosed in the first year of life due to severe and sometimes life-threatening bleeds.

Managing von Willebrand Disease

The treatment options for vWD are dependent on the subtype of the disease. The main goal of treatment is to normalise the levels of both vWF and FVIII to achieve haemostasis.[6] Demopressin (DDAVP) is the gold standard for the treatment of type 1 vWD. DDAVP induces the release of endogenous vWF and helps to correct vWF/FVIII levels in the majority of these patients. However, DDAVP is not effective in type 3 vWD or in severe forms of types 1 and 2 vWD. Also, DDAVP is not recommended in patients with type 2A vWD because any increase in vWF is dysfunctional.[7] In patients with type 2B vWD, DDAVP can induce transient thrombocytopenia, thus it is generally contraindicated.[8] In patients in whom DDAVP either is not effective or is contraindicated, the current treatment option of choice is transfusional therapy with virally inactivated plasma-derived FVIII/vWF concentrates. Since the 1980s, plasma-derived FVIII/vWF concentrates have been used successfully to treat types 3 and 2B vWD patients and types 1 and 2 patients who are unresponsive to DDAVP.[9] Currently, recombinant-concentrate-containing vWF is unavailable, and the majority of products are intermediate-purity plasma-derived FVIII concentrates containing vWF. Approved in 1981, Haemate P has become the most widely used concentrate in vWD.[9] Haemate P has demonstrated a good safety record in clinical practice.[10–12]

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The Importance of Pharmacokinetics

The pharmacokinetic profiles of the various concentrates are important considerations in the treatment of vWD. Although they are all considered members of the same drug class, it is important to note that they are not equivalent products for the treatment of vWD. This is because each concentrate possesses a different spectrum of vWF molecular weight multimers and different ratios of vWF ristocetin co-factor/FVIII activity (vWF:RCo/FVIII:c) (see *Table 2*). The vWF:RCo/FVIII:c properties of concentrates have clinical importance since these data contribute to more precise dosing regimens. Although rare, thrombotic complications may arise from repeated administrations of concentrate during vWF replacement therapy, especially in a post-operative setting.[6–13] Due to the different ratios of vWF:RCo/FVIII:c, the various available concentrates sustain FVII levels at different rates.

Although the minimal vWF:RCo level required to maintain sufficient haemostasis in vWD has not yet been determined, current practice is to adjust dosage and timing of FVIII/vWF infusions to maintain an FVIII level between 50 and 150Udl^{-1}, particularly in the post-operative period.[9] If the activity of FVIII within the concentrate is relatively higher than that of vWF, repeated doses may lead to exaggerated FVIII activity due to an accumulative rise in both exogenous and endogenous FVIII. This may be detrimental to the patient due to overdosing. Therefore, a good understanding of the pharmacokinetic profile of the product will help with appropriate dosing and minimise the potential for thrombotic complications during vWD replacement therapy. Conversely, underdosing of either vWF or FVIII during vWD replacement therapy increases the risk of inefficient control of bleeding episodes.[14] Currently, pharmacokinetic and clinical studies on efficacy and safety for new concentrates for vWD are recommended by regulatory agencies in Europe and the US.

Pharmacokinetics of First-generation Factor VIII/ von Willebrand Factor Concentrates

Currently, only a few FVIII/vWF concentrates have been extensively studied in pharmacokinetic trials.[9] The most widely used concentrate in

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Table 1: International Society on Thrombosis and Haemostasis Classification of von Willebrand Disease

Phenotype	Description
Quantitative defects	
Type 1	Partial quantitative deficiency of vWF
Type 3	Virtual complete deficiency of vWF
Qualitative defects	
Type 2A	Decreased vWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight vWF multimers
Type 2B	Increased affinity for platelet glycoprotein Ib
Type 2M	Decreased vWF-dependent platelet adhesion without a selective deficiency of high-molecular-weight vWF multimers
Type 2N	Markedly decreased binding affinity for factor VIII

vWF = von Willebrand factor. Source: adapted from Sadler et al.[3]

Table 2: Selected Plasma-derived Concentrates Containing von Willebrand Factor

Concentrate	vWF:RCo/FVIII:c Ratio
Haemate P	2.5
Alphanate	1.2
Wilate	0.8

vWF = von Willebrand factor; RCo = ristocetin co-factor activity; FVIII = factor VIII.

vWD, Haemate P, has a vWF:RCo/FVIII:c ratio of 2.5. The first Haemate P pharmacokinetic study was conducted in 1998 and involved four patients with type 3 vWD.[11] The median half-life for vWF:RCo was 11.3 hours and 15.2 hours for vWF antigen (vWF:Ag). A high concentration of multimers appeared after transfusion of Haemate P; however, only small levels of vWF protein were present after 48 hours. Retrospective data demonstrated an excellent to good response in 99% of surgical procedures and in 97% of bleeding episodes. A Canadian study was the first to use vWF:RCo to determine the dose of Haemate P to administer during bleeding episodes and surgeries.[12] Excellent to good clinical responses were noted in 99% of surgical procedures, 97% in bleeding episodes, 86% in other cases and 100% in prophylaxis. There were no reports of adverse effects in the study. Similar results have been noted in other pharmacokinetic trials of Haemate P in Italy and the US.[15–17]

The Alphanate Study Group published results reporting an efficacy of 75% for controlling bleeding episodes in type 3 patients and types 1 and 2 patients treated with the concentrate Alphanate who were DDAVP-ineffective.[18] Alphanate has a vWF:RCof/FVIII:c ratio of 1.2. This study was the first to assess the dose and efficacy of Alphanate not only in type 3 vWD but also in types 1 and type 2 vWD patients. A good clinical response was noted in 71% administered on short-term prophylaxis with Alphanate before invasive or surgical procedures. Importantly, the authors reported that the average half-life of FVIII:c – at 23.8 hours in type 3 patients – was almost double that of 12.9 hours for vWF:Ag due to endogenous FVIII:C. Importantly, studies with the first-generation FVIII/vWF concentrates highlighted that the recommended dosages of vWF:RCo should be similar to those of FVIII. This is because *in vivo* recovery of the two haemostatic components is similar.[15–18]

Next-generation Factor VIII/ von Willebrand Factor Concentrates

Recently, a new-generation, high-purity, albumin-free, double-virus inactivated FVIII/vWF concentrate, designed specifically for the treatment of vWD, has been introduced. This new product, Wilate, has the physiological ratio of FVIII to vWF of 0.8 (see *Table 2*). Thus, Wilate has the potential to minimise the risk of thrombogenicity caused by the FVIII 'overshoot' observed with the administration of other vWF/FVIII concentrates. In addition, the FVIII/vWF ratio close to one may simplify the replacement dosing in the post-operative scenario to maintain adequate haemostatic FVIII activity levels in vWD patients.

A prospective multicentre study in 47 vWD patients investigated the pharmacokinetics, clinical efficacy and safety of Wilate in acute bleeding episodes and surgical prophylaxis. In the study, the pharmacokinetics of Wilate was evaluated in 20 vWD patients. The interim analysis found a mean half-life of vWF:RCo in type 3 vWD patients (n=8) of 17.5 hours. Mean recovery for vWF:RCo was 1.5% per IU/kg and 2% per IU/kg for FVIII:c. The efficacy and safety of Wilate was studied in 20 patients undergoing 24 elective or urgent surgical procedures. The overall efficacy (achievement of haemostasis) of Wilate was rated as excellent or good for 23/24 procedures (96%).[19] Currently, controlled clinical trials to evaluate the safety and efficacy of Wilate in major surgeries are ongoing in both vWD and haemophilia A patients.

Conclusion

Recently, there has been considerable progress in the safety and efficacy of transfusional therapies for vWD not responsive to or contraindicated to DDAVP. Furthermore, a growing body of pharmacokinetic data for the various concentrates has helped to improve and refine the use of FVIII/vWF concentrates in vWD replacement therapy. The introduction of a new-generation product with a FVIII/vWF ratio close to one is an important addition to the vWD armamentarium and has the potential to improve the treatment of vWD. A high-purity vWF concentrate with little FVIII content has also become available (Wilfactin), but in type 3 patients a priming dose of FVIII concentrate needs to be co-administered in emergency situations to ensure adequate haemostasis because it can take up to 24 hours for endogenous FVIII synthesis to reach sufficient levels. Continuing scientific and commercial efforts to further elucidate the structure and function of the vWF gene and protein will hopefully help to provide new paradigms and products for the diagnosis and treatment of vWD. ■

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