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# Concentrated von Willebrand factor for treating patients with von Willebrand disease

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A B S T R A C T

For patients with von Willebrand disease, functional levels of circulating von Willebrand factor (VWF) need to be raised to establish hemostasis or prevent excessive or delayed bleeding as immediately prior to and then after invasive procedures. For the common, mild deficiencies, an initial response to DDAVP (desmopressin) is usually sufficient for hemostasis; additional or follow-up dosing may be required, however. For those patients in whom an adequate hemostatic response cannot be achieved with DDAVP, on in whom DDAVP is contraindicated, treatment or supplementation with a plasma-derived concentrate containing VWF is necessary. The functional content of VWF in concentrates varies, however, and optimal dosing in terms of activity and frequency remain to be defined. For perspective, previous clinical usage of cryoprecipitate is compared to recent series with different concentrates. The latter include use to provide hemostasis for acute bleeding episodes or to prevent excessive bleeding from invasive procedures including surgeries.

Key words: von Willebrand factor concentrates; von Willebrand disease; treatment

Von Willebrand disease (VWD) results from deficient activity of von Willebrand factor (VWF). VWF has two major functions in hemostasis, to support platelet-endothelial interactions and to stabilize clotting factor VIII in circulation by direct binding to form a complex. Platelet support is assessed by ristocetin cofactor activity (agglutination of normal platelets) or a collagen binding ELISA. The in vivo correlate is a bleeding time, or, ex-vivo, platelet function analysis on a whole blood specimen.

Several types and subtypes of VWD are known.[1] These are broadly categorized as type 1, with mild to moderate, but comparable deficiency of VWF activity, VWF antigen, and factor VIII; type 2 with disproportionately deficient VWF activity compared to VWF antigen level and (usually) factor VIII clotting activity; or type 3 with severe to undetectable deficiency of VWF activity and antigen, usually with residual factor VIII clotting activities that are 2-4% of the normal average. Many patients with type 1 deficiency are DDAVP responsive. Types 2A and 2B are usually distinguished by different patterns of loss of high molecular weight multimers of VWF, ie. species most active in supporting platelet function; in type 2B there is often increased agglutination to low dose ristocetin (RIPA) as observed in an aggregometer.

Concentrates containing VWF are indicated when DDAVP will not provide sufficient hemostasis for a given bleeding episode or prophylactically as prior to invasive procedures.[1,2] Contraindications to the use of DDAVP include age (antidiuretic effects are too strong if <2 yo), migraine headaches or coronary artery disease, tachyphylaxis on recurrent dosing, thrombocytopenia (especially in type 2B) and unresponsiveness. Patients with type 3 are too low to respond to DDAVP. Although type 1 may be difficult to diagnose,[3] these are generally ones with borderline values. Among 26 patients with more severe type 1 (RCo <10%, VIII:C <20% or bleeding time >15 min), 7 had a good hemostatic response to DDAVP 2 hours post infusion whereas only 1 of 15 with 2A responded.[4] The factor VIII:C elevation was greater than that of RCo in the type 2A subjects, consistent with an elevation of levels that bind factor VIII but are limited in their ability to support platelet function.

It was appreciated that normal plasma contained VWF activity; furthermore, plasma from severe hemophilia A patients also corrected the defect in severe VWD.[5] To achieve hemostatically significant levels, however, concentration and partial purification is required. Cryoprecipitate was developed as a concentrate of factor VIII to treat patients with hemophilia A but it also

contained a 6 to 8-fold concentration of VWF.[6] When care was taken to preserve factor VIII yields in cryoprecipitate, comparable amounts of both factors were recovered.[7] Intermediate purity, plasma-derived commercial concentrates of factor VIII contain variable amounts of VWF:Ag. The presence of at least some high molecular weight multimers that are able to sustain the functional platelet defect in VWD, however, varies.[8]

### *Concentrates with VWF activity*

It has been apparent that infusion of either normal plasma or a concentrated preparation of factor VIII and VWF that the VWF survives considerably longer in severely affected (type 3) VWD patients than does the factor VIII in patients with severe hemophilia A.[5] It was also recognized that concentrates only transiently corrected the platelet defect whereas a prolonged response was seen with factor VIII. Cryoprecipitate provided a readily prepared concentrated preparation of factor VIII and VWF.[6,7] An example of the response to infused cryoprecipitate in severe, type 3, VWD is shown in Figure 1. The Ivy template bleeding time was transiently decreased during the first 4 hours post infusion; in contrast, even after 25 hours, factor VIII clotting activity remained at a hemostatic level. This is due to the loss of the highest molecular weight multimers that are necessary to sustain platelet-subendothelial binding whereas even low molecular weight multimers have a high capacity to bind endogenous factor VIII, stabilizing it in circulation. Bleeding time correction after *wet* cryoprecipitate was also partial in 5 type 3 patients despite a correction of the RCo activity up to the low-normal range and the appearance of high molecular weight multimers for 3 hours post infusion.[8]

The majority of concentrates used to treat patients with VWD were prepared from pooled normal plasma as intermediate purity preparations of factor VIII. The amounts of VWF antigen vary and are negligible in the higher purity preparations of factor VIII such as those purified using insolubilized monoclonal antibodies. Intermediate purity factor VIII concentrates have a wide variation of the relative amounts of factor VIII clotting activity and VWF antigen.[9] Within intermediate purity factor VIII concentrates, VWF multimer patterns all lack the very high molecular weight species seen in plasma; however, some do show high molecular weight multimers. For example, Lethagan *et al.*[9] found that high molecular weight multimers were largely absent in lots of Immunate, Koate and 8Y and that in each of these, there was an excess of VWF antigen over VWF activity. High molecular weight multimers were better preserved in Humate-P, Innobrand and the French VHP vWF (Facteur Willebrand). The

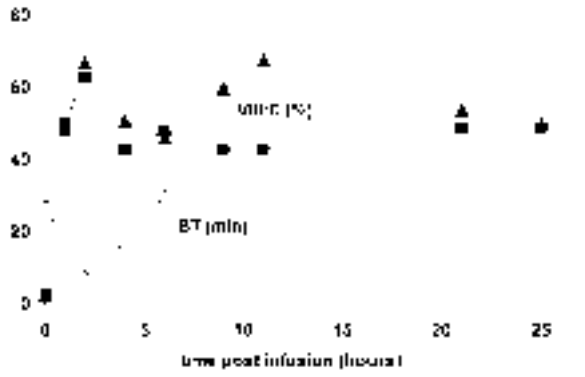


**Figure 1. Response of two type 3 VWD subjects to cryoprecipitate. BT is for ivy-template bleeding time in min with maximal value of 30 (open symbols, followed for 6 hours post infusion); VIII:C is for factor VIII clotting activity by one-stage assay (filled symbols, followed for 25 hours). Individual subjects are represented by squares or triangles, respectively; each received ~20 factor VIII units per kg infused over 20 min. Zero time point represents baseline values with no cryoprecipitate for at least 2 weeks prior to the study.**

ratio of factor VIII clotting activity to functional VWF by either ristocetin cofactor or collagen binding assays was 1:4. 1:2 and 1:50, respectively for the latter 3. In general, those with low VWF activity to antigen have the majority of antigen in lower molecular weight multimers that are ineffective in supporting platelet function. Other concentrates shown to have VWF activity when infused into deficient subjects are Alphanate,[10] which has more factor VIII than VWF activity, and Fanhdi.[11] Another concentrate, Wiloctin, appears effective in clinical trials in Europe.[12]

### *Treatment of bleeding episodes or prophylactically for invasive procedures*

Concentrates containing VWF are indicated for patients unresponsive to DDAVP[4] or in whom the hormone is contraindicated or insufficient for the degree of hemostatic challenge.[1,2,13] Although there is general agreement on when these concentrates should be used, recommended doses, frequency of infusions and duration of coverage vary considerably. The types of VWD and of hemostatic challenges as well as properties of the concentrate used are all important variables to consider. Even when these are taken into account, it often remains unclear how much of a given concentrate it will take to achieve or maintain hemostasis.

Although dosing and frequency of concentrate use in VWD patients varies considerably, there are general guidelines. In recent years, attention has been paid to the actual dose in RCo units rather than that in factor VIII clotting activity because the ratio's are quite different in different products. Although initial doses between

**Table 1. Von Willebrand factor concentrates for bleeding episodes or invasive procedures in von Willebrand disease.**

| *Concentrate* | *N. subjects* | *N courses* | *Median dose (range)* | *N Rx (range)* | *% response* | *Reference* |
|---|---|---|---|---|---|---|
| **A. bleeding** | | | | | | |
| VHP vWF | 13 (4) | 14 | 47 RCo U/kg (±12) | 7 (1-19) | 100 | 14 |
| Humate-P† | 97 (28)* | 344 | 55 RCo U/kg (17-228) | 1 (1-21) days | 97 | 16 |
| Humate-P† | 33 | 53(27) | 67 RCo U/kg (26-143) | 2 (1-34) | 98 | 18 |
| Alphanate | 14 | 87 | 47 RCo U/kg (14-79) | 1 (1-7) | 100 | 10 |
| Fanhdi | 10 (4)* | 11 | 38 RCo U/kg (22-88) | 1 (1-26) | 92 | 11 |
| **B. surgery** | | | | | | |
| VHP vWF | 75 (4)* | 84 | 53 RCo U/kg (±10) | (1-16) | 100 | 14 |
| Humate-P† | 97 (28)* | 73 | 69 RCo U/kg (12-223) | 2(1-20) days | 99 | 16 |
| Humate-P† | 26 (0) | 43 | 32 RCo U/kg (21-53)+ | 6 (1-23)+ | 100 | 17 |
| Humate-P† | 39 (8) | 42 | 82 RCo U/kg (33-217) | 6 (1-67) | 100 | 19 |
| Alphanate | 39 (32*) | 71 | 60 RCo U/kg (20-76) | 3 (1-18) | 100 | 10 |
| Fanhdi | 13 (2) | 14 | 66 RCo U/kg (38-157) | 4 (1-11) | 93 | 11 |

*N: number (subjects were variably distributed among types; number with type 3 VWD is in parentheses; courses are numbers of bleeding episodes or invasive procedures treated). Bleeding (A) is for bleeding episodes requiring concentrate therapy; dose is median for initial dose (RCo U/kg as provided or as calculated from factor VIII units using the average ratio for lots of Fanhdi); Rx is for median number and range of treatment doses per course; % response is as "excellent" or "good" (clinically). Surgery includes variable numbers of major or minor operative or otherwise invasive procedures treated prophylactically. References are indicated as either retrospective (r) or prospective (p) studies. *Number of subjects studied did not distinguished between bleeding episodes and surgeries (may overlap). † Humate-P is labeled as Haemate-P in Europe. +Dosing reported as mean daily dose and/or mean days of treatment.*

40 to 60 RCo U/kg are specified for different clinical situations[1,2,13] it is clear from the clinical trial results that there is a broad range used clinically, even within a given center. Recent series with specific concentrates are discussed below and summarized in Table 1.

A concentrated VWF preparation from solvent-detergent treated plasma is the only one designed to optimize the recovery of VWF, as opposed to factor VIII.[14] A retrospective series from 1989 to1997 in France included its use in 99 patients with VWD, with nearly half having type 1 and only 4 having type 3.[14] Within this cohort, there were 15 treatments of acute bleeding episodes and 84 courses for surgical or invasive procedures. As there is little factor VIII in the preparation, an initial dose of a factor VIII concentrate was administered with the VWF concentrate in the more severe patients except for elective surgeries where administration of VWF could begin several hours prior to the procedure. The latter allowed the patient's own factor VIII to increase to hemostatic levels by the time of surgery as it was stabilized by binding to the infused VWF. Doses averaged 50 RCo U/kg and hemostasis was essentially normal, even in orthopedic and other major surgeries.

Humate-P or Haemate-P, as it is called in North America or Europe, respectively, has been used to treat VWD patients for several years with several small series published.[15] This concentrate was originally developed for use in hemophilia A but more recently it has been labeled with its activity based upon the RCo units. In Canada, retrospective data on 97 patients with VWD and treated with Humate-P between 1991 and 1996 were published.[16] Of 344 bleeding episodes, the median dose was 55 RCo units/kg (Table 1A) whereas the median initial dose for 73 surgeries or invasive procedures was 69 RCo units/kg (Table 1B). Although response were very good or excellent in nearly all treatment courses, the range of doses used was quite large, even when accounting for the type or severity of VWD. In another recent retrospective series, 26 patients with either type 1 or type 2B were supported through 43 surgical, invasive or diagnostic procedures (Table 1B).[17] As only 3 centers were involved and none of the patients had type 3, there was a narrower range of dosing. For example, the mean initial dose for 14 major surgical procedures was 61 RCo units/kg and the range was 48-81; for 11 dental extractions, it was 35 RCo units/kg and the range was 21-46.

In a recent prospective series, 53 bleeding episodes in 33 VWD subjects were treated with Humate-P.[18] The mean dose was 67 RCo units/kg (Table 1A) and again nearly all responses were rated as excellent or good. In a prospective use of Humate for 39 surgeries or invasive procedures in 36 subjects, the median initial dose was 82 RCo units/kg (Table 1B) and all responded well. As treating physicians in both of these trials were only given general guidelines on dosing, and there was heterogeneity of severity of VWD and the degree of trauma, doses varied widely. In the series of bleeding episodes, 27 of the 53 episodes occurred in the 12 subjects with type 3 VWD.[18] In the surgical

study,[19] in addition to heterogeneity of procedures, 9 of the evaluable procedures were in 7 subjects with type 3. The wide range of initial and follow-up dosing (Table 1B), however, largely reflects the variability in the interpretation of the general dosing guidelines among the 28 participating centers, and the degree of hemostatic challenge was better correlated with dose than was the severity by VWD type.

Post-infusion recoveries of RCo activity were determined in 8 subjects participating in the bleeding episode study[18] and in 15 (8 prior to the procedure and the other 7 following the initial treatment dose) in the prospective surgical series.[19] In those 7 following an initial pre-operative therapeutic dose, for example, the mean rise in RCo was from 25 to 183% of normal, primarily varying by dose;[19] the mean increment within the first hour from the 8 in the bleeding episode study was from 18 to 130% RCo activity. The duration of therapy varied with 6 procedures (including a cardiac catheterization, colonoscopy, skin biopsy, amniocentesis, root canal and tooth extraction) managed with a single pre-procedure dose. Of the other 33 procedures, 4 had prolonged treatment. These were: an open synovectomy in a type 3 subject treated daily for 2 weeks then every-other day for 4 more doses, a type 3 patient with incision and drainage of a retroperitoneal abscess who received 32 daily doses until the wound cavity had healed, a type 3 subject given 4 doses over 2 days for placement of a central venous access device and then treatment every two to three days for 13 more doses, and a type 1 subject who post radical mastectomy received daily dosing for 9 days then 3 more doses 1 to 2 weeks apart.

In a prospective series with Alphanate, 81 subjects with VWD were treated in 27 centers between 1993 and 1998; 32 had type 3 VWD.[10] The concentrate was prepared from solvent-detergent treated plasma and this formulation was compared to one with an added dry heat step of the lyophilized material. In cross-over pharmacokinetic studies in 11 selected type 3 patients (in all, 24 of the type 3 subjects participated in pharmacokinetic studies and not in treatment or prevention of bleeding), there were no significant differences from the addition of the heat treatment. The lots averaged 1.6-fold more factor VIII clotting activity than RCo (VWF) activity. In all, 14 subjects were treated for 87 bleeding episodes including 16 in 4 subjects with type 3. For bleeding episodes, the initial doses were lower for gastrointestinal or naso-pharyngeal mucosal episodes (that included the majority of episodes in type 2A subjects); over three quarters of these 76 episodes responded to a single treatment. The 8 musculoskeletal (predominantly in type 3 subjects) or 3 gynecologic bleeding episodes had a median of 3 daily doses required to stop bleeding; these latter 11 also were treated with a higher median initial dose, 55-60 RCo U/kg compared to 40 for the mucosal sites. Of 39 subjects treated to prevent bleeding from 71 surgical or other invasive procedures, 14 had type 3. Over three quarters of these invasive procedures were minor and the overall median number of treatments was 3 with a range from 1 to 18.The median dose prior to the procedure was 60 RCo U/kg and median follow-up dose 40 U/kg. Again, there was considerable variability, however (Table 1). Antifibrinolytic therapy as an adjunct was used in 8, mostly among the 22 dental procedures (16 of which were extractions of one or more teeth).

In a retrospective series, 22 patients (6 with type 3) were given a purified concentrate, Fanhdi, from 1999-2001; this concentrate averaged 1.6-fold more VWF/RCo activity than factor VIII clotting activity.[11] It was prepared from solvent-detergent treated plasma and the lyophilized concentrate was heat treated. Of 11 bleeding episodes treated in 10 patients, 6 were in type 3 patients and half of those were the 3 hemarthroses that were treated. Doses were reported in factor VIII units and ranged from 14 to 38 U/kg for the 6 episodes that responded to a single dose; one muscle hematoma and one episode of gastrointestinal bleeding required prolonged therapy, the latter was in a type 3 patient and was the only one rated as a poor response. Of 14 invasive procedures in 13 patients, 7 were major, 4 minor and 2 others were dental extractions. All but one of the latter had good to excellent responses.

Other concentrates have been used to manage bleeding in VWD, including 8Y,[20] Koate[21] and Immunate,[22] but each of these have an excess of VWF antigen to activity and on multimer analysis are more deficient than those in Table 2 in terms of high molecular weight species.[9] Thus higher doses appear to be required to promote hemostasis in VWD patients. Post-operative experience with continuous infusion suggests that VWF in several of the preparations is stable and can also provide hemostasis,[22-25] although current licensures have only approved intermittent bolus infusions and clinical situations where continuous infusion may improve hemostasis remain to be identified.

### *Unresolved issues in VWF concentrate use*

There are clinical situations, especially in patients with *responsive* type 1 or 2A VWD where it is unclear if DDAVP will suffice.

In general, if both the risk of bleeding and the consequences of prolonged oozing or delayed wound healing are low, there are situations where DDAVP can be tried, having a treatment plan in place to infuse concentrate if needed. Post-operatively, repeated dosing

with DDAVP can lead to tachyphylaxis, especially when doses are more frequent than every 24-48 hours. In some less severe patients that are at least marginally DDAVP responsive, post operative hemostasis can be managed with alternating concentrate and DDAVP although there are no clear guidelines as to the optimal frequency of dosing.

It is unclear to what extent the post-infusion assessment of platelet function correlates with a hemostatic outcome. One might think that more prolonged restoration of platelet function would be required for mucosal bleeding whereas normal factor VIII clotting activities would suffice after primary hemostasis has been achieved. Hemostasis can be achieved even if the bleeding time is only transiently or partially corrected.[1,8] RCo activity remains normalized longer although its use to monitor response is cumbersome and the clinical correlates post infusion of this diagnostic test remain unclear. The adjunctive use of antifibrinolytic therapy in mucosal bleeding is advocated by many but following tooth extractions, for example, it may not be as necessary as in hemophilia where the therapeutic factor VIII response is shorter.

For the concentrate of purified VWF that contains little factor VIII, when and how much initial factor VIII should be infused? If the more severely affected VWD patients with low factor VIII activity increase their endogenous circulating levels after a few hours, when are levels sufficient for normal hemostasis? The recommended trigger for infusing an initial dose of factor VIII of having a baseline factor VIII activity under 30%[16] appears prudent but a lower trigger may still allow normal initial hemostasis, especially with correction of the platelet defect.

It is unclear what dosing levels and frequency of infusions are necessary, especially with major bleeding or surgery. Clearly the hemophilia model of every 12 hours for 10 to 14 days would result in gross overtreatment for even those patients with type 3 VWD. An interesting approach to dosing comes from a study of 5 subjects with type 2 VWD who underwent surgery.[26] Pharmacokinetic measurements indicated that doses of 60 to 80 RCo U/kg would have been sufficient to achieve normal VWF activities whereas the initial doses of 88-110 that were used were unnecessarily high; follow-up doses could also have been lower. The minimum levels for hemostasis are not known and will vary with the hemostatic challenge, the type of VWD, the particular concentrate, and individual variations in recovery and half-lives. It is worthwhile to design studies, especially in patients with type 3 VWD to attempt to isolate the effects of these variables to provide more useful data upon which to base decisions on the doses of concentrates and the frequency infusions.

It is also unresolved if an acute elevation of factor VIII increases the risk of venous thrombosis. Clearly a constitutional elevation increases the risk 4 to 5-fold.[27] One subject in the Alphanate trial did develop deep venous thrombosis after 12 days of being treated when his factor VIII had risen to over 200%.[11] Thus elevation of factor VIII must be considered a potential risk[1] albeit one that may interact with a post-operative risk in a patient whose hemostatic mechanism has been normalized. In this regard, the ratio of factor VIII to functional VWF may be a consideration, especially in older individuals.

Recombinant VWF has been prepared and studied in severely deficient VWD dogs.[28,29] Higher molecular weight multimers were observed post infusion and hemostasis was achieved in episodes of epistaxis, for example. Prior to developing this preparation for potential clinical use, however, the expression will have to be optimized and its *specific activity* or the relative amount of functional versus total antigenic VWF improved.

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