[haematologica reports]
2005;1(4):21-24

Desmopressin in von Willebrand disease: limits of hemostatic effect in different subtypes. Antidiuretic effect of hemostatic dosage

STEFAN LETHAGEN

From the Department for Coagulation Disorders Malmö University Hospital Sweden

Correpondence: Stefan Lethagen, MD, PhD, Associate Professor, Department for Coagulation Disorders, Malmö University Hospital, SE-205 02 Malmö, Sweden. E-mail: stefan.lethagen@medforsk.mas.lu.se

A B S T R A C T

Desmopressin is an important hemostatic agent for patients with von Willebrand disease. It stimulates endogenous hemostasis by releasing von Willebrand factor (VWF) and coagulation factor VIII (FVIII) from storage sites. Most patients with the most prevalent subtype, type 1, respond well with sufficient increases of factor levels and shortening of the bleeding time. The post desmopressin levels of VWF and FVIII are dependent on the basal levels, and may be insufficient if basal levels are very low. In patients with type 2 VWD, desmopressin is usually not effective as the VWF is functionally defective. A recent European multicenter study investigated the effect of desmopressin in patients with severe type 1 and 2 and showed that only a minority of patients with VWF activity < 0.10 kIU/L or FVIII activity < 0.20 kIU/L or bleeding time >15 minutes responded sufficiently. Therefore it is important to test the effect of desmopressin in such patients before clinical use. Desmopressin is also a potent antidiuretic. There is a concern for side effects as it is used in 10-20 times higher doses than those used for antidiuretic purposes. Despite the larger doses, the magnitude of the antidiuretic effect is the same, indicating that this effect reaches a plateau already at low dosage levels. The duration of the antidiuretic effect after single hemostatic doses is about 24 hours. If treatment is prolonged with repeated doses, factor levels as well as serum sodium should be monitored and fluid intake restricted.

Key words: Willebrand, desmopressin , FVIII, antidiuretic effect

There are two main treatment options for normalization of hemostasis in patients with von Willebrand disease (VWD), either substitution with plasma-derived factor VIII/von Willebrand factor (FVIII/VWF) concentrates or treatment with desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]). This manuscript reviews three factors that may limit the use of desmopressin in patients with VWD: firstly the phenotype or genotype of the patients, secondly the risk of tachyphylaxis and thirdly the potential risk of side effects due to desmopressin's antidiuretic effect.

Desmopressin was first synthesized as an analogue of the native hormone vasopressin.[1] It was initially used for the treatment of diabetes insipidus. In the mid-1970s the first reports were published that desmopressin stimulated endogenous hemostasis.[2,3] Desmopressin has been used since then for treatment of bleedings and in connection with invasive procedures in patients with VWD, and also in those with mild hemophilia A or congenital or acquired platelet dysfunction. The hemostatic effects of desmopressin are well known. It increases plasma concentrations of coagulation factor VIII (FVIII) and von Willebrand factor (VWF) 2-6-fold through endogenous release. The drug is an attractive therapeutic alternative, as it carries no risk of transmission of infectious diseases.[4]

Phenotypic and genotypic aspects

In VWD, the best effect has been seen in patients with type 1, as this subtype is caused by a quantitative deficiency of a normally functioning VWF. Desmopressin will therefore temporarily normalize hemostasis in most patients with type 1. The effect may be limited though in patients with very low levels of VWF and FVIII, as the achieved levels of VWF and FVIII after desmopressin may be insufficient. In patients with type 2 variants, the VWF is dysfunctional. Therefore, one would not

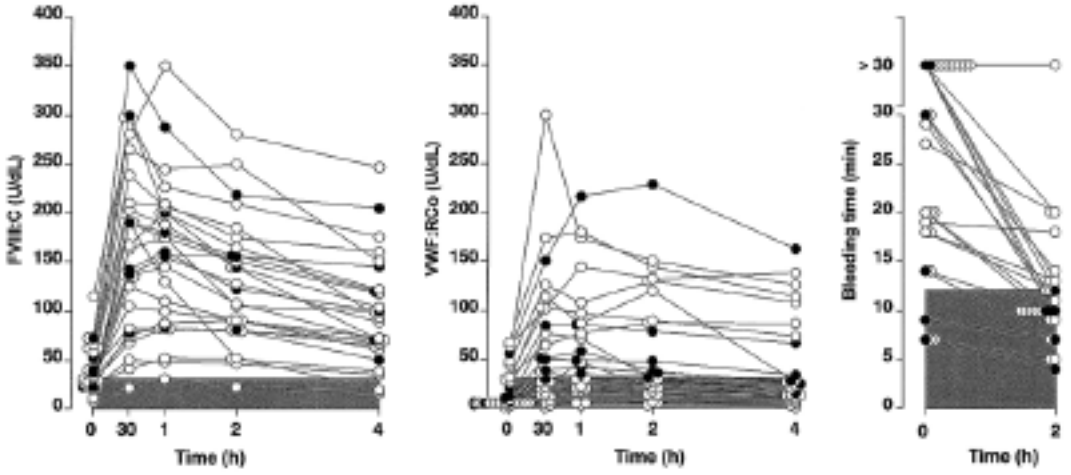

Figure 1. Biologic responses to desmopressin in 26 patients with type 1 VWD. Changes of FVIII:C (U/dL), VWF:RCo (U/dL) and bleeding time (BT). Limits of FVIII:C, VWF:RCo, and BT. Criteria used in this study to define responsiveness are shown by the zone indicated in gray. Patients responsive (filled circles) and unresponsive (open circles) to desmopressin.[5] This research was originally published in Blood. *©2004. the American Society of Hematology.*

expect desmopressin to have a significant hemostatic effect, as the VWF that is released by desmopressin is also dysfunctional. In type 2B, desmopressin may even be contraindicated, as the released abnormal VWF will induce a temporary thrombocytopenia due to platelet aggregation caused by the abnormal VWF. These limitations to the clinical usefulness of desmopressin in patients with VWD are well known to most clinicians with experience in VWD, but it has not been evaluated systematically before.

In a recently published European multicenter study, desmopressin was tested in patients with severe type 1 or type 2 VWD.[5] The study provided an opportunity to test the limits of clinical efficacy of the drug in relation to severity of VWD. The study tried to establish whether there is a relationship between responsiveness, phenotype, and genotype. Severe VWD type 1 and 2 was defined as a lifelong history of bleeding (including at least 2 episodes severe enough to require replacement therapy) and at least one of the following laboratory abnormalities according to the records kept at each center: bleeding time (BT) longer than 15 minutes, ristocetin cofactor activity (VWF:RCo) less than 0.10 kIU/L, and factor VIII coagulant activity (FVIII:C) less than 0.20 kIU/L.

Before the study, responsive patients were defined as those who, 2 hours after infusion of 0.3 Ìg/kg DDAVP, had increased baseline values of VWF:RCo and FVIII:C by at least 3-fold and achieved levels of at least 0.30 kIU/L for both and a BT of 12 minutes or less.

With these strict criteria only 7 of 26 (27%) patients with type 1 (Figure 1) met the criteria for responsiveness to desmopressin. This response rate is much lower than what we are used to see from the clinical routine when we treat patients from the whole population of type 1 cases which mainly consists of patients with a milder phenotype. The low response rate seen in the study is a result of the strict criteria used both for inclusion and for the definition of responsiveness. The threshold levels of both measurements had to be attained for both FVIII and VWF, which was not the case in 19/27 patients. The VWF:RCo/Ag ratio seemed to separate responders from non-responders, as a larger proportion of patients with a VWF:RCo/Ag >0.6 responded. On the other hand, a ratio <0.6 implies that the VWF is dysfunctional and that these patients may have type 2 variants and therefore rarely respond to desmopressin.

The result emphasizes that a proportion of patients with severe type 1 do not respond sufficiently to desmopressin. It is therefore important to perform a test with desmopressin in VWD patients, at least in patients that do not have the mildest phenotype with VWF levels close to normal.

In type 2 (all subtypes except 2B) 7 patients of 40 (18%) met the criteria for responsiveness to desmopressin. The low response rate in type 2 patients is less surprising, as the VWF by definition is functionally defective. Even if desmopressin release VWF, the factor is still defective and will usually not improve hemostasis sufficiently. Interestingly, patients with type 2A mutations causing increased proteolysis of the VWF (R1597W and G1629R) had a transient release of normal VWF multimers and a short lasting improvement of the VWF:RCo, whereas those with mutations causing defective intracellular transport and assembly of VWF (S1506L and V1665E) had few improvements in the multimeric structure and only a small increase of

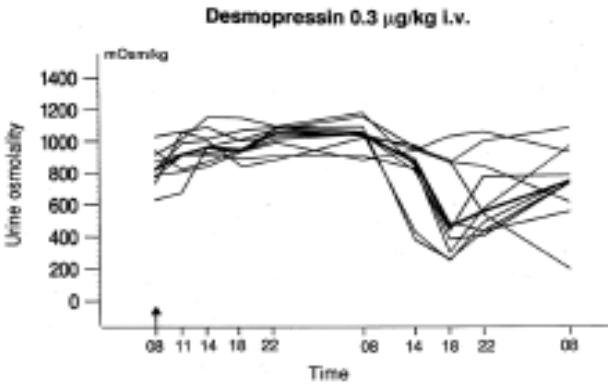

Figure 2. Urine osmolality (mOsm/kg) in ten healthy volunteersafter a single dose of desmopressin 0.3 µg/kg intravenously. Thick line represents median values.[8] This research was originally published in Am J Hematol. ©*1998 Wiley-Liss, Inc.*

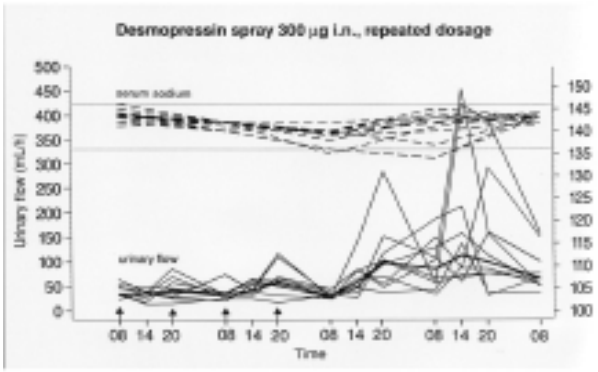

Figure 3. Urinary flow (mL/h) and serum sodium (mmol/L) in ten healthy volunteers after four intranasal spray doses of 300 µg desmopressin with 12-h intervals. The horizontal lines indicate the upper and lower limits of the normal reference range of serum sodium.[8] This research was originally published in Am J Hematol. ©*1998 Wiley-Liss, Inc.*

VWF:RCo. Most patients with type 2M VWD were poorly responsive to desmopressin. Three of 4 patients with type 2N responded sufficiently, with 6.7-8.8-fold increases of FVIII. All 3 responders shared the same mutation (R854Q), whereas the fourth patient with a null mutation and a mutation associated with a complete absence of FVIII binding, was unresponsive (C1060R). This study showed that the response rate to desmopressin is limited in patients with a relatively severe type 1 phenotype, and much lower than what has been shown in earlier studies in which also patients with milder phenotypes were included. As expected, the response rates were low in type 2A and 2M. In type 2A and 2N, the response rate was dependent on the type of mutation. The results underline the importance of giving a test dose of desmopressin to patients with VWD to ensure that the response is sufficient, before the patients are treated in connection with bleedings or surgery.

Tachyphylaxis

Decreased responsiveness after repeated administration of desmopressin at short intervals (tachyphylaxis) has been reported in some patients. The response to the second dose is usually approximately 30% less than that to the first, with an individual variation. After the second dose, the responsiveness is generally not reduced further.[6] In cases when prolonged desmopressin treatment is given, tachyphylaxis is seldom a problem, though in cases in which there is a borderline response it is recommended that treatment be closely monitored.

Antidiuretic effect

Desmopressin has been used for many years for its antidiuretic properties, e.g., in patients with diabetes insipidus or nocturnal enuresis or for diagnostic purposes in dosages of 2–8 µg parenterally or 20–80 µg intranasally.[8] In order to achieve hemostatic effects, 10–20 times higher dosages are used than those given for antidiuretic indications, which causes concern for the potential risk of water retention and fluid overload. The magnitude and duration of the antidiuretic effect of desmopressin in high dosage intravenously (i.v.) (0.3 µg/kg) or intranasally (i.n.) (300 µg) has been studied in healthy volunteers.[8] In this study the urine osmolality increased to peak levels of about 1,060–1,090 mOsmol/kg (Figure 2), which is only slightly higher than the urine osmolality of about 950 mOsmol/kg seen after the antidiuretic dosages of 2–8 µg s.c. or 20–80 vg i.n.. The magnitude of the antidiuretic effect measured as change in urine osmolality, therefore seems to plateau already at low dosage indicating that higher dosage does not give a higher maximal antidiuretic effect. The duration of the antidiuretic effect, on the other hand, was 24 hours after single hemostatic dosages, as compared to 12 hours after the antidiuretic dosages. Single doses of desmopressin can safely be given only with a modest limitation of water intake. When repeated doses are given, fluid intake should be more restricted. It is wise to monitor serum sodium, if treatment is prolonged over a longer period (Figure 3).

Summary

Desmopressin is an important treatment alternative for patients with VWD. Most patients with type 1 respond well, but amongst those with low pre-treatment levels, e.g. VWF activity < 0.10 kIU/L, FVIII activity < 0.20 kIU/L or bleeding time >15 minutes, only few patients will respond. Therefore it is important to test the effect of desmopressin in such patients, in order to ensure that the hemostatic effect is sufficient. Also in patients with type 2A and 2M, only a minority will respond. In type 2A, the response seems to be dependent on the type of mutation. In type 2B, desmopressin is often contraindicated because it may cause thrombocytopenia.

Patients with type 2N, often have a good increase of FVIII, but the FVIII half-life may be short due to defective binding to VWF. Patients with type 3 do not respond as they lack VWF.

There may be a tendency to decreased FVIII and VWF response with repeated doses of desmopressin (tachyphylaxis) but this is generally not an important clinical problem. If repeated doses are given over a longer period, however, FVIII and VWF levels should be monitored, especially in patients that only have a borderline response after the first dose. Although desmopressin is a strong antidiuretic, hyponatremia and fluid overload are seldom seen. Fluid intake should, however, be restricted, especially if treatment is prolonged.

References

1. Zaoral M, Kolc J, Sorm F. Amino acids and peptides. LXXI. Synthesis of 1-deamino-8-D-amino-butyrine vasopressin, 1-deamino-8-D-lysine vasopressin and 1-deamino-8-D-arginine vasopressin. Collection Czechoslov. Chem Commun 1967; 32:1250-7.
2. Cash JD, Gader AMA, Da Costa J. The release of plasminogen activator and factor VIII by LVP, AVP, DDAVP, AT III and OT in man. Br J Haematol 1974; 27:363 -4.
3. Mannucci PM, Åberg M, Nilsson IM, Robertsson B. Mechanism of plasminogen activator and factor VIII increase after vasoactive drugs. Br J Haematol 1975; 30: 81-93.
4. Mannucci PM. Desmopressin (DDAVP) in the Treatment of Bleeding Disorders: The First 20 Years. Blood 1997;90:2515-21.
5. Federici AB, Mazurier C, Berntorp E, Lee CA, Scharrer I, Goudemand J, Lethagen S, Nitu I, Ludwig G, Hilbert L, Mannucci PM. Biologic response to desmopressin in patients with severe type 1 and type 2 vonWillebrand disease: results of a multicenter European study. Blood 2004; 103: 2032-8.
6. Mannucci PM, Bettega D, Cattaneo M. The development of tachyfylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP). Br J Haematol 1992; 82:87-93.
7. Tryding N, Sterner G, Berg B, Harris A, Lundin S. Subcutaneous and intranasal administration of 1-deamino-8-d-arginine vasopressin in the assessment of renal concentration capacity. Nephron 1987; 45:27–30,
8. Lethagen S, Frick K, Sterner G. Antidiuretic effect of desmopressin given in hemostatic dosages to healthy volunteers. Am J Hematol 1998; 57:153-9.