TREATMENT OF HEMOPHILIA

November 2012 · No. 11

DESMOPRESSIN (DDAVP) IN THE TREATMENT OF BLEEDING DISORDERS

Revised edition

Pier Mannuccio Mannucci
Angelo Bianchi Bonomi Hemophilia
and Thrombosis Center
IRCCS Cà Granda Maggiore
Policlinico Foundation
Milan, Italy

WFH 50 YEARS OF ADVANCING TREATMENT FOR ALL

WORLD FEDERATION OF HEMOPHILIA
Fédération mondiale de l'hémophilie
Federación Mundial de Hemofilia

Table of Contents

This document was originally published by *Blood*, Vol. 90, No. 7, 1997 and is reprinted with their permission; revised 2012.

This publication is accessible from the World Federation of Hemophilia's web site at www.wfh.org. Additional copies are also available from the WFH at:

World Federation of Hemophilia
1425, boul. René-Lévesque O. Bureau 1010
Montréal, Québec H3G 1T7 Canada
Tel. : (514) 875-7944
Fax : (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

Treatment of Hemophilia Series Editor:
Dr. Johnny Mahlangu

DESMOPRESSIN (DDAVP) IN THE TREATMENT OF BLEEDING DISORDERS

Revised edition

Introduction

In 1977 desmopressin (1-deamino-8-D-arginine vasopressin, abbreviated DDAVP), a synthetic derivative of the antidiuretic hormone, was used for the first time to treat patients with hemophilia A and von Willebrand disease (VWD), the most frequent congenital bleeding disorders [1]. After the original clinical study performed in Italy, desmopressin was used in many other countries and the World Health Organization included it in the list of essential drugs. A drug that could raise plasma levels of factor VIII and von Willebrand factor (VWF) without the need of blood products was especially attractive in the late 1970s and early 1980s, a time when the human immunodeficiency virus (HIV) began to be transmitted by infected coagulation factor concentrates to patients with congenital coagulation disorders.

The potential clinical indications for desmopressin quickly expanded beyond hemophilia and VWD. The compound was claimed to be efficacious in bleeding disorders not involving a deficiency or dysfunction of factor VIII or VWF, including congenital and acquired defects of platelet function and such frequent abnormalities of hemostasis as those associated with chronic kidney and liver disease. Desmopressin has also been used prophylactically in patients undergoing surgical procedures characterized by significant blood loss and transfusion requirements, especially cardiac and orthopedic surgery.

Thirty-five years of clinical experience have now established more firmly the clinical indications of desmopressin. Some of these indications have been strengthened by the experience accumulated, while others have not been supported by rigorous clinical trials or have been overcome by the advent of more efficacious treatments. This report reviews the spectrum of indications in bleeding disorders, in an attempt to establish which indications remain valid and which do not. The pharmacokinetics, pharmacodynamics, and side effects of desmopressin have been dealt with in previous reviews [2-4].

Historical background

In 1772, William Hewson noticed that blood collected under conditions of stress clotted rapidly [5]. Hewson's observations, described in detail in *An Inquiry into the Properties of the Blood,* triggered a series of animal experiments performed by the physiologist Cannon and his associates at the beginning of the 20th century. They showed that the enhancement of blood clotting associated with stress was caused by the liberation of adrenaline in plasma [6,7]. In 1957, a mechanism for faster clotting after adrenaline was provided by Marciniak [8], who found a transient increase in coagulation factor VIII after injection in rabbits. Reports of raised factor VIII after adrenaline infusion in humans soon followed: the average increase was to about twice the starting level, with no measurable change in other coagulation factors [9]. In patients with mild hemophilia, the magnitude of factor VIII increase induced by adrenaline was similar to that elicited in healthy individuals [9,10]. These findings stimulated further research, with the goal of identifying a factor VIII-increasing agent free of the side effects of adrenaline that could be administered to people with hemophilia as autologous replacement therapy.

Vasopressin and insulin were shown to induce an increase of factor VIII [11], but their side effects were not milder than those of adrenaline, making clinical use unrealistic. An important step forward was made with the observation that desmopressin, a synthetic analogue of vasopressin, increased factor VIII and VWF in healthy individuals [12,13]. Unlike the natural antidiuretic hormone, desmopressin produces little or no vasoconstriction, no increase

in blood pressure, and no contraction of the uterus or gastrointestinal tract, so that it is well tolerated when administered to humans [12,13].

A big step forward was made when desmopressin was used for the prevention and treatment of bleeding, first during dental extractions and then during major surgical procedures in patients with mild hemophilia A or VWD [1]. Surgery was performed without blood products, demonstrating that autologous factor VIII and VWF increased in patient plasma and that desmopressin could effectively replace homologous factors contained in blood products [1]. These clinical results were soon confirmed [14-16].

Mechanism of action

The increase in plasma levels of factor VIII and VWF occur not only in deficient patients, but also in healthy individuals and in patients who already have high levels of these factors. Desmopressin shortens the prolonged activated partial thromboplastin time and the bleeding time [17]. These effects probably result from the rise in factor VIII and VWF, which plays a rate-accelerating role in these global tests of intrinsic coagulation and primary hemostasis. Desmopressin has no dramatic effect on platelet count or aggregation, but enhances platelet adhesion to the vessel wall [18,19]. Release into plasma of large amounts of tissue plasminogen activator is another short-lived effect of desmopressin [12,13]. Plasminogen activator generates plasmin *in vivo*, but most of the plasmin is quickly complexed to α_2 –antiplasmin, so that it does not produce fibrin(ogen)olysis in circulating blood [20]. Accordingly, it is usually unnecessary to inhibit fibrinolysis when desmopressin is used for clinical purposes.

How do factor VIII and VWF increase in plasma? Because the increase is rapid and transient, it is most likely that desmopressin causes these factors to be released from storage sites. The vascular endothelium is presumably the main source of VWF. This view is supported by the observation that, in rats, injections of desmopressin elicit biological responses that are clearly related to the activation of endothelial cells, such as surface expression of P-selectin and subsequent margination of leukocytes [21]. In normal individuals, desmopressin infusion produces important changes in the content and localization of VWF in vascular endothelial cells [22]. There is a reduction in the amount of the protein and a change in its localization, which causes a tendency for the protein to move abluminally toward the cellular basement membrane [22].

Notwithstanding these data focusing on the endothelial cell as the most likely source of VWF, addition of desmopressin to cultured endothelial cells *in vitro* does not release VWF [23]. This apparent paradox was solved by the demonstration that the lack of direct effect of desmopressin on human vascular endothelial cells (HUVEC) is attributable to the fact that these cells do not express the V2 receptor (V2R) [24]. When desmopressin was added to cultured HUVEC transfected to express V2R or to lung microvascular endothelial cells (which naturally express V2R), the compound did elicit a release of VWF, which was mediated by an increase in intracellular cAMP [24].

The interactions between released factor VIII and concomitantly released VWF and tPA are not well established. The observation that patients with VWD type 3 treated with desmopressin not only fail to release VWF (which is not synthesized in these patients), but also factor VIII and tPA (which are normally synthesized), supports the hypothesis that these effects are regulated by a single mechanism defective in type 3 VWD [25].

The site of cellular storage and release of factor VIII is less well established than that of VWF [26]. Desmopressin did elicit the expected VWF rise but no factor VIII rise in dogs with hemophilia A after hepatocyte-driven neonatal gene therapy [27]. This observation suggests that the increase of factor VIII induced by desmopressin in normal dogs and perhaps in humans is due to its release from cells other than the hepatocyte, perhaps endothelial cells where factor VIII is co-localized and complexed with VWF [27].

That the cellular co-localization of factor VIII and VWF is required for the plasma rise in factor VIII after desmopressin is also demonstrated by the observation that, following liver transplantation, patients with hemophilia A infused with desmopressin showed the expected VWF rise but no change in plasma factor VIII [28]. Because factor VIII is synthesized only in the transplanted liver, this observation supports the views that co-localization of factor VIII and VWF in extrahepatic cells is necessary for *in vivo* release of factor VIII after desmopressin [28].

TABLE 1. Recommended dosages of desmopressin and factor VIII/VWF responses in patients with hemophilia and VWD

Single dose	Intravenous and subcutaneous: 0.3 μg/kg Intranasal: 300 μg/kg
Mean factor increase over baseline	2-4 times (range: 1.5-20 times)
Time to peak levels	30-60 min after intravenous injection 90-120 min after subcutaneous injection and intranasal application
Plasma half-life	5-8 hours for factor VIII 8-10 hours for VWF

Desmopressin in the management of congenital bleeding disorders

In hemophilia and VWD, desmopressin is efficacious because it provides a form of autologous replacement therapy. Table 1 summarizes the routes of administration, the recommended dosages, and the pharmacokinetic properties of desmopressin-induced factor VIII and VWF.

The patients who respond to desmopressin and avoid the use of coagulation factor concentrates are those with measurable levels of factor VIII and VWF, i.e. patients with mild hemophilia A and type 1 VWD, [14-16], whereas patients with unmeasurable levels do not respond at all [17]. In mild hemophilia A, the efficacy of desmopressin usually correlates with the post-infusion plasma levels of factor VIII [14-16]. Accordingly, therapeutic indications are defined by the nature of the bleeding episode, the baseline factor VIII levels, and the levels that must be attained and maintained for hemostasis.

Clinical failures of desmopressin can usually be explained by the attainment of factor VIII levels in plasma that are insufficient to control bleeding. For instance, a major surgical procedure in a patient with factor VIII levels of 10 U/dL may not be successfully managed with desmopressin, because the expected post-treatment levels of 30 to 50 U/dL are not high enough to secure hemostasis. On the other hand, these levels should be sufficient for the patient to have a minor procedure, such as circumcision or dental extraction.

Most patients with type 1 VWD, who have a functionally normal VWF but reduced plasma levels, respond to desmopressin with plasma increases in factor VIII and VWF that are usually larger than those seen in people with hemophilia [29,30]. Hence, desmopressin should be the first choice for treatment of these patients. There is, however, some variability in response to desmopressin between patients with type 1 VWD [31-33]. The reasons for these different behaviours are not clear and a test dose is the only way to distinguish good responders from poor or non-responders. The defects of patients with type 3 VWD and of those with dysfunctional molecules (type 2 VWD) are usually not corrected by desmopressin, with some exceptions [34,35].

General guidelines for the use of desmopressin or plasma product in the different subtypes of VWD are given in Table 2, which shows the schedule of desmopressin administration and blood sampling recommended to evaluate the degree of laboratory response to a test dose. On the basis of the results obtained, one can predict whether the attained factor levels and the duration of their persistence in plasma are sufficient to successfully manage a given clinical situation.

TABLE 2. Indication for desmopressin in different types of VWD

Established	Type 1, "platelet normal" Type 2N
Possible	Type 1, "platelet low" and types 2A and 2B
Doubtful	Type 3 (severe)

Patients treated repeatedly with desmopressin may become less responsive, perhaps because stores are exhausted [29]. Some experimental data support this hypothesis, because repeated infusions of desmopressin lower the amount of VWF contained in vascular endothelial cells [22]. The average factor VIII responses obtained if desmopressin is repeated at 24-hour intervals are approximately 30% less than those obtained after the first dose [29]. The clinical implications are that the efficacy of desmopressin may be limited when factor VIII levels must be maintained above the baseline levels for a prolonged period of time. In these situations, which occur relatively seldom in the clinical management of mild hemophilia and type 1 VWD, it may become necessary to use plasma-derived or recombinant factors, or to supplement desmopressin with them.

Subcutaneous and intranasal desmopressin are at least as efficacious as intravenous desmopressin and can be self-administered. Although intravenous desmopressin is recommended before surgery or for treating severe hemorrhages, because very consistent responses are required in these situations, subcutaneous desmopressin can be used at home to prevent or treat minor bleeding episodes and in women with VWD who have excessive bleeding at menstruation [36]. Others prefer to use intranasal desmopressin in these situations, even to handle major bleeding episodes and surgical operations [37].

Despite the fact that neither *in vitro* nor *in vivo* studies have clearly proved a direct stimulatory effect of desmopressin on platelets (reviewed by Wun et al) [38], the drug shortens or normalizes the bleeding time of some patients with congenital defects of platelet function [39,40]. Defects associated with normal dense granule stores benefit more from the compound [40]. Accordingly, there is usually a good response in patients with defects of the release reaction, with cyclooxygenase deficiency, and in those with isolated and unexplained prolongations of the bleeding time.

Most patients with storage pool deficiency respond to desmopressin but a few do not [40], so a test dose is recommended to select responders. Whether the effect on a laboratory test such as the bleeding time corresponds to a hemostatic effect is not well-established. On the other hand, the data obtained from a few well-conducted but non-randomized studies would indicate that desmopressin can be a useful alternative to blood products during or after surgery or delivery, assuring satisfactory hemostasis [39,40].

To sum up, desmopressin is efficacious in mild hemophilia and type 1 VWD and usually permits the avoidance of concentrates, with significant reductions in costs. In the United States, for instance, an average dose of factor VIII concentrate (2,000 IU) costs between US$1,000 and $2,000. An average dose of desmopressin (21 μg) is much cheaper (US$100) and is even less expensive in Europe (the equivalent of US$20-$40).

The benefits of desmopressin are not limited to cost savings. The compound may be needed to meet religious requests, such as the avoidance of blood products in Jehovah's witnesses. More importantly, it is likely to have spared many patients from infection of the type 1 human immunodeficiency virus (HIV). In Italy, where desmopressin was used earlier and more extensively than in other countries, the prevalence of HIV infection in patients with mild hemophilia (2.1%) was much lower than in patients with mild hemophilia B (13.5%) [41]. The latter is a suitable comparison group, because these patients need treatment as frequently as hemophilia A patients, but are unresponsive to desmopressin. Hence, they could only be treated with plasma concentrates during the critical years between 1977 (when desmopressin was first used clinically and the HIV outbreak started) and 1985-1987 (when the outbreak was halted by the development of virus-inactivation methods and their application to plasma concentrates). Additional evidence of the HIV-sparing effect of desmopressin stems from the comparison of the prevalence of HIV infection in Italian patients with mild hemophilia A to the corresponding patients from other countries where the compound was used later. In the United States, for instance, where in the period 1977-1985 people with mild hemophilia were mainly treated with plasma concentrates because desmopressin was not yet licensed, anti-HIV prevalence is 18.4%, nine times higher than in Italy [41].

Desmopressin in acquired and drug-induced bleeding disorders

The hemostatic defect in uremia is characterized by a prolonged bleeding time, a laboratory abnormality that correlates with the hemorrhagic symptoms of these patients, mainly epistaxis and bleeding from the gastrointestinal tract. Dialysis may improve the bleeding time and the bleeding tendency, but this is not always the case. In the search for pharmacological agents that could improve hemostasis in uremia, desmopressin was considered, despite the fact that factor VIII and VWF are normal or even high in uremic patients [42]. The post-infusion bleeding time became normal in about 75%, and returned to baseline values after approximately 8 hours [42].

Well-conducted but non-controlled clinical studies have shown that desmopressin can be used successfully to prevent bleeding before invasive procedures (biopsies and major surgery) and to stop spontaneous bleeding [42]. Conjugated estrogens are a long-acting alternative

to desmopressin, because they shorten the bleeding time with a more sustained effect lasting for 10 to 15 days [43]. The two products can be given together, exploiting the different timings of their maximal effects. Currently, most patients with chronic renal insufficiency are regularly treated with erythropoietin. This practice has led to the sustained improvement not only of anemia but also of the hemostatic defect [44], so that short-acting compounds such as desmopressin and conjugated estrogens are unusually needed.

The bleeding time is prolonged in some patients with liver cirrhosis. There is usually mild or moderate thrombocytopenia, but platelet counts do not correlate negatively with the bleeding time. Factor VIII and VWF are in the high-normal range, or even higher, yet intravenous desmopressin shortens the bleeding time of cirrhotic patients [45,46]. However, a controlled clinical trial has shown that desmopressin is not useful in the management of acute variceal bleeding in cirrhotic patients [47]. Because this is the most frequent and serious hemorrhagic problem, the overall clinical impact of desmopressin in liver cirrhosis is relatively small.

Desmopressin counteracts the effects of some antithrombotic drugs on hemostasis measurements. It shortens the prolonged bleeding time of individuals taking antiplatelet agents, the prolonged bleeding time and activated partial thromboplastin time of patients receiving heparin [48], and the bleeding time of rabbits treated with streptokinase [49] or hirudin [50] (without corresponding human data). It also counteracts the antihemostatic effects of dextran, with no apparent impairment of the antithrombotic properties [51].

In summary, in chronic renal disease desmopressin remains indicated only for those patients with renal failure not treated or unresponsive to erythropoietin. Desmopressin is a possible treatment for patients with liver cirrhosis and prolonged bleeding time who need invasive diagnostic procedures such as liver biopsies. Notwithstanding the fact that there is only preliminary evidence that desmopressin prevents or stops bleeding complications that develop in association with the use of antithrombotic agents, the compound may provide an opportunity to control drug-induced bleeding without stopping treatment and perhaps avoiding recurrence or progression of thrombosis.

Desmopressin as a blood-saving agent

The broadening indications of desmopressin led several investigators to evaluate whether or not the compound was beneficial during surgical operations in which blood loss is great and for which multiple blood transfusions are needed.

Open-heart surgery with extracorporeal circulation is the epitome of operations that warrant the adoption of blood-saving measures. In addition to techniques such as pre-surgical removal of autologous blood for post-surgical retransfusion, returning all oxygenator and tubing contents to the patient, and autotransfusion of the mediastinal shed blood, prophylaxis with pharmacological agents might help reduce blood transfusion further.

Since 1986 desmopressin has been evaluated for this purpose. In the first controlled randomized study carried out in patients undergoing complex cardiac operations associated with large blood losses, results were impressive [52]. On the other hand, in subsequent large studies of patients undergoing less complex operations with lesser blood loss, there were no significant differences between desmopressin- and placebo-treated patients in either total blood loss or transfusion requirements [53,54]. Other studies, mainly in patients undergoing coronary artery bypass grafting and uncomplicated valve replacement, failed to find any benefit of desmopressin [55,56].

The conflicting results of desmopressin in open-heart surgery might be due to the fact that most studies were of small size and had insufficient statistical power to detect true differences in blood loss. A meta-analysis of 17 randomized, double-blind, placebo-controlled trials, which included 1,171 patients undergoing open-heart surgery, has attempted to overcome this pitfall [57]. Overall, desmopressin reduced post-operative blood loss by 9%, a value that is statistically significant but of little clinical impact. Although desmopressin had no blood-saving effect when the total blood loss in placebo-treated patients decreased in the lower- and middle-thirds of distribution (687 to 1,108 ml), the compound reduced blood losses by 34% when blood loss was larger [57]. The modest results obtained with desmopressin were substantially confirmed in a more recent meta-analysis of 38 randomized, placebo-controlled trials on 2,488 undergoing various surgical procedures (mainly cardiac surgery) [58].

TABLE 3. Indications for desmopressin in the treatment of bleeding disorders

		Grading of recommendation	Level of evidence
Established	Mild hemophilia A	B	III
	VWD (see Table 2)	B	III
Possible	Congenital defects of platelet function	C	IV
	Uremia	C	IV
	Liver cirrhosis	C	IV
	Drug-induced bleeding (heparin, hirudin, antiplatelet agents, dextran, streptokinase)	C	IV
Doubtful	Cardiac surgery	A	I
	Orthopedic surgery	A	I

Therefore, desmopressin seems beneficial only in operations associated with large blood loss (>1 l). It is not easy to predict which patient will bleed more, but situations such as re-operation, pre-surgical use of antiplatelet agents, pre-existing coagulation defects, and sepsis might help to identify the cases suitable for prophylaxis. Lower pre-operative plasma levels of factor VIII and VWF may also help to identify patients most at risk of bleeding [52,53]. However, the overlap of values is so large that it is not possible to use these measurements to select patients with the most to gain from the use of desmopressin.

Desmopressin is not the only blood-saving agent that can be used in cardiac surgery. The synthetic antifibrinolytic amino acids aminocaproic acid (EACA) and tranexamic acid, and the broad-spectrum protease inhibitor aprotinin have also been used, particularly after the recognition that acquired immunodeficiency syndrome (AIDS) could result from blood transfusions contaminated with HIV. A few direct comparison studies [59,60] and a meta-analysis [61] have shown that the order of efficacy of these hemostatic agents (greatest to least) is aprotinin, tranexamic acid, EACA, and desmopressin [61]. The order of drug cost is also the same. However, aprotinin has been withdrawn from use in cardiac surgery because it was shown to be associated with an increased death rate associated with cardiovascular complications [62].

The efficacy of desmopressin has also been evaluated in noncardiac surgical operations characterized by large blood loss. When administered to hemostatically normal children before spinal fusion for idiopathic scoliosis, desmopressin reduced their average operative blood loss by about one third [63], but these favorable results were not confirmed in a subsequent study [64]. Desmopressin did not reduce blood loss or transfusion requirement after total hip or knee arthroplasty [65].

In summary, the efficacy of desmopressin as a blood-saving agent in cardiac and noncardiac surgical operations appears doubtful at the moment.

Therapeutic guidelines

The main therapeutic guidelines for desmopressin are summarized in Table 3. It is the treatment of choice for patients with mild hemophilia A and type 1 VWD (grade B recommendation). The evidence of its efficacy as autologous replacement of the deficient factors is so clear that no randomized controlled clinical trial was ever necessary (level III evidence).

In patients with congenital defects of platelet function, with the hemostatic abnormalities associated with chronic liver disease, and with those induced by the therapeutic use of antiplatelet and anticoagulant agents, desmopressin has been used successfully to prevent or stop bleeding. However, there is still no well-designed clinical trial that truly shows efficacy of the compound in these conditions (grade C recommendation based on level IV evidence).

Currently, the widespread use of erythropoietin and the resulting sustained correction of the hemostatic defect make the use of desmopressin unnecessary in the majority of patients with chronic renal insufficiency. Antifibrinolytic amino acids should be preferred to desmopressin in reducing blood loss and transfusion requirements during cardiac surgery with extracorporeal circulation (grade A recommendation based on level I evidence).

The use of desmopressin in surgical operations other than cardiac surgery is not warranted at the moment. On the whole, more than 200 years of research have provided an agent that makes the blood clot faster, and William Hewson, who so ingeniously inquired into the properties of blood in the 18th century, perhaps would be content with the outcome of his pioneer studies.

References

1. Mannucci PM, Ruggeri ZM, Pareti FI, Capitanio A. DDAVP: A new pharmacological approach to the management of hemophilia and von Willebrand disease. *Lancet 1*:869, 1977.
2. Mannucci PM. Desmopressin: A non transfusional agent. *Annu Rev Med* 41:55, 1990.
3. Schulman S. DDAVP: The multipotent drug in patients with coagulopathies. *Transf Med Rev* 5:132,1991.
4. Lethagen S. Desmopressin (DDAVP) and haemostasis. *Ann Hematol* 69:173, 1994.
5. Hewson W. Experimental inquiries. Part I. An inquiry into the properties of the blood, with remarks on some of its morbid appearances, in Gulliver G (ed): The Works of William Hewson, FRS. London, UK, *The Sydenham Society*, 1846.
6. Cannon WB, Gray H. Factors affecting the coagulation time of blood. II. The hastening or retarding of coagulation by adrenaline injections. *Am J Physiol* 34:231, 1914.
7. Cannon WB, Mendenhall WL. Factors affecting the coagulation time of blood. IV. The hastening of coagulation in pain and emotional excitement. *Am J Physiol* 34:251, 1914.
8. Marciniak E. The influence of adrenaline in blood coagulation. *Acta Physiol Pol* 8:224, 1957
9. Ingram GIC: Increase in antihemophilic globulin activity following infusion of adrenaline. *J Physiol* 156:217, 1961.
10. Ingram GIC, Vaughan Jones R, Hershgold EJ, Denson KWE, Perkins JR. Factor VIII activity and antigen, platelet count and biochemical changes after adrenoceptor stimulation. *Br J Haematol* 35:81, 1977.
11. Mannucci PM, Gagnatelli G, D'Alonzo R. Stress and blood coagulation, in Brinkhous KM, Hinnom S (eds): Thrombosis: Risk factors and diagnostic approaches. Stuttgart, Germany, Schattauer Verlag, 1972, p 105.
12. Cash JD, Gader AMA, de Costa J. The release of plasminogen activator and factor VIII by LVP, AVP, DDAVP, AT III, and OT in man. *Br J Haematol* 27:363, 1974.
13. Mannucci PM, Aberg M, Nilsson IM, Robertson B. Mechanism of plasminogen activator and factor VIII increase after vasoactive drugs. *Br J Haematol* 30:81, 1975.
14. Warrier L, Lusher JM. DDAVP: A useful alternative to blood components in moderate hemophilia A and von Willebrand's disease. *J Pediatr* 102:228, 1983.
15. Mariani G, Ciavarella N, Mazzucconi MG, Antoncecchi S, Solinas S, Ranieri P, Pettini P, Agrestini F, Mandelli F. Evaluation of the effectiveness of DDAVP in surgery and bleeding episodes in hemophilia and von Willebrand's disease. A study of 43 patients. *Clin Lab Hematol* 6:229, 1984.
16. de la Fuente B, Kasper CK, Rickles FR, Hoyer LW. Response of patients with mild and moderate hemophilia A and von Willebrand disease to treatment with desmopressin. *Ann Intern Med* 103:6,1985.
17. Mannucci PM, Pareti FI, Holmberg L, Ruggeri ZM, Nilsson IM. Studies on the prolonged bleeding time in von Willebrand disease. *J Lab Clin Med* 88:62, 1976.
18. Barnhart MI, Chen S, Lusher JM. DDAVP: Does the drug have a direct effect on the vessel wall. *Thromb Res* 31:239, 1983.
19. Sakariassen KS, Cattaneo M, van der Berg A, Ruggeri ZM, Sixma JJ. DDAVP enhances platelet adherence and platelet aggregate growth on human artery subendothelium. *Blood* 64:229, 1984.
20. Levi M, de Boer JP, Roem D, ten Cate JH, Hack CE. Plasminogen activation in vivo upon intravenous infusion of DDAVP .Quantitative assessment of plasmin-alpha2-antiplasmin complex with a novel monoclonal antibody based radioimmunoassay. *Thromb Haemost* 67:111,1992.
21. Kanwar S, Woodman RC, Poon MC, Murohara T, Lefer AM, Davenpeck KL, Kubus P. Desmopressin induces endothelial P-selectin expression and leukocyte rolling in post-capillary venules. *Blood* 86:2760, 1995.

22. Takeuchi M, Naguza H, Kanedu T. DDAVP and epinephrine induce changes in the localization of von Willebrand factor antigen in endothelial cells of human oral mucosa. *Blood* 72:850, 1981.
23. Booyse EM, Osikowicz G, Fedr S. Effects of various agents on ristocetin-Willebrand factor activity in long-term cultures of von Willebrand and normal human umbilical vein endothelial cells. *Thromb Haemost* 46:668, 1981.
24. Kaufmann JE, Oksche A, Wollheim CB, Gunther G, Rosenthal W, Vischer UM (2000). Vasopressin-induced von Willebrand factor secretion from endothelial cells involves V2 receptors and cAMP. *J. Clin. Invest.* 106:107-116.
25. Cattaneo M, Simoni L, Gringeri A, Mannucci PM (1994). Patients with severe von Willebrand disease are insensitive to the releasing effect of DDAVP: evidence that the DDAVP-induced increase in plasma factor VIII is not secondary to the increase in plasma von Willebrand factor. *Br. J. Haematol*. 86:333-337.
26. Kaufmann JE, Vischer UM (2003). Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). *J Thromb Haemostas.* 1: 682-689.
27. Xu L, Nichols TC, Sarkar R, McCorquodale S, Bellinger DA, Ponder KP (2005). Absence of a desmopressin response after therapeutic expression of factor VIII in hemophilia A dogs with liver-directed neonatal gene therapy. *Proc Natl Acad Sci USA* 102:6080-6085.
28. Lamont PA, Ragni MV (2005). Lack of desmopressin (DDAVP) response in men with hemophilia A following liver transplantation. *J. Thromb Haemsot* 3:2259-2263.
29. Mannucci PM, Bettega D, Cattaneo M. Patterns of development of tachyphylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP). *Br.J.Haematol*. 1992;82:87-93.
30. Ruggeri ZM, Mannucci PM, Lombardi R, Federici AB, Zimmerman TS. Multimeric composition of factor VIII/von Willebrand factor following administration of DDAVP: implications for pathophysiology and therapy of von Willebrand's disease subtypes. *Blood* 1982;59:1272-1278.
31. Federici AB, Mazurier C, Berntorp E et al. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. *Blood* 2004;103:2032-2038.
32. Castaman G, Lethagen S, Federici AB et al. Response to desmopressin is influenced by the genotype and phenotype in type 1 von Willebrand disease (VWD): results from the European Study MCMDM-1VWD. *Blood* 2008;111:3531-3539.
33. Haberichter SL, Castaman G, Budde U et al. Identification of type 1 von Willebrand disease patients with reduced von Willebrand factor survival by assay of the VWF propeptide in the European study: molecular and clinical markers for the diagnosis and management of type 1 VWD (MCMDM-1VWD). *Blood* 2008;111:4979-4985.
34. Gralnick HR, William SB, McKeon LP, Rick ME, Maisonneuve P, Jenneau C, Sultan Y. DDAVP in type IIa von Willebrand's disease. *Blood* 67:465, 1986.
35. Castaman G, Rodeghiero F. Desmopressin and type IIB von Willebrand disease. *Haemophilia* 2:73,1996.
36. Rodeghiero F, Castaman G, Mannucci PM. Prospective multicenter study of subcutaneous concentrated desmopressin for home treatment of patients with von Willebrand disease and mild or moderate hemophilia A. *Thromb Haemost* 76:692, 1996.
37. Rose EH, Aledort LM. Nasal spray desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease. *Ann Intern Med* 114:563, 1991.
38. Wun T, Paglieroni TG, Lachant NA. Desmopressin stimulates the expression of P-selectin on human platelets in vitro. *J Lab Clin Med* 125:40, 1995.
39. Di Michele DM, Hathaway WE. Use of DDAVP in inherited and acquired platelet dysfunction. Am J *Hematol* 33:39, 1990.
40. Rao AK, Ghosh S, Sum L, Yang X, Disa J, Pickens P, Polanski M. Mechanisms of platelet dysfunction and response to DDAVP in patients with congenital platelet function defects. A double- blind placebo controlled trial. *Thromb Haemost* 74:1071, 1995.
41. Mannucci PM, Ghirardini A. Desmopressin twenty years after. *Thromb Haemost* 78:958, 1997.
42. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, Zimmerman TS. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 308:8, 1983.
43. Livio M, Mannucci PM, Viganò G, Mingardi G, Lombardi R, Mecca G, Remuzzi G. Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 315:731, 1986.
44. Moia M, Mannucci PM, Vizzotto L, Casati S, Cattaneo M, Ponticelli C. Improvement in the hemostatic defect of uremia after treatment with recombinant human erythropoietin. *Lancet* 2: 1227,1987.
45. Burroughs AK, Matthews K, Qadiri M, Thomas N, Kernoff PBS, Tuddenham EGD, McIntyre N. Desmopressin and bleeding time in patients with cirrhosis. *Br J Med* 291:1377, 1985.
46. Mannucci PM, Vicente V, Vianello L, Cattaneo M, Alberca I, Coccato MP, Faioni E, Mari D. Controlled trial of desmopressin (DDAVP) in liver cirrhosis and other conditions associated with a prolonged bleeding time. *Blood* 67:1148,1986.
47. de Franchis F, Arcidiacono PG, Carpinelli PG, Andreoni B, Cestari L, Brunati S, Zambelli A, Battaglia G, Mannucci PM. Randomized controlled trial of

desmopressin plus terlipressin and terlipressin alone for the treatment of acute variceal hemorrhage in cirrhotic patients: A multicenter, double blind study. *Hepatology* 18:1102, 1993.

48. Schulman S, Johnsson H. Heparin, DDAVP and the bleeding time. *Thromb Hemost* 65:242, 1991.
49. Johnstone MT, Andrews T, Ware JA, Rudd MA, George D, Weinstein M, Loscalzo J. Bleeding time prolongation with streptokinase and its reduction with 1-deamino-8-D-arginine vasopressin. *Circulation* 82:2142, 1990.
50. Bove CM, Casey B, Marder VJ. DDAVP reduces bleeding during continued hirudin administration in the rabbit. *Thromb Haemost* 75:471, 1996.
51. Flordal PA, Ljungstrom KG, Svensson J. Desmopressin reverses effects of dextran on von Willebrand factor. *Thromb Hemost* 61:541, 1989.
52. Salzman EW, Weinstein MJ, Weintraub RM, Ware JA, Thurer RL, Robertson L, Donovan A, Gaffney T, Bertelé V, Troll J. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. *N Engl J Med* 314:1402, 1986.
53. Rocha E, Llorens R, Paramo JA, Arcas R, Cuesta B, Trenor A. Does desmopressin acetate reduce blood loss after surgery in patients on cardiopulmonary bypass? *Circulation* 77:1319, 1988.
54. Hackmann T, Gascoyne R, Naiman SC, Growe GH, Burchill LD, Jamieson WR, Sheps SB, Schechter MT, Townsend GE. A trial of desmopressin to reduce blood loss in uncomplicated cardiac surgery. *N Engl J Med* 321:1437, 1989.
55. Anderson TL, Solem JO, Tengborn L, Vinge E. Effects of desmopressin acetate on platelet aggregation, von Willebrand factor and blood loss after cardiac surgery with extracorporeal circulation. *Circulation* 81:872, 1990.
56. Sean MD, Wadsworth LD, Rogers PC. The effect of desmopressin acetate (DDAVP) on postoperative blood loss after cardiac operations in children. *J Thorac Cardiovasc Surg* 48:217, 1988.
57. Cattaneo M, Harris AS, Stromberg U, Mannucci PM. The effect of desmopressin on reducing blood loss in cardiac surgery . A meta-analysis of double-blind, placebo-controlled trials. *Thromb Haemost* 74;1064, 1988.
58. Crescenzi G, Landoni G, Biondi-Zoccai G et al. Desmopressin reduces transfusion needs after surgery: a meta-analysis of randomized clinical trials. *Anesthesiology* 2008;109:1063-1076.
59. Rocha E, Hidalgo F, Llorens R, Melero JM, Arroyo SL, Paramo JA. Randomized trial of aprotinin and DDAVP to reduce postoperative bleeding after cardiopulmonary surgery. *Circulation* 90;921,1994.
60. Aron KV, Emery RW. Decreased postoperative drainage with addition of epsilonaminocaproic acid before cardiopulmonary bypass. *Ann Thorac Surg* 57;1108, 1994.
61. Fremes SE, Wong BI, Lee E, Mai R, Christakis GT, McLean RF, Goldman BS, Naylor CD. Meta- analysis of prophylactic drug treatment in the prevention of postoperative bleeding. *Ann Thorac Surg* 58;1580, 1994.
62. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R. BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 358:2319, 2008.
63. Kobrinsky NL, Letts RP, Patel R, Israels ED, Monson RC, Schwetz N, Cheang MS. DDAVP shortens the bleeding time and decreases blood loss in hemostatically normal subjects undergoing spinal fusion surgery. *Ann Intern Med* 107:446, 1987.
64. Guay J, Rainberg C, Poitras B, David M, Mathews S, Lortie L, Rivard GE. A trial of desmopressin to reduce blood loss in patients undergoing spinal fusion for idiopathic scoliosis. *Anesth Analg* 75;405, 1992.
65. Karnezis TA, Stulberg SD, Wixson RL, Reilly P. The hemostatic effects of desmopressin on patients who had total joint arthroplasty. A double-blind randomized trial. *J Bone Joint Surg Am* 76:1545,1994.