BLOOD

The Journal of The American Society of Hematology

VOL 90, NO 7 OCTOBER 1, 1997

REVIEW ARTICLE

Desmopressin (DDAVP) in the Treatment of Bleeding Disorders: The First 20 Years

By Pier Mannuccio Mannucci

IN 1977 DESMOPRESSIN (1-deamino-8-D-arginine vasopressin, abbreviated DDAVP), a 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 the 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 began to be transmitted by infected coagulation factor concentrates to patients with congenital coagulation disorders.

The clinical indications for desmopressin quickly expanded beyond hemophilia and vWD. The compound was shown to be efficacious even 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 diseases. Desmopressin has also been used prophylactically in patients undergoing surgical operations characterized by large blood loss and transfusion requirements.

Twenty 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, 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 the attempt to establish which indications remain valid and which do not. Topics such as pharmacokinetics, pharmacodynamics, and side effects of desmopressin will not be dealt with because they are covered in previous reviews.[2-4]

HISTORICAL BACKGROUND

It was in 1772 when William Hewson noted 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 this 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 possible 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 clotting factors.[9] In patients with mild hemophilia the magnitude of the factor VIII increase induced by adrenaline was similar to that elicited in healthy individuals.[9,10]

These findings stimulated further research, with the goal to identify a factor VIII–increasing agent that would be free of the side effects of adrenaline and could be administered to hemophilic patients as autologous replacement therapy. Vasopressin and insulin also induced 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 produced little or no vasoconstriction, no increase in blood pressure, and no contraction of the uterus or gastrointestinal tract, so that it was well tolerated when administered to humans.[12,13]

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

From the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Institute of Internal Medicine, IRCSS Maggiore Hospital and University of Milan, Milan, Italy.

Submitted February 20, 1997; accepted May 15, 1997.

Address reprint requests to Pier Mannuccio Mannucci, MD, Via Pace 9, 20122 Milano, Italy.

0006-4971/97/9007-0001$3.00/0

MECHANISMS OF ACTION OF DESMOPRESSIN

Despite 20 years of clinical use of desmopressin, mechanisms of action are still not completely understood. The increases in the 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 increases in factor VIII and vWF, which play a rate-accelerating role in these global tests of intrinsic coagulation and primary hemostasis. Desmopressin has no 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 and does not produce fibrin(o-gen)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 these factors increase rapidly and transiently, it is most likely that desmopressin causes them to be released from storage sites. The storage site(s) of factor VIII and the interaction between released factor VIII and concomitantly released vWF are not well established. 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, like 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] Even though cultured cells may not be identical to native cells and might have lost specific receptors during culture, these observations suggest an indirect action of desmopressin through a second messenger. In the search of such a second messenger, it was shown that release of vWF from endothelial cells occurred after the addition of desmopressin to monocytes.[24] These data, and those implicating monocyte-derived platelet activating factor as the second messenger acting upon endothelial cells,[25] need confirmation. Desmopressin acts on storage sites via its strong V_2 agonist activity, since patients with nephrogenic diabetes insipidus, who are unresponsive to V_2 agonists, do not have increased factor VIII and vWF levels after treatment with desmopressin.[26] Anephric patients respond normally,[13] indicating that the site of the V_2-like receptors involved in the hemostatic properties of desmopressin is not in the kidney. Their location is currently unknown.

A puzzling, unresolved question is how desmopressin is efficacious in bleeding disorders other than hemophilia and vWD, in patients who have normal or even high levels of factor VIII and vWF. The favorable effects of the compound may be mediated by increased platelet adhesion to the vessel wall,[18,19] due not only to the rise of plasma vWF but also to the abluminal secretion of the protein toward the subendothelium[22]; by heightened coagulability, due to supranormal levels of factor VIII, a rate-accelerating factor in the process of fibrin formation[27]; and by the fresh appearance in plasma of ultralarge vWF multimers.[28] These are hemostatically very effective because they support to a higher degree platelet adhesion to the vascular subendothelium and induce platelet aggregation under conditions of high shear.[29] Other putative mechanisms or mediators have been proposed to explain the hemostatic efficacy of desmopressin. For instance, the compound induces the adhesion of erythrocytes to the endothelium[30] and decreases the endothelial production of 13-hydroxyoctadecadienoic acid (HODE), a derivative of linoleic acid that powerfully inhibits platelet adhesion to the vessel wall.[31] The role of these mechanisms is uncertain and the search for additional or alternative mechanisms of action has been unfruitful so far.

Table 1. Recommended Dosages of Desmopressin and Factor VIII With 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	3-5 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 prototypes of patients who respond to desmopressin and avoid the use of coagulation factor concentrates are those with measurable levels of factor VIII and vWF, ie, patients with mild hemophilia A and type 1 vWD,[1,14-16] whereas patients with unmeasurable levels do not respond at all.[17] In mild hemophilia A the efficacy of desmopressin usually correlates with the postinfusion plasma levels of factor VIII.[1,14-16] 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.[1,14-16] For instance, a major surgical procedure in a patient with factor VIII levels of 10 U/dL may not be successfully managed with desmo-

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)

''Established'' indications are those in which desmopressin normalizes the bleeding time and factor VIII levels, and is clinically efficacious; ''Possible'' indications, those in which the effect on the bleeding time is absent or inconsistent, with little data on clinical efficacy; ''Doubtful'' indications, those in which desmopressin does not normalize factor VIII levels or the bleeding time, and is not clinically efficacious.

pressin because the expected posttreatment levels of 30 to 50 U/dL are not high enough for hemostasis. On the other hand, these levels should be sufficient for the patient to have a minor procedure, such as circumcision or dental extractions.

Most patients with type 1 vWD respond to desmopressin with increases in factor VIII and vWF that are larger than those seen in hemophiliacs.[32] In addition to factor VIII, in these patients a determinant of the clinical efficacy of the compound is its capacity to shorten or normalize the bleeding time. Although in type 1 vWD this effect is usually achieved in proportion to the levels of normally functioning vWF attained in plasma,[28] the bleeding times of patients with type 3, characterized by complete deficiency of vWF, and of those with dysfunctional molecules are usually not shortened.[17,28] There are, however, a few patients with type 2A vWD in whom desmopressin does shorten the bleeding time.[33] The reasons for these different behaviors are not clear and a test dose is the only way to differentiate responders from nonresponders. In theory, the administration of desmopressin to patients with heightened interactions between platelet glycoprotein Ib and vWF (type 2B and platelet-type or ''pseudo'' vWD) might be potentially dangerous, because it is followed by platelet aggregation and, in most instances, by thrombocytopenia.[34] Although there is some evidence that desmopressin is clinically efficacious in these patients (reviewed by Castaman and Rodeghiero[35]), most hematologists would be reluctant to use it. Table 2 summarizes the indications for desmopressin in patients with different types of vWD.

Patients treated repeatedly with desmopressin may become less responsive, perhaps because stores are exhausted.[32] 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 when desmopressin is repeated three to four times at 24-hour intervals are approximately 30% less than those obtained after the first dose.[32] 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 as spray 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 nonrandomized 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 $800 and $2,000, depending on the source (plasma-derived or recombinant). An average dose of desmopressin (21 μg) is much cheaper ($100) and is even less expensive in Europe (the equivalent of $20 to $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 with the human immunodeficiency virus type 1 (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%) is much lower than in patients with mild hemophilia B (13.5%).[41] The latter is a suitable comparison group, because these patients need treatment at least 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 (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 hemo-

philia 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 mild hemophiliacs were mainly treated with plasma concentrates because desmopressin was not licensed until 1984, 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 strongly 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, intravenous desmopressin was considered, despite the fact that factor VIII and vWF are normal in uremic patients.[42] The postinfusion bleeding time became normal in about 75% of them, and returned to baseline values after approximately 8 hours.[42] Well-conducted but noncontrolled 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 now less frequently 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 on hemostasis measurements of some antithrombotic drugs. It shortens the prolonged bleeding time of individuals taking widely used antiplatelet agents such as aspirin and ticlopidine,[46] 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. There is as yet little clinical 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, since the first use in hemophilia and vWD in 1977, led several investigators to evaluate whether the compound was beneficial during surgical operations in which blood loss is large 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 presurgical removal of autologous blood for postsurgical 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] Given at the time of chest closure, desmopressin reduced dramatically perioperative and early (12 hours) postoperative blood loss and transfusion requirements by about one third.[52] On the other hand, in two 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 postoperative 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] Therefore, desmopressin seems beneficial only in cardiac operations associated with large blood loss (>1 L). It is not easy to predict which patient will bleed more, but situations such as reoperation, presurgical use of antiplatelet agents, preexisting coagulation defects, and sepsis might help to identify the cases suitable for prophylaxis. Lower preoperative plasma levels of factor VIII and vWF may also help to

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
	General surgery	A	I

''Established'' indications are those in which the hemostatic efficacy of desmopressin has been demonstrated clinically; ''Possible'' indications, those in which clinical data are too preliminary or inconclusive; ''Doubtful'' indications, those in which desmopressin is not efficacious clinically. Grading of recommendations and levels of evidence are those proposed by the Agency for Health Care Policy and Research Publications of the US Department of Health and Human Services.

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 epsilon-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[58-60] 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] On the other hand, the order of drug cost is also the same. Cost-effectiveness analysis is necessary to help the clinicians in making a choice that currently would be directed to aprotinin, but with formidable costs.

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,[62] but these favorable results were not confirmed in a subsequent study.[63] Desmopressin did not reduce blood loss or transfusion requirement after total hip or knee arthroplasty.[64] Preoperative desmopressin failed to reduce blood loss in patients undergoing debridement and grafting of burn wounds, a procedure in which extreme blood loss is a frequent occurrence.[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 and are graded upon the criteria proposed by the Agency for Health Care Policy and Research Publications of the US Department of Health and Human Services.[66] Twenty years after the first clinical application, the compound is still 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 and aprotinin 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 bio-

chemical 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. Hashemi S, Tackaberry ES, Palmer DS, Rock G, Ganz PR: DDAVP-induced release of von Willebrand factor from endothelial cells in vitro: The effect of plasma and blood cells. Biochim Biophys Acta 1052:63, 1990

25. Hashemi S, Palmer DS, Aye MT, Ganz PR: Platelet activating factor secreted by DDAVP-treated monocytes mediates von Willebrand factor release from endothelial cells. J Cell Physiol 154:496, 1993

26. Kobrinsky ML, Doyle JJ, Israel ED, Winter JSD, Chenay MS, Walker RD, Bishop AJ: Absent factor VIII response to synthetic vasopressin analogue (DDAVP) in nephrogenic diabetes insipidus. Lancet 1:1293, 1985

27. Ibbotson SH, Davies JA, Grant PJ: The influence of infusions of 1-desamino-8-D-arginine vasopressin (DDAVP) in vivo on thrombin generation in vitro. Thromb Haemost 68:37, 1992

28. 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 58:1272, 1982

29. Moake JL, Turner NA, Stathopoulos NA, Nolasco LH, Hellum JD: Involvement of large plasma von Willebrand factor (VEF) multimers and unusually large VWF forms derived from endothelial cells in shear-stress induced platelet aggregation. J Clin Invest 78:1456, 1986

30. Tsai J-M, Sussman II, Nagel RL, Kaul DK: Desmopressin induces adhesion of normal human erythrocytes to the endothelial surface of a perfused microvascular preparation. Blood 75:261, 1990

31. Setty BNY, Dampier CD, Stuart MJ: 1-Deamino-8-D-arginine vasopressin decreases the production of 13-hydroxyoctadecadienoic acid by endothelial cells. Thromb Res 67:545, 1992

32. Mannucci PM, Bettega D, Cattaneo M: Patterns of development of tachyphylaxis in patients with hemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP). Br J Haematol 82:87, 1992

33. 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

34. Holmberg L, Nilsson IM, Borge L, Gunnarson M, Sjorin E: Platelet aggregation induced by 1-deamino-8-D-arginine vasopressin (DDAVP) in type IIB von WIllebrand's disease. N Engl J Med 309:816, 1983

35. Castaman G, Rodeghiero F: Desmopressin and type IIB von Willebrand disease. Hemophilia 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. Horrow JC, van Riper DF, Strong MD, Brodsky I, Parmet JL: Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. Circulation 84:2063, 1991

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. 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

63. 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

64. 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

65. Haith LR, Patton ML, Goldman WT, McCutchan KM: Diminishing blood loss after operation for burns. Surg Gynaecol Obstet 176:119, 1993

66. AHCPR: Acute Pain Management: Operative or Medical Procedures and Trauma (Agency for Health Care Policy and Research Publications). Bethesda, MD, US Department of Health and Human Services, 1992