The enhancement of blood clotting associated with stress was caused by the liberation of adrenaline in plasma. In 1957, a possible mechanism for faster clotting after adrenaline was provided by Marciniak, 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.

In patients with mild hemophilia the magnitude of the factor VIII increase induced by adrenaline was similar to that elicited in healthy individuals. 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, 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. 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.

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. 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. These clinical results were soon confirmed.

HISTORICAL BACKGROUND

It was in 1772 when William Hewson noted that blood collected under conditions of stress clotted rapidly. 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.

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

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

© 1997 by The American Society of Hematology.

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

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

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
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.\textsuperscript{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.\textsuperscript{18,19} Release into plasma of large amounts of tissue plasminogen activator is another short-lived effect of desmopressin.\textsuperscript{12,13} Plasminogen activator generates plasmin in vivo, but most of the plasmin is quickly complexed to \textalpha\textsubscript{2}-antiplasmin and does not produce fibrin(ogen)olysis in circulating blood.\textsuperscript{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.\textsuperscript{21} In normal individuals, desmopressin infusion produces important changes in the content and localization of vWF in vascular endothelial cells.\textsuperscript{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 abuminally toward the cellular basement membrane.\textsuperscript{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.\textsuperscript{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.\textsuperscript{24} These data, and those implicating monocyte-derived platelet activating factor as the second messenger acting upon endothelial cells,\textsuperscript{25} need confirmation. Desmopressin acts on storage sites via its strong V\textsubscript{2} agonist activity, since patients with nephrogenic diabetes insipidus, who are unresponsive to V\textsubscript{2} agonists, do not have increased factor VIII and vWF levels after treatment with desmopressin.\textsuperscript{26} Anephric patients respond normally,\textsuperscript{13} indicating that the site of the V\textsubscript{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,\textsuperscript{18,19} due not only to the rise of plasma vWF but also to the abuminial secretion of the protein toward the subendothelium;\textsuperscript{22} by heightened coagulability, due to supranormal levels of factor VIII, a rate-accelerating factor in the process of fibrin formation;\textsuperscript{27} and by the fresh appearance in plasma of ultralarge vWF multimers.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{31} The role of these mechanisms is uncertain and the search for additional or alternative mechanisms of action has been fruitless so far.

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 I vWD.\textsuperscript{1,14-16} whereas patients with unmeasurable levels do not respond at all.\textsuperscript{17} In mild hemophilia A the efficacy of desmopressin usually correlates with the postinfusion plasma levels of factor VIII.\textsuperscript{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.\textsuperscript{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 1. Recommended Dosages of Desmopressin and Factor VIII With vWF Responses in Patients With Hemophilia and vWD

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage</th>
<th>Time to Peak Levels</th>
<th>Mean Factor Increase Over Baseline</th>
<th>Plasma Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous and subcutaneous</td>
<td>0.3 μg/kg</td>
<td>30-60 min after intravenous injection</td>
<td>(range: 1.5-20 times)</td>
<td>5-8 hours for factor VIII</td>
</tr>
<tr>
<td>Intranasal</td>
<td>300 μg/kg</td>
<td>90-120 min after subcutaneous injection and intranasal application</td>
<td></td>
<td>8-10 hours for vWF</td>
</tr>
</tbody>
</table>

For personal use only.
DESMOPRESSIN: THE FIRST 20 YEARS

Table 2. Indication for Desmopressin in Different Types of vWD

<table>
<thead>
<tr>
<th>Indication</th>
<th>Type 1, “platelet normal”</th>
<th>Type 2N</th>
<th>Type 1, “platelet low” and types 2A and 2B</th>
<th>Type 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doubtful</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“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.

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.35 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 al38), 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-
philic 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.43 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,48 the prolonged bleeding time and activated partial thromboplastin time of patients receiving heparin,49 and the bleeding time of rabbits treated with streptokinase50 or hirudin51 (without corresponding human data). It also counteracts the antithrombotic 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

<table>
<thead>
<tr>
<th>Grading of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established</td>
<td>Mild hemophilia A</td>
</tr>
<tr>
<td>vWD (see Table 2)</td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>Congenital defects of platelet function</td>
</tr>
<tr>
<td></td>
<td>Uremia</td>
</tr>
<tr>
<td></td>
<td>Liver cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Drug-induced bleeding (heparin, hirudin, antiplatelet agents, dextran, streptokinase)</td>
</tr>
<tr>
<td>Doubtful</td>
<td>Cardiac surgery</td>
</tr>
<tr>
<td></td>
<td>General surgery</td>
</tr>
</tbody>
</table>

“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.

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. 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

10. Ingram GIC, Vaughan Jones R, Hershgold EJ, Denson KWE, Perkins JR: Factor VIII activity and antigen, platelet count and bio-

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


47. de Franchis F, Arcidiacono PG, Carpinelli PG, Andreoni B,


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

Pier Mannuccio Mannucci