The use of desmopressin as a hemostatic agent: A concise review

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Desmopressin, a synthetic derivative of the antidiuretic hormone vasopressin, is the treatment of choice for most patients with von Willebrand disease and mild hemophilia A. Moreover, the compound has been shown to be useful in a variety of inherited and acquired hemorrhagic conditions, including some congenital platelet function defects, chronic liver disease, uremia, and hemostatic defects induced by the therapeutic use of antithrombotic drugs such as aspirin and ticlopidine. Finally, desmopressin has been used as a blood saving agent in patients undergoing operations characterized by large blood loss and transfusion requirements, but studies suggest that this is not as effective as other methods. This review briefly summarizes the current clinical indications on the use of desmopressin as a hemostatic agent. Am. J. Hematol. 82:731–735, 2007.

Introduction

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) is a synthetic analogue of the antidiuretic hormone vasopressin originally designed for the treatment of diabetes insipidus [1]. DDAVP increases factor VIII (FVIII) and von Willebrand factor (VWF) plasma concentrations without important side effects when administered to healthy volunteers or patients with mild hemophilia and von Willebrand disease (VWD) [2,3]. The first clinical trial of DDAVP was successfully performed in 1977, with the aim of avoiding the use of blood products in mild hemophilia and VWD patients who needed dental extractions and other surgical procedures [4]. Following these early observations, DDAVP has become widely used for the treatment of these diseases [5]. However, the clinical indications for desmopressin quickly expanded beyond hemophilia and VWD and this drug was shown to be efficacious in many hemorrhagic situations not involving a deficiency or dysfunction of FVIII or VWF or as a blood saving agent [1].

In this review, the present knowledge on the use of DDAVP as a hemostatic agent is concisely analyzed. Table I reports the most important clinical conditions where DDAVP has been successfully used as a hemostatic drug.

Mechanisms of Action of Desmopressin

Despite 20 years of extensive clinical use, the mechanisms of action of DDAVP remain incompletely understood. Desmopressin induces an increase in plasma levels of VWF, FVIII, and tissue plasminogen activator (t-PA) and also has a vasodilatory effect. Desmopressin shortens the prolonged activated partial thromboplastin time (aPTT) and the bleeding time. These effects probably result from the increases in FVIII and VWF, which play a rate-accelerating role in these global tests of intrinsic coagulation and primary hemostasis. By contrast, the compound has no effect on platelet count or aggregation, but enhances platelet adhesion to the vessel wall [6].

Its effect on VWF and t-PA as well as its vasodilatory effect are explained by a direct action on the endothelium, via activation of the endothelial vasopressin V2 receptor (V2R) and c-AMP-mediated signaling. This leads to exocytosis of VWF and t-PA from endothelial cell Weibel-Palade bodies (where VWF and t-PA are stored). In addition, nitric oxide (NO) is produced via activation of NO synthase. The mechanism of FVIII increase is less clear but seems critically dependent from the carrier function made available from released VWF [7].

Desmopressin in the Treatment of Inherited Bleeding Disorders

Desmopressin has been successfully used in several inherited bleeding disorders, first of all VWD, mild hemophilia A, and some inherited platelet function defects [8].

von Willebrand disease

DDAVP is most effective in patients with Type 1 VWD (see Table II for the classification of VWD), especially those who have normal VWF in storage sites (Type 1, platelet normal) [9,10]. In these patients FVIII, VWF, and bleeding time (BT) are usually corrected within 30 min and remain normal for 6–8 hr. In other VWD subtypes, responsiveness to DDAVP is variable. A response of small magnitude and short duration is observed in a subset of patients with VWD Type 1 and decreased platelet VWF (Type 1, platelet low). In Type 2A, FVIII levels are usually increased by DDAVP but BT is shortened in only a minority of cases. Many experts consider DDAVP to be contraindicated in Type 2B because of the transient appearance of thrombocytopenia. Type 2M shows a variable pattern of response and the decision to use desmopressin should be made based on the results of a test infusion. In Type 2N, relatively high levels of FVIII are observed following DDAVP, but released FVIII circulates for a shorter time period in patient plasma because the stabilizing effect of VWF is impaired. Finally, patients with Type 3 VWD are usually unresponsive to DDAVP [11].

DDAVP is usually administered intravenously at a dose of 0.3 μg/kg diluted in 50 mL saline, infused over 30 min. This treatment increases plasma FVIII-VWF two to five times above the basal levels within 30 min, and high FVIII-

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TABLE I. Clinical Conditions Where Desmopressin Has Been Successfully Used as a Hemostatic Agent

Inherited bleeding disorders
(a) von Willebrand disease (Type 1, Type 2A, Type 2M, Type 2N)
(b) Mild hemophilia A
(c) Congenital disorders of platelet function (storage pool deficiency, primary secretion defects, Bernard-Soulier syndrome, Hermansky-Pudlak syndrome, May-Hegglin anomaly)
(d) Vascular disorders (Ehlers-Danlos syndrome, Marfan syndrome), heterozygous factor XI deficiency
Acquired bleeding disorders
(a) Acquired von Willebrand syndrome
(b) Acquired hemophilia A
(c) Uremia, hepatic cirrhosis, antiplatelet drugs (aspirin, ticlopidine), heparin, thrombocytopenia
In patients without preexisting bleeding disorders
(a) To reduce perioperative blood loss and transfusion requirements

VWF concentrations usually last in plasma for at least 8 to 10 hrs [12]. For instance, plasma levels of FVIII and VWF that are 10% of the normal levels are likely to increase to 30–50% of the normal levels after treatment; those increases may be sufficient for dental extraction, but not for major surgery. On the other hand, plasma factor levels that are 20% of the normal levels or more may increase to 60–100% after the administration of desmopressin, and these levels should be high enough for any surgical procedure.

A retrospective review over 10 years conducted by Nitu-Whalley et al. [13] found an excellent effectiveness (91%) of hemostasis of desmopressin in VWD patients undergoing elective surgery. However, a recent large prospective study of the biological response to desmopressin in severe forms of VWD has shown that only 27% of Type 1 and 18% of Type 2 VWD patients demonstrated a satisfactory increment of VWF levels and a shortening of the BT [14]. Thus, given the currently unpredictable nature of the desmopressin response, all VWD patients should undergo a therapeutic trial of administration to assess their individual level of response. Infusions can be repeated every 12–24 hr depending on the type and severity of the bleeding episode. However, most patients treated repeatedly with DDAVP over a short time period become less responsive to therapy, phenomenon which is called as tachyphylaxis [15]. The drug is also available in concentrated formulations for subcutaneous injection (at a dose of 0.3 μg/kg, as for the intravenous route) and nasal inhalation (at a fixed dose of 300 μg in adults and 150 μg in children), which can be convenient for home treatment [16,17].

Mild hemophilia A

Desmopressin has been successfully used for patients with mild hemophilia A in order to prevent bleeding complications in connection with dental extractions or surgical procedures and for acute bleeding such as hemarthroses, muscular hematomas, or mucosal bleeding [18–20]. However, the efficacy of desmopressin in such a condition is correlated with the postinfusion plasma levels of FVIII, which in turns depends on the patient's basal FVIII [21,22]. Moreover, as not all mild hemophilia A patients respond adequately, candidate patients must be tested with DDAVP prior to any surgical procedure. Thus, the therapeutic indications are defined by the nature of the bleeding episode, the baseline FVIII levels, and the levels that must be attained and maintained for hemostasis. For instance, a major surgical procedure in a patient with FVIII levels of 10% may not be successfully managed with desmopressin because the expected posttreatment levels of 30–50% 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 dental extractions [19,20,23].

The optimal dose of desmopressin to obtain maximum response of FVIII and VWF is 0.3 μg/kg intravenously, giving an increase in FVIII of three to five times that of baseline 1 hr after completion of the infusion with a half-life of the circulating FVIII of ~2–5 hr. If needed doses can be repeated at 8- to 12-hr interval although a single dose may be sufficient for the management of minor surgical interventions [21]. While subcutaneous injection (0.3 μg/kg) produces a similar, although slower, response to that seen with intravenous infusion, intranasal inhalation (250 μg) of DDAVP elicits a slower and less marked response, with a maximum FVIII level of ~2.5-times the baseline value. Thus, the subcutaneous or intravenous routes of administration should be preferred when a maximum response is required [24,25].

Congenital disorders of platelet function

Desmopressin shortens or normalizes the BT of most patients with congenital defects of platelet function [26]. There is usually a good response in patients with defects of the release reaction such as primary secretion defects or storage pool disease [27,28]. However, a lack of response to DDAVP has been observed in those patients with a severe deficiency of platelet δ-granule content [28]. Patients with Glanzamann's thromboasthenia, which is characterized by a missing or dysfunctional glycoprotein (GP)IIa/IIIb receptor on platelets, do not respond to DDAVP as this receptor is required for the binding of fibrinogen and platelet-platelet interaction [29]. The documented efficacy in patients with Bernard-Soulier syndrome, who lack the GPIb-IX-V complex, the platelet receptor for VWF that is essential for platelet adhesion to the vessel wall at high shear, supports the opinion that desmopressin can shorten the prolonged BT through mechanisms that are independent of released VWF [30]. Finally, patients with Hermansky-Pudlak syndrome and the May-Hegglin anomaly have been successfully treated with DDAVP [8]. However, as the response to DDAVP in patients with congenital platelet defects is often unpredictable, we advise a DDAVP tests in each patient.

Others

Desmopressin has been successfully used in patients with Ehlers-Danlos syndrome to control bleeding or to prevent hemorrhage during surgery [31,32]. Similarly, thanks to the use of DDAVP, we recently provided an excellent hemostasis in a patient with another vascular disorder causing a bleeding tendency, the Marfan syndrome, who underwent a cardiovascular surgery [33].

DDAVP has been also tried with success in patients heterozygous for factor XI (FXI) deficiency for prevention of surgical bleeding [34,35]. Moreover, Castaman et al. demonstrated that in such patients DDAVP led to an increase of both FXI activity and antigen levels [34].

Finally, DDAVP failed to shorten the prolonged BT in patients with congenital afibrinogenemia [36].

Desmopressin in the Treatment of Acquired Bleeding Disorders

DDAVP has been tried with success in a variety of acquired bleeding disorders, first of all acquired von Willebrand syndrome and acquired hemophilia A.

Acquired von Willebrand syndrome

Acquired von Willebrand syndrome (aVWS) is a rare bleeding disorder with laboratory findings similar to those

TABLE II. Classification of von Willebrand Disease

VWD	Transmission	Pathogenic mechanism	Laboratory parameters						Therapy
			VWF:Ag	VWF:RCo	FVIII:C	VWF:RCo/VWF:Ag	RIPA	Multimers	
Type 1	AD	Partial quantitative deficiency of VWF	↓	↓	N/↓	>0.7	↓	Uniform ↓ of all multimers	DDAVP
Type 2	AD, AR	Qualitative defects of VWF							
2A		Decreased platelet-dependent VWF function	↓↓		N/↓	<0.7	↓	Lack of HMWM	DDAVP, FVIII/VWF concentrate
2B		Increased platelet-dependent VWF function	↓↓		N/↓	<0.7	↑	Lack of HMWM	FVIII/VWF concentrate
2M		Decreased platelet-dependent VWF function	↓	↓	N/↓	<0.7	↓	Normal or supranormal	DDAVP, FVIII/VWF concentrate
2N		Deacreased VWF affinity for FVIII	N	N	↓	>0.7	N	Normal	DDAVP, FVIII concentrate
Type 3	AR	Complete deficiency of VWF	↓↓↓	↓↓↓	↓↓↓	–	↓↓↓	Undetectable	FVIII/VWF concentrate

Abbreviations: N, normal; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor; HMWM, high molecular weight multimers; RIPA, ristocetin-induced platelet agglutination; FVIII, factor VIII; FVIII:C, factor VIII coagulant; DDAVP, desmopressin.

for congenital VWD. However, unlike congenital VWD, it arises in individuals with no personal or family history of bleeding. aVWS occurs in association with a variety of underlying disorders, most frequently in lymphoproliferative disorders, myeloproliferative disorders, and cardiovascular diseases. The treatment of aVWS is targeted in two main directions: to correct the acute bleeding episode and to treat the underlying disorder [37]. The main therapeutic approaches involve DDAVP, FVIII/VWF concentrates, and high-dose immunoglobulins. In the recently published survey of the International Registry of the aVWS, Federici et al. [38] reported that DDAVP was given in 55/89 (66%) patients and stopped bleeding in 26 (44%) of them by restoring normal plasma levels of FVIII/VWF. However, although DDAVP is inexpensive and carries no risk of blood-borne infections, its usefulness in aVWS is limited by the short half-life of the endogenous FVIII/VWF released. Thus, a DDAVP infusion test should be recommended for every newly diagnosed case of aVWS, because the response to DDAVP therapy could vary from patient to patient.

Acquired hemophilia A

Acquired hemophilia A is a rare but severe autoimmune bleeding disorder, resulting from the presence of autoantibodies directed against clotting FVIII. The etiology of the disorder remains obscure, although approximately half of all cases are associated with other underlying conditions such as pregnancy, autoimmune disorders, and neoplasia [39]. The basic therapeutic strategy in patients with acquired hemophilia A is to treat any bleeding episodes and eradicate the autoantibody. While patients with high titer inhibitors (>5 Bethesda Units [BU]/mL) require by-passing agents (i.e., activated prothrombin complex concentrates or recombinant factor VII activated) to treat bleeding episodes, those with low titer inhibitors (<5 BU/mL) can be successfully treated with DDAVP alone or in association with FVIII concentrates [40,41].

Others

Desmopressin can shorten the prolonged BT in patients with hepatic cirrhosis or chronic uremia, conditions characterized by hemostatic abnormalities [42]. Thus the compound may be used to prevent hemorrhages in patients with liver diseases and prolonged BT who need invasive procedures such as liver biopsies. However, a controlled clinical trial has shown that the drug is not effective in controlling acute variceal bleeding in cirrhotic patients [43]. Patients with prolonged BT secondary to antiplatelet drugs (aspirin or ticlopidine) may also benefit from the effect of desmopressin as it promptly normalizes primary hemostasis and shortens the BT in most of these patients [44]. Moreover, as DDAVP was found to shorten BT and aPTT of patients receiving heparin, it could be helpful for the management of hemorrhagic complications during treatment with heparin [45].

Finally, desmopressin has been successfully used in patients with thrombocytopenia associated with hematologic malignancies for prevention or treatment of bleeding [46].

Desmopressin in Patients Without Preexisting Bleeding Disorders

The broadening indications of desmopressin since its first use in hemophilia and VWD patients in 1977, led several investigators to evaluate whether the compound was beneficial in patients undergoing surgical operations characterized by large blood loss and transfusion requirements [47–49].

Thus, desmopressin has been used in patients undergoing cardiac operations as a blood saving measure [50]. In a study of 70 patients undergoing cardiac surgery, desmopressin was able to reduce blood loss and transfusion requirements by about 30% [51]. However, subsequent studies did not confirm these preliminary results. In 1995, Cattaneo et al. [52] published a metaanalysis of 17 randomized, double blind, placebo-controlled trials which included 1,171 patients undergoing cardiac surgery: 579 of them were treated with desmopressin and 592 with placebo. Desmopressin significantly reduced postoperative blood loss by 9% but had no significant effect on transfusion requirements. In 1997, Laupacis and Fergusson [53] published another metaanalysis showing that desmopressin was ineffective in reducing blood loss in cardiac surgery. Another metaanalysis of randomized controlled trials studying the role of desmopressin in cardiac surgery was per-

formed by Levi et al. [54] in 1999, in which the use of desmopressin resulted in a small decrease in perioperative blood loss but was not associated with a beneficial effect on other clinical outcomes (mortality, repeat thoracotomy, proportion of patients receiving transfusion). Moreover, desmopressin was associated with a 2.4-fold increase in the risk of myocardial infarction. However, the most recent metaanalysis was that published in 2004 by Carless et al. [55]. After the analysis of 18 trials, the authors concluded that there is no benefit from using DDAVP as a means of minimizing perioperative allogeneic blood transfusion. Moreover, a few direct comparison studies [56,57] and a metaanalysis [58] on blood-saving agents in cardiac surgery have shown that other nontransfusional hemostatic agents such as aprotinin, tranexamic acid, and ε-aminocaproic acid are more effective than DDAVP.

There are few clinical trials evaluating the prophylactic use of DDAVP in noncardiac surgery. There have been two studies evaluating the use of DDAVP in patients having spinal fusion surgery with contrasting results. In fact, while Kobrinsky et al. [59] reported a beneficial effect in terms of blood loss and transfusion requirements, Guay et al. found no benefit [60]. Three trials showed no significant differences in blood loss or transfusion requirements when desmopressin was used in elective total hip/knee arthroplasty [61–63]. Moreover, a comparative prospective study found that tranexamic acid had better postoperative blood-sparing effects than desmopressin after total knee replacement [64]. In aortoiliac surgery, Lethagen et al. [65] reported a small difference in blood loss with desmopressin, although this difference was not statistically significant. Another more recent randomized, double-blind, placebo-controlled study found no benefit in elective aortic surgery when desmopressin was given at the time of aortic clamp placement [66].

In conclusion, the current literature data do not support a beneficial effect of desmopressin in hemostatically normal patients undergoing elective noncardiac surgical procedures.

Safety

Besides the obvious advantage that it is relatively inexpensive, DDAVP is safer than blood products as it carries no risk of transmitting blood-borne viruses.

The side effects of desmopressin have been well characterized and, in the vast majority of cases, they are transient and mild [1]. Mild tachycardia, headache, and facial flushing are not infrequent. Because of the mild antidiuretic effect of the agent, fluid intake should be regulated in the 24 hr following administration. Fortunately, episodes of fluid overload and severe hyponatremia are rare, and most often involve the very young patients who received closely repeated infusions [67,68]. Therefore, it is generally recommended that desmopressin is used cautiously in small children or in patients with congestive heart failure. As occasional reports have been published on the occurrence of arterial thrombosis during DDAVP treatment [69–72] this drug should be avoided in patients with cardiovascular diseases. Moreover, we have recently described an episode of deep vein thrombosis following DDAVP administration in a young VWD patient undergoing orthopedic surgery [73]. Finally, DDAVP is not contraindicated in uncomplicated pregnancy though like all drugs it should be used with caution. No teratogenic effect has been observed in animals and its prolonged use in diabetes insipidus has shown no adverse effects for mother or fetus [74].

Conclusions

The analysis of the literature data shows that desmopressin is the treatment of choice for most patients with VWD and mild hemophilia A. Moreover, in the last years the clinical indications of DDAVP as a hemostatic agent have been expanded and the compound have been successfully used in a broad spectrum of inherited and acquired bleeding disorders.

However, most of the studies published on these less well standardized clinical indications are anecdotal or include small series of patients. Thus, larger trials are needed in order to confirm these preliminary positive results.

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