PILOT STUDY ON THE SAFETY AND EFFICACY OF DESMOPRESSIN FOR THE TREATMENT OR PREVENTION OF BLEEDING IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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ABSTRACT

Background and Objectives. Desmopressin is the treatment of choice for patients with von Willebrand's disease and mild hemophilia A. This compound is also useful in other congenital and acquired disorders of hemostasis, reducing the need for blood derivatives with the inherent risks of infections and alloimmunization. The following article presents a pilot study on the safety and efficacy of desmopressin for the treatment or prevention of bleeding in 15 patients with thrombocytopenia associated with hematologic malignancies.

Methods. Cases were consecutively recruited from February to June 1995. Fifteen patients were treated with desmopressin for prevention or treatment of bleeding. Desmopressin was diluted in 100 mL of isotonic saline and infused for 30 minutes. Bleeding time (BT) was carried out using the Simplate II device, making two standardized incisions on the forearm: the mean between the two incisions was recorded.

Results. Significant reduction of BT was observed in three out of four patients with myelodysplastic syndrome who were successfully treated for active bleeding or dental extraction. In the remaining patients, the effect of desmopressin on BT was not tested. Nevertheless, in all of them bleeding mainly due to epistaxis or persistent gum oozing was stopped by a single infusion of desmopressin. In three patients, desmopressin infusion had been successfully administered on a different occasion. No side effects were observed.

Interpretation and Conclusions. Desmopressin could be a safe and immediately effective option for the treatment or prevention of bleeding in selected patients with hematologic malignancies.
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Key words: desmopressin, bleeding time, thrombocytopenia, hematologic malignancies, acquired bleeding disorder

The vasopressin analogue 1-desamino-8-D-arginine vasopressin (desmopressin, DDAVP) is the treatment of choice for patients with von Willebrand's disease and mild hemophilia A.[1,2] Its clinical efficacy in these disorders has been ascribed to the rise of VIII/von Willebrand factor (vWF) circulation and the concomitant shortening of the bleeding time (BT). The compound has also proved useful for the treatment of patients with other inherited or acquired hemostasis disorders because of its ability to correct or significantly reduce the BT, the only *in vivo* parameter reflecting a derangement of primary hemostasis, even in the presence of a normal level of vWF (for review, see ref. #1). The mechanism by which DDAVP modifies the BT in these disorders remains unclear. In an investigational study, desmopressin was tested in patients with severe thrombocytopenia, but the basal prolonged BT remained unchanged, suggesting that its effect may depend on a minimal availability of circulating platelets.[3] There has been only one report which evaluated the clinical usefulness of desmopressin in a few patients with thrombocytopenic disorders associated with acute leukemia,

thrombocytopenia due to bone marrow failure or idiopathic thrombocytopenic purpura, suggesting a possible efficacy of this treatment in this clinical setting.[4] In patients with bleeding who have treatment-related thrombocytopenia or thrombocytopenia due to hematologic malignancy, desmopressin could reduce the risks of blood-borne virus transmission. Furthermore, platelet alloimmunization may be overcome, thus allowing for the treatment of patients already refractory to platelet transfusions with reduced treatment costs.

In this pilot study, we have administered desmopressin to 15 patients with various hematologic malignancies and thrombocytopenia for the treatment or prevention of bleeding episodes. The results indicate that the compound is safe and effective and suggest that wider, controlled experimentation should be fostered.

Materials and Methods

Patients

Fifteen patients (12 M, 3 F, median age 55.5 years; range 24-82 years) were treated with desmo-

pressin for prevention or treatment of bleeding. In three patients the compound was also given as a test-infusion to assess its possible efficacy prior to planned dental procedures (Table 1). Two patients had refractory anemia and one had refractory anemia with excess of blasts. Table 2 summarizes the underlying hematologic disorders in the remaining 12 patients. Six patients had acute leukemia, 3 had a blast crisis of chronic myelogenous leukemia, two had refractory anemia (one with blast excess) and one had non-Hodgkin's lymphoma. The majority of patients were on chemotherapy or in chemotherapy-induced aplasia for the underlying disease.

The cases were consecutively recruited from February to June of 1995. As for age, inclusion limits were not considered. Patients with a history of cardiovascular disease, presence of disseminated intravascular coagulation, life-threatening bleeding or serum electrolytic imbalance due to concomitant administration of antibiotics or Amphotericin B were not considered eligible for treatment with desmopressin. The patient selection for treatment required the direct supervision of one of the authors who had experience with the use of desmopressin; we also asked for the confirmation of the attending physician that desmopressin treatment could spare the patient the exposure to or the additional use of platelet transfusion therapy, or that platelet transfusion was ineffective for refractoriness. The goal of test-infusion or of treatment and the possible side effects and risks were explained in detail to the patients and all gave informed consent to be treated. The study was approved by the local Institutional Review Board.

Bleeding time

Bleeding time (BT) was carried out using the Simplate II device (General Diagnostics, Morris Plains, USA), making two standardized incisions on the forearm. The mean between the two incisions was recorded.

Desmopressin infusion

Desmopressin (Minirin, Valeas, Milan, Italy; 0.4 µg/kg), was diluted in 100 mL of isotonic saline and infused over 30 minutes. In some cases, BT was assessed before the start of infusion, at 1 and 4 hours after the infusion.

Results

Table 1 shows the results obtained with test-infusion in three patients. These patients suffered from epistaxis and mucocutaneous bleeding after the diagnosis of myelodysplastic syndrome. The compound was tested prior to planned dental extraction, which was then safely carried out in patient #1 and #3. BT showed significant modification in patient #1 and #3, whereas only a short-lived reduction was evident in patient #2, who showed

Table 1. Clinical features and bleeding time changes in three patients infused for investigational purpose with desmopressin.

Case	Age (yr)	Blood disorder	Platelet count (10^9/L)	Hematocrit (L/L)	Bleeding time (min)		
					0	1h	4hr
1	77	Refractory anemia	43	32	13	6	ND
2	61	RAEB	41	18	> 20	15	> 20
3	48	Refractory anemia	57	30	16	10	11

RAEB = refractory anemia with excess of blasts; ND = Not done

the lowest platelet count and hematocrit. None of the patients had been previously given platelet concentrates.

Table 2 summarizes the relevant clinical data and bleeding circumstances treated with desmopressin in 12 additional cases. Six patients had epistaxis, four had gingival bleeding, two had persistent oozing and hematoma after insertion of a central venous catheter. Patients #1, 4 and 6 had HLA platelet antibodies with very poor or no response to random donor platelets. In eight cases, bleeding was present despite the fact that platelet count was greater than 30×10^9/L. In none of the patients was there clinical or laboratory evidence of disseminated intravascular coagulation (data not shown).

A favorable response was observed in all the patients after a single infusion. Usually, bleeding slowed down during desmopressin infusion and completely stopped within 1 hour after infusion. No nasal packing was required. Seven patients had never been transfused with platelet concentrates and all had platelet counts greater than 30×10^9/L. None required administration of platelet concentrates for control of bleeding after the use of DDAVP. All of the remaining five patients received or were already taking tranexamic acid (3 g/daily) as a mouthwash (in case of gum bleeding) or intravenously. The patients who were receiving tranexamic acid for control of bleeding did not show any clinical benefit prior to the infusion of desmopressin. Patients #1, 4 and 5 were treated on another occasion with consistent clinical results. No adverse effects were observed and only 3 patients had mild facial flushing after infusion.

Bleeding time was measured only in patient #12. The baseline value was > 25 min. One hour after it was reduced to 13 min and the reduction persisted even after 4 hours (11 min). In the other cases BT was not measured for fear of infection or prolonged oozing; in some cases it would have been impractical, since the majority of patients were aplastic or were treated for acute bleeding.

Table 2. Main laboratory and clinical features of patients with blood malignancy treated with desmopressin.

No.	Sex/Age	Blood malignancy and treatment	WBC	Blasts	Platelets	Type of bleeding	Outcome	Comments
					$(x10^9/L)$			
1	M/48	Relapse of AML, chemotherapy	0.7	0	2	Gum bleeding (> 4 hours)	Bleeding stopped during DDAVP	HLA-antibodies present; new episode 3 days later again successfully treated
2	F/44	AML, chemotherapy	1.8	1.67	15	Gum bleeding (24 hours)	Bleeding stopped during DDAVP	—
3	M/44	Blast crisis of CML	62.3	22.4	33	Severe epistaxis#	Bleeding stopped during DDAVP	Never transfused with platelet concentrates
4	F/60	ALL in relapse	9.9	0.9	5	Epistaxis	Bleeding slowed down and stopped within 1 hour after the end of infusion	HLA-antibodies present; new episode 4 days later again successfully treated
5	M/62	RAEB	2.3	0.2	61	Gum bleeding (> 6 hours)	Bleeding slowed down and stopped within 1 hour after the end of infusion	Never transfused with platelet concentrates; new episode 21 days later again successfully treated
6	M/51	Blast crisis of CML, chemotherapy	0.5	0	22	Gum bleeding (intermittent, 3 days duration)	Bleeding abruptly stopped within 1 hour after the end of infusion	HLA-antibodies present
7	M/68	AML	39.9	38	71	Severe epistaxis#	Bleeding slowed down and stopped within 1 hour after the end of infusion	Never transfused with platelet concentrates
8	M/78	AML	42.5	40	40	Oozing and hematoma after CVC insertion	Bleeding slowed down and stopped within 3 hours after the end of infusion	Never transfused with platelet concentrates
9	M/60	NHL, chemotherapy	6.5	0	53	Epistaxis	Bleeding abruptly stopped within 1 hour after the end of infusion	Never transfused with platelet concentrates
10	M/24	ALL, relapse	29.6	28	39	Oozing and hematoma after CVC insertion	Bleeding slowed down and stopped within 1 hour after the end of infusion	—
11	F/39	Blast crisis of CML	74.3	60	47	Epistaxis	Bleeding slowed down and stopped within 2 hours after the end of infusion	Never transfused with platelet concentrates
12	M/82	Refractory anemia	2	0.1	44	Epistaxis	Bleeding abruptly stopped within 1 hour after the end of infusion	Never transfused with platelet concentrates

AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; ALL = acute lymphoblastic leukemia; RAEB = refractory anemia with excess of blasts; NHL = Non-Hodgkin lymphoma; CVC =central venous catheter; #bilateral epistaxis.

Platelet count was carried out in 12/15 patients at the end of infusion. No change over the baseline was observed (data not shown).

Discussion

There is much clinical and laboratory evidence as to the biological and clinical efficacy of desmopressin in patients with von Willebrand disease, mild or moderate hemophilia A and congenital platelet function disorders.[1,2,5] Also several acquired disorders of hemostasis, like acquired hemophilia, acquired von Willebrand syndrome, platelet dysfunction due to drug intake, uremia, and liver cirrhosis may benefit from its use (for review, ref. #6). The compound appears to be safe, economical and effective, allowing for substantial cost reduction and avoiding the risks of transmission of blood-

borne viruses and precocious platelet alloimmunization inherent to replacement therapy.

It appears that the effect of desmopressin is not entirely dependent on the release of vWF from storage compartments, since the bleeding time, which reflects impairment of primary hemostasis, is shortened in patients with normal levels and structure of vWF as well.[6] No *in vitro* or *in vivo* studies have demonstrated a direct stimulatory effect of desmopressin on platelets.[7-10] However, recent discoveries suggest that the compound, through a mechanism that is unknown as of yet, is able to induce an increased expression of platelet surface glycoprotein Ib, the receptor of vWF in platelet adhesion, and an increased expression of P-selectin (CD62).[11,12] These mechanisms could also compensate for reduced platelet count in patients with normal or even increased levels of plasma vWF. Considering this background, we chose to use desmopressin to treat 15 patients with thrombocytopenia due to hematologic malignancies. In 12 patients, the compound was used for treatment of active bleeding, and two patients were infused prior to planned dental extraction. In one case, the compound was infused solely as test-infusion. The clinical results were good. Remarkably, all the patients responded to a single infusion and no side effects were observed. Nevertheless, in view of the potential thrombogenicity of the compound,[13] its use in older patients, after evaluation for underlying cardiovascular disorders, should be carefully weighted. Furthermore, none of our patients had clinical or laboratory evidence of disseminated intravascular coagulation, which should also be considered a counterindication to the use of the compound.

Eleven patients (including the patients reported in Table 1, subsequently treated after test-infusion) had basal platelet count $\geq 30 \times 10^9$/L. This threshold level could be a major determinant of efficacy of desmopressin.[3] However, also patients with lower platelet counts, as reported in Table 2, showed some clinical benefit. It is interesting to note that patients with myelodysplastic syndrome, whose platelet counts are usually not as dramatically reduced as in patients with acute leukemia, appear to be responsive in terms of bleeding time modifications as well, as observed in the patients described in Table 1 and patient #12 of Table 2. Platelet dysfunction or reduced platelet vWF content have been observed in these disorders,[14] and these abnormalities could be responsible for the bleeding tendency sometimes observed, despite hemostatically safe platelet counts.

There is only one clinical study which reported the use of desmopressin for treatment of bleeding in thrombocytopenic disorders. Kobrinsky *et al*.[4] successfully used desmopressin in treating six children with various hematologic disorders, thrombocytopenia and active bleeding. In that report, as is true here, a single infusion was usually sufficient, followed by a prompt clinical effect. On the other hand, Mannucci *et al*.[3] in a biological study evaluating the effect of DDAVP on the BT anticipated no clinical role for desmopressin in thrombocytopenic states since the prolonged BT was not affected by the compound. On the contrary to this latter study, Di Michele and Hathaway[15] showed significant modification of BT in four thrombocytopenic patients infused for investigational purposes. Platelet count could be a major determinant in the effect of DDAVP on the BT in such disorders since in Mannucci's study[3] the mean platelet count was 13×10^9/L, in Kobrinsky's study 27×10^9/L[4] and in the present study 41×10^9/L. However, in Mannucci's study,[3] none of the patients received desmopressin for clinical purpose and thus any significant comparison is not possible. Whatever the possible biological explanation for these discrepancies, it appears that DDAVP could be a safe and immediately effective option for the treatment or prevention of bleeding episodes in selected patients with thrombocytopenia due to hematologic malignancies. Its use could lead to a substantial reduction of platelet concentrate transfusions in selected patients. Nevertheless, controlled studies are necessary prior to recommending its extensive use.

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