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Clinical Efficacy of Desmopressin Acetate for Hemostatic Control in Patients With Primary Platelet Disorders Undergoing Surgery

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Desmopressin acetate (DDAVP) is efficacious in patients with von Willebrand's disease. It additionally appears to have value in patients with uremic or aspirin-induced platelet dysfunction. We report here three patients with primary platelet defects who had previously experienced grossly inadequate hemostasis to whom we administered DDAVP. Each successfully underwent surgical procedures with DDAVP as the only hemostatic agent. Although the mechanism of these salutary effects is unclear, DDAVP may exert an influence directly on the endothelium independent of correcting abnormalities of the factor VIII:von Willebrand complex associated with von Willebrand's disease.

Key words: DDAVP, von Willebrands disease, platelet defects, hemostasis in surgery

INTRODUCTION

Desmopressin acetate (DDAVP: 1-deamino-8-D-arginine-vasopressin) is a synthetic analogue of arginine vasopressin which has been shown to increase temporarily plasma concentrations of the various moieties of the factor VIII:vWF complex [1]. Because of the increasing concern of transmitting infections such as hepatitis and acquired immunodeficiency syndrome (AIDS) via blood transfusions, DDAVP is appropriately assuming a growing role in the treatment of mild hemophilia A and type I von Willebrand's disease as well as in the management of the hemostatic defect associated with uremia [1,2]. Additionally, a recent report described at least partial correction of the bleeding time with DDAVP in patients with platelet function defects, simultaneous von Willebrand disease and platelet defects, aspirin-induced platelet defects, and isolated prolonged bleeding time [3]. The mechanism of this effect is unclear. Because of the frequency of mild platelet defects, often not associated with clinical bleeding, the meaning of the previous report to the practicing hematologist is unclear.

Herein we report three patients with primary platelet defects who had previously experienced grossly inadequate hemostasis and in whom surgical hemostatic control was attained solely with preoperative DDAVP infusion. In spite of this control,

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platelet aggregation studies were not improved by the administration of DDAVP. This report confirms and supplements the observation of Kobrinsky et al [3].

MATERIALS AND METHODS

All three patients were evaluated by the hematology service of Shands Hospital of the University of Florida. Evaluation included bleeding time using a commercially available device (Simplate, General Diagnostics, Morris Plains, NJ). Platelet counts were normal on all patients. Platelet aggregation was evaluation by the technique of Born [4] using collagen, adenosine diphosphate (ADP), epinephrine, and ristocetin. Plasma was assayed for factor VIII coagulant activity (factor VIII:C), factor VIII:von Willebrand factor antigen (factor VIII:vWF), and ristocetin cofactor (factor VIII: RCoF) by routine methods. Multimeric analysis of the factor VIII:von Willebrand complex was performed by the method of Ruggeri and Zimmerman [5]. DDAVP (Stimate®, Armour Pharmaceuticals) was administered, 0.3 μg/kg in normal saline, intravenously over a 30-min period. Blood samples were studied before and 60 min after infusion with DDAVP. Platelet aggregation was evaluated as a percent of maximal aggregation 5 min after the addition of the aggregating agent. The presence or absence of a secondary wave when using epinephrine or ADP as aggregating agent was observed.

Platelet defects were defined as occurring in persons with no evidence of von Willebrand disease but who had a long bleeding time and in whom platelet aggregation studies were normal using ristocetin but abnormal using collagen, ADP, and epinephrine, with only a primary wave being generated by the latter two agents.

Case Reports

Case 1. This 18-year-old man had a personal and family history of abnormal hemostasis. He and his mother had been diagnosed as having a primary platelet defect. He consistently had a bleeding time averaging 19 min and required surgery for removal of a ganglion cyst from his left ankle. The bleeding time corrected toward normal following a trial infusion of DDAVP (see Table I).He was given DDAVP immediately prior to surgery and at 12 and 24 hr postoperatively. Hemostasis during and after surgery was normal.

Case 2. This 45-year-old woman had a lifelong history of increased menstrual bleeding and excessive bleeding following minor surgical or dental procedures. She required extensive oral and gingival surgery. Her bleeding time corrected from 20 min to 8 1/2 min following DDAVP infusion. She underwent three dental extractions and gingival surgery procedures on four separate occasions using only DDAVP as a hemostatic agent. She experienced no abnormal bleeding.

Case 3. This 22-year-old woman had a lifelong history of easy bruisability, recurrent epistaxis, and prolonged bleeding following dental work. Previous evaluations had shown her to have borderline factor VIII:C, and platelet aggregation studies were consistent with our definition of a primary platelet defect. Preoperative examination in our clinic disclosed a bleeding time greater than 20 min. This corrected to 8 min following DDAVP infusion. She underwent bilateral reduction mammoplasty without hemostatic failure using only DDAVP.

DISCUSSION

Factor VIII:C, factor VIII:vWF, and factor VIII:RCoF all increased in response to DDAVP. Multimeric analysis of factor VIII:von Willebrand factor complex was

TABLE I. Hemostatic Functions Before and After Infusion of Desmopressin Acetate

		Case 1		Case 2		Case 3	
	Normal	Pre-DDAVP	Post-DDAVP	Pre-DDAVP	Post-DDAVP	Pre-DDAVP	Post-DDAVP
Bleeding time, min	⩽9	19	10.5	20	8.5	>20	8
Factor VIII:C, % normal	60–200	100	140	82	140	55	100
Factor VIII:vWF, % normal	60–200	100	130	95	190	60	118
Factor VIII:RCoF, % normal	60–200	80	110	90	155	80	90
Factor VIII:vWF multimeric analysis	Normal	Normal	Increased	Normal	Increased	Normal	Increased
Aggregation %, @ 5 min[a]							
ADP, 3.0 μm	50–100[2]	20[1]	15[1]	12[1]	8[1]	2[1]	14[1]
Epinephrine, 10 μM	50–100[2]	24[1]	13[1]	16[1]	10[1]	8[1]	6[1]
Collagen, 0.2 mg/ml	60–100	65	64	10	17	53	47

[a]A superscript of 1 indicates only a primary wave was seen; a superscript of 2 indicates both a primary and secondary wave were seen.

normal prior to the infusion of DDAVP. Infusion of DDAVP altered the complex by increasing the concentration of all multimeric forms while especially increasing the larger multimeric forms as described in normals by Ruggeri et al [6].

The postulated mechanism of action for DDAVP in mild to moderate hemophilia A and type I von Willebrand's disease is the rapid release of various preformed endogenous moieties of the factor VIII:von Willebrand complex from endothelial cells. Tissue plasminogen activator also appears to be released by DDAVP. Whether this is achieved by direct effect of DDAVP on the endothelium or via an as yet unidentified central nervous sytem second messenger is not established. The mechanism of action of DDAVP in the hemostatic defect of uremia and primary platelet disorders is not clear; however it would appear to be independent of ameliorating any of the known alterations of the known factor VIII:vWF moieties associated with von Willebrand's disease. The possibility of a direct effect on the vessel wall as evidenced by increased platelet adhesion and increased platelet spreading at sites of injury has been noted [7,8]. The failure to normalize or improve platelet aggregation after DDAVP administration concomitant with normalization of the prolonged bleeding time and adequate hemostasis with surgical challenge in these three patients is consistent with the hypothesis. Both Mannucci's and Lusher's [7,8] groups noted no direct correlation between increases in any of the factor VIII:vWF moieties and the effect of DDAVP on platelet function. We do disagree with the statement of Mannucci's group that normal platelet function is required for the action of DDAVP. It is also possible that the supranormal levels of the larger and perhaps more adhesive multimeric forms of factor VIII:vWF complex released by the DDAVP somehow compensate for the decreased platelet function in these patients.

Although plasma levels of plasminogen activator have been shown to be increased by DDAVP administration and there is a theoretical increased production generation of plasmin with subsequent increased hemorrhage, we have not experienced that side effect. We do not administer antifibrinolytic agents at the time of administration of DDAVP.

We conclude that DDAVP has a role in the operative management of patients with primary platelet disorders and these salutary effects appear independent of correcting deficiencies in the factor VIII:vWF complex and platelet function at least as determined by platelet aggregation studies. We completely concur with a recent study in recommending that response to DDAVP infusion be established prior to its therapeutic use on each patient [2].

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