

DDAVP (desmopressin) in the dental management of patients with mild or moderate hemophilia and von Willebrand's disease

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Abstract

Seven mild or moderate hemophilia A and 4 von Willebrand's disease patients were infused with desmopressin (DDAVP), a synthetic analogue of vasopressin, prior to their dental treatment. An assessment of the individual's response to desmopressin was performed initially in all patients using a dose of 0.3 µg/kg intravenously. This procedure resulted in a mean 4.7-fold increase in plasma Factor VIII levels 30–60 min after infusion, an increase sufficient to allow dental treatment to be performed without the use of plasma products. A wide variety of dental procedures were performed after a single infusion of desmopressin per treatment visit without any bleeding episodes. Thus, desmopressin appears to be a useful alternative in the dental management of patients with mild or moderate hemophilia A and von Willebrand's disease without the risks associated with plasma product use.

The advent of suitable blood product Factor concentrates has revolutionized the dental management of patients with congenital bleeding disorders. Many patients previously considered virtually unmanageable without prolonged hospitalization now can be treated in ambulatory dental settings.

Vasoactive drugs such as vasopressin derivatives, catecholamines and insulin have been demonstrated to increase plasma Factor VIII (FVIII) levels, but their side effects involving blood pressure, gastrointestinal, and renal problems has limited their clinical usefulness.^{1, 2} Desmopressin (1-deamino 8 D-arginine vasopressin, DDAVP), is a synthetic analogue of the antidiuretic pituitary hormone vasopressin.

Mannucci et al. were the first to report that desmopressin produced a marked rise in FVIII levels without these side effects. In 1971 they published the results of a clinical trial with desmopressin and showed that it produced a two- to threefold increase in FVIII/VWF levels in hemophilia A and von Willebrand's disease patients.² Subsequent trials in normal and hemophilic subjects by several groups confirmed these results.²⁻¹⁰

The optimal dose of desmopressin appears to be 0.3 µg/kg intravenously.⁸ In several studies surgical procedures ranging from dental extractions and minor oral surgery, to tonsillectomy, cholecystectomy and major surgery were performed on mild and moderate hemophilia patients after infusion with desmopressin.²⁻¹⁰ These references suggest that desmopressin has a role in the dental management of some hemophilic and von Willebrand's disease patients.

Methods and Materials

The study consisted of 7 mild hemophilia A (FVIII 10-24%) and 4 mild (VW FVIII 10-35%) or moderate (VW FVIII 6-10%) von Willebrand's disease patients. These patients either were seen regularly in the University of Connecticut's Comprehensive Hemophilia Care Center or referred by outside practitioners for dental evaluation and treatment.

Because of the experimental nature of desmopressin at the time of the study, subjects who had any complicating health problems were excluded. Institutional Review Board-approved informed consent was obtained from all participants.

Evaluation

Baseline FVIII values were obtained to measure FVIII response to desmopressin prior to dental treatment. The magnitude of variation in individual responses to desmopressin and the time of peak FVIII activity in each individual also were assessed. Blood samples for coagulation studies were obtained by venipuncture at time 0 and at intervals of 30, 60, 180, and 360 min after the infusion of desmopressin. Blood pressure and pulse also were taken at 5, 16, and 30 min.

Each patient received a dose of 0.3 $\mu\text{g}/\text{kg}$ of desmopressin^a in 50 ml of isotonic saline by intravenous infusion over 15 min.

The following coagulation studies were performed: PTT, FVIII procoagulant activity (VIII:C),¹¹ FVIII procoagulant antigen (VIII:Ag),¹² FVIII related antigen (VIII:Ag),¹³ and ristocetin cofactor activity.¹⁴ For von Willebrand's disease patients, bleeding time also was measured.¹⁵ Since this is most relevant to safe dental treatment only procoagulant activity (VIII:C) is reported here. The other coagulant data is reported elsewhere.⁹

Dental Treatment

After baseline coagulation studies were obtained, dental treatment under controlled observation was initiated. In all cases the treatment was begun 30–60 min after infusion of desmopressin. If extractions were performed, the sockets were sutured and collagen hemostat^b was placed where appropriate. Oral E-amino caproic acid^c was given to each patient 1–4 hr prior to dental treatment because of the potential role of desmopressin to increase fibrinolysis.^{4, 5, 16–20} The dose was 24 g/day for adults and 400 mg/kg/day for children in 4 divided doses, continued for 5–7 days postoperatively.

Blood samples for coagulation studies again were performed at 0, 180, and 300 min postinfusion during dental treatment.

Patients were examined after 24 hr for any bleeding and 1 week postoperatively. If continued dental treatment was indicated, it usually was performed at weekly intervals and factor levels were measured at 0, 3, and 5 hr after infusion with desmopressin. E-amino caproic acid was given routinely at the previous dose levels 1–4 hr preoperatively in all subjects and routine dental treatment was performed.

Results

Table 1 shows the results obtained with the 11 patients managed for dental treatment (7 mild hemo-

philia A, 4 mild–moderate von Willebrand's patients). The age of the patients was 7–50 years with baseline FVIII:C levels between 0.08 and 0.28 $\mu\text{g}/\text{ml}$. Following administration of desmopressin, a mean 4.7-fold increase in FVIII:C levels occurred at 30–60 minutes. The range of increase varied from 2.0- to 8.7-fold and the percentage rise did not always correlate directly with the baseline FVIII value since the lowest initial values did not always show the greatest proportionate rise. All types of dental procedures were performed requiring single or multiple visits at least 1 week apart.

FVIII:C levels were consistent with those obtained at initial evaluation for each individual within this time framework. In all 11 subjects, the peak levels obtained were sufficient to perform all types of dental surgery after a single administration per treatment visit. Figure 1 shows the longitudinal time course of FVIII:C values for 24 hr after administration of desmopressin in 4 representative subjects (1, 2, 4, 9). For ease of interpretation the other subjects were excluded from this figure but the curves were similar for all individuals. Satisfactory levels for treatment were still present at 3 hr.

Ristocetin cofactor levels, which are not shown, also were increased after desmopressin infusion in von Willebrand's subjects, but often did not remain as high for longer than 3 hr. PTT values also dropped to baseline levels at 3 hr postinfusion in von Willebrand subjects. No changes in vital signs were noted before or during treatment. Dental procedures included restorative dentistry, deep scaling, endodontics, and single, multiple, or surgical extractions. No postoperative bleeding was experienced in any case. Repeat infusion was not necessary for any single procedure or visit. Extraction sites were not sutured routinely, but for traumatic third molar extractions, sockets were packed with Avitene and sutured. In 2 cases (4, 8), intravenous and/or inhalation sedation also was used to reduce anxiety without complications.

Discussion

Seven patients with mild hemophilia A and 4 patients with mild or moderate von Willebrand's disease were treated with desmopressin before undergoing dental treatment. A wide spectrum of dental procedures was performed. While the baseline values of some subjects were high enough to question the need to increase FVIII levels — particularly where treatment was minor — the safety and efficacy of desmopressin encouraged its use and in turn, decreased any possible risk for bleeding based upon the patient's history. Repeated visits were possible on a weekly basis with no diminution in the response to desmopressin (Table 1).

^a Desmopressin Stimat — Armour Pharmaceutical Co: Kankakee, IL.

^b Avitene — Avicon Inc, Distrib: Fort Worth, TX.

^c Amicar — Lederle Laboratories Div: Pearl River, NY.

TABLE 1. Summary of Dental Patients Managed with Desmopressin (DDAVP)

Diagnosis	Age	Baseline (U/ml)*	Peak (U/ml)*	VIII:C			
				Time of Peak Activity (min)	Relative Increase	Number of Treatment Visits	Dental Procedure
1. Mild Hemophilia A	25	0.18	0.48	30	2.7x	1	Restorative
2. Mild Hemophilia A	10	0.24	0.87	30	3.6x	2	Extractions (caries)
3. Mild Hemophilia A	14	0.14	0.36	30	2.6x	2	Restorative, Extractions
4. Mild Hemophilia A	17	0.20	1.60	30	8.0x	1	3rd Molar Extractions (surgical)
5. Mild Hemophilia A	7	0.20	0.55	30	2.8x	2	Restorative
6. Mild Hemophilia A	28	0.10	0.53	60	8.7x	1	Restorative
7. Mild Hemophilia A	9	0.14	0.38	60	2.7x	1	Restorative
8. von Willebrand	18	0.13	1.08	30	8.3x	2	3rd Molar Extractions (surgical)
9. von Willebrand	39	0.35	1.34	60	3.8x	>4	Endodontics, Restorative
10. von Willebrand	8	0.08	0.54	30	6.7x	1	Canine Extractions (crowding)
11. von Willebrand	50	0.28	0.55	60	2.0x	>5	Restorative, Extractions
				Mean increase	4.7x.		

U = Bethesda units.

The mean half-life of response to desmopressin as measured by VIII:C levels is reported to be 9–10 hr in mild hemophilia A patients while von Willebrand's disease patients and normal subjects return more rapidly to baseline.⁸ Although studies of the half-life of desmopressin were not reported in this paper similar results were obtained in another study.⁹ FVIII levels still were elevated after 5 hr in most cases and returned to baseline values after 24 hr. No bleeding episodes were noted in any of the patients postoperatively and a second infusion of desmopressin was not necessary.

If a second administration of desmopressin is needed, this can be given safely, but there is some reduction in FVIII response in some patients.⁸ In this study, the only untoward response to desmopressin was occasional facial flushing. Significant changes in pulse and blood pressure were not noted during staging or treatment phases.

A recognized complicating effect of desmopressin is the increase of plasminogen activator (t-PA) levels after its administration.^{4, 16-19} The maximum levels of t-PA appear 10-30 min after the infusion and fall off quickly. This increase in t-PA probably increases fibrinolysis.^{4, 16} Therefore, E-amino caproic acid was used consistently in conjunction with treatment in all instances, although for minor procedures it may not have been completely necessary. The antifibrinolytic agent, however, is recommended where a significant clot may be formed e.g., inferior alveolar block anesthesia, deep scaling, and extraction.

The use of intranasal desmopressin in bleeding disorders has been reported in the literature. This method

of administration is quicker and often simpler but requires a tenfold larger dose to achieve the same effect and the response is unpredictable.^{7, 8, 21}

The precise mechanism of action of desmopressin is unknown. Since FVIII levels rise rapidly after desmopressin administration, it may be assumed that it stimulates endogenous release of FVIII from storage sites, possibly the endothelial cell, rather than de novo synthesis.^{2,7,16,19}

Desmopressin should be administered to patients undergoing dental procedures who will benefit clinically from a transient rise in FVIII levels. These patients are:

1. Mild and moderate hemophilia A patients with FVIII levels higher than 5%
2. von Willebrand's disease Type I patients with von Willebrand's FVIII levels between 10–35% (mild) and 4–10% (moderate).

Although little data exists, von Willebrand's disease Type II patients probably are not good candidates for DDAVP use as they have qualitative abnormalities of FVIII:Ag and could be at risk for thrombocytopenia. Further data on this group of patients are needed. In individuals with severe von Willebrand's disease, i.e., with bleeding times greater than 15 min and very low FVIII:Ag, desmopressin is not effective and cryoprecipitate should be used.³ Severe hemophilia A patients or patients with levels of FVIII below 4% sometimes do not respond sufficiently well to benefit from DDAVP and factor concentrates are still recommended where indicated.³ However, further evaluation of the use of desmo-

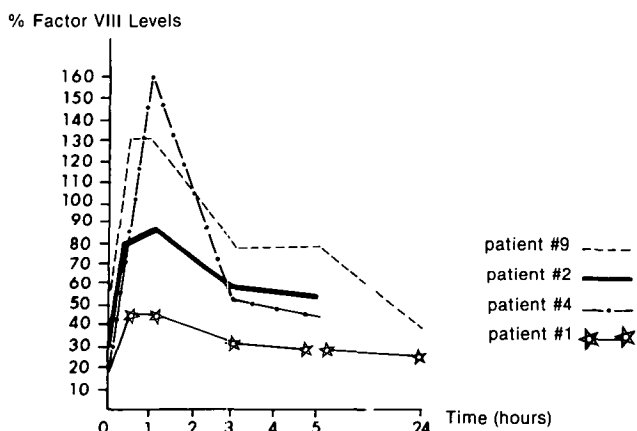


FIG 1. The response with time of 4 representative patients to 0.3 µg/kg of desmopressin (DDAVP) infused intravenously.

pressin in these patients should be performed because variable response in severe hemophilia and von Willebrand's disease patients is common.^{4, 9} Preliminary evidence suggests DDAVP may be of value for nonhemophilic patients with low titer FVIII inhibitor.²²

Despite the above limitations, desmopressin has been shown herein to be a useful drug of substantial value in the dental management of mild or moderate hemophilia A and von Willebrand's disease patients confirming the results in other centers. Its ease of preparation and administration give desmopressin advantages over cryoprecipitate and, by avoiding the use of plasma products, reduces the risk for infusion of blood borne viruses. This is especially true of patients who have no history of the need for blood products but who are at risk to bleed with extensive surgery. An initial evaluation by a hematologist competent to determine the individual's response to desmopressin is essential prior to proceeding with dental treatment. For some individuals, however, this response is quite predictable and subsequent treatment can be performed without risk of bleeding.

Summary and Conclusions

The mean circulating FVIII:C levels were increased by 4.7-fold following administration of desmopressin to 7 mild hemophilia A patients and 4 von Willebrand's disease patients.

FVIII levels which allowed safe dental treatment were reached in 15–60 min in all subjects. A two-stage approach to the patient is recommended: (1) an evaluation to determine the patient's response to 0.3 µg/kg of desmopressin and (2) dental treatment of the individual patient following satisfactory results from the evaluation stage.

The major advantages of desmopressin over plasma

products in these patients are: lowered risk for hepatitis and other viral infections; lower cost; and ease of preparation, administration, and storage.

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Quotable Quote: children of divorce

It has been established from the work of many observers that divorce ushers in an extended period of psychological and social disequilibrium that a great many children and adults find exceedingly stressful. The work of Hetherington, as well as our own, has demonstrated the critical significance of the child's age and developmental stage in governing his initial response in white middle class populations. The greater vulnerability among boys, especially young boys, compared to the relatively rapid recovery among young girls within the observed families has been noted as well. The expected duration of early stress-induced responses and the extent to which these initial responses (reinforced by the many additional changes and stresses that occur within the postdivorce or remarried family) are likely to have a continuing impact on the child's development (whether in the direction of greater enhancement or in the direction of skewing) has not been established; nor has it been demonstrated whether the differences between sexes, namely the greater vulnerability among young boys during the early postdivorce years, can be expected to hold up during later developmental stages.

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