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Desmopressin Stimulation Testing: Response to Intravenous and Intranasal Forms

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Abstract

Introduction—Desmopressin is commonly used to reduce bleeding in patients with mucocutaneous bleeding disorders and is available in both intravenous and intranasal forms. Given the variability in response to desmopressin at an individual level, its effectiveness should be assessed with a test dose prior to being advised for use. At this time, no trial has extensively compared the use of intranasal desmopressin to intravenous desmopressin.

Aims—To determine if both forms of desmopressin are equally effective in yielding a positive response in laboratory assays in pediatric patients with von Willebrand disease or probable von Willebrand disease.

Methods—We evaluated medical record data for 58 patients who underwent desmopressin stimulation testing in our Hematology Clinic during a one year period. Data was collected on demographic information and hematologic laboratory assays prior to desmopressin administration and one hour following desmopressin.

Results—There was an absolute increase in von Willebrand antigen to levels appropriate for hemostasis following both forms of desmopressin, although this increase was significantly greater in the intravenous group compared to the intranasal group. There was also a significant absolute increase in Ristocetin Cofactor and Factor VIII levels following desmopressin in both groups.

Conclusion—Both intravenous and intranasal forms of desmopressin produce a positive response during desmopressin stimulation testing and can be used to identify patients for whom this medication would be effective.

Introduction

von Willebrand Disease (VWD) is the most common inherited disorder of coagulation with an estimated prevalence of up to 1.3%, and it is attributed to the presence of either deficient or defective von Willebrand Factor (VWF) [1, 2]. One of the main modalities of treatment currently available is desmopressin. Desmopressin is a synthetic analog of vasopressin, which acts by stimulating the release of endogenous stores of VWF from Weibel-Palade

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bodies in the vascular endothelium to transiently improve platelet-VWF-vessel interactions [2].

Given the variability in response to desmopressin at an individual level, its effectiveness in those diagnosed with VWD should be assessed with a test dose prior to it being advised for use in the prophylaxis or management of bleeding episodes [2–5]. Optimal dosing regimens for both the intravenous and intranasal forms of this medication are well-published [2]. In children, intravenous desmopressin is prescribed with weight-based dosing. However, this form requires IV access, a treatment center, and a specialized pharmacy to dispense. As a result, it is not a convenient therapy option for a disorder which can be managed largely on an outpatient basis. On the other hand, intranasal desmopressin is administered with much looser dosing guidelines and advantages can include its ease of administration and accessibility for home use. This is also a more expensive form of medication.

There is no current guideline which directs practitioners as to which form of desmopressin is optimal for use in desmopressin stimulation testing. Currently at our institution, the preparation used for stimulation testing is based upon the geographic location of the Hematology clinic appointment. Studies comparing the hemostatic effects of intranasal and intravenous desmopressin in the pediatric population are limited. Our primary goal of this study was to ascertain if intravenous and intranasal desmopressin yield the same rates of positive response of laboratory assays in VWD. Our secondary goal was to identify if any other clinical predictors of response could be identified.

Materials and Methods

Our study population was limited to pediatric patients between 2 and 26 years of age who received care through the Hematology clinic at the Children's Hospital of Pittsburgh of UPMC. All patients carried the diagnosis of von Willebrand Disease (if VWF:Ag <0.3 U/mL or VWF:RCo <0.3 U/mL) or probable von Willebrand Disease (if VWF:Ag 0.3-0.5 U/mL or VWF:RCo 0.3-0.5 U/mL or positive family history and bleeding symptoms consistent with diagnosis). Patients underwent desmopressin stimulation testing from January 01, 2016 through December 31, 2016. At our institution, children who undergo desmopressin stimulation testing at the main hospital campus receive intravenous desmopressin and children undergoing testing at the satellite location receive intranasal desmopressin.

All included patients had baseline laboratory studies drawn by peripheral IV immediately prior to desmopressin administration, which included the following: von Willebrand antigen (VWF:Ag), Ristocetin Cofactor (VWF:RCo), Factor VIII (FVIII:C). Labs were then redrawn one hour following desmopressin administration. All samples were transported (at room temperature) to the on-site phlebotomy lab, where they were promptly centrifuged to separate plasma. Samples remained in the lab for a maximum of two hours prior to being collected by courier. All samples were then brought to the same location, our standardized coagulation laboratory for the area, where assays were run immediately upon receipt. Travel time from the main hospital campus and the satellite location to the coagulation laboratory were approximately 15 minutes and 25 minutes respectively.

Dosing for intravenous desmopressin was 0.3 µg per kilogram, with no maximum dose. Dosing for intranasal desmopressin was 150 µg for weight <50 kilograms or 300 µg for weight >50 kilograms. Eligible patients were identified through the electronic medical record by selecting for patients who had desmopressin ordered through the “Desmopressin Stimulation Testing” powerplan in our electronic medical record. Demographic data collected included patient age, sex, body weight, medications being taken at the time of evaluation, and form and dose of desmopressin administered. Laboratory data collected included baseline levels of the above-described labs as well as one-hour post-test levels.

Demographic data between the intranasal and intravenous desmopressin groups was compared using t-test of means for continuous variables and χ^2 test or Fisher’s Exact Test for binomial data. A 2-tailed independent t-test of means was used to compare the absolute increase in laboratory assays above baseline (pre-test value subtracted from post-test value) and the relative increase in assays above baseline (n-fold above baseline, or post-test value divided by pre-test value). Mixed Effects Models were used to assess whether desmopressin form resulted in differing degrees of response, with random effects parameters to adjust for baseline patient levels. In these models, we further adjusted for potential confounding by age, weight and oral contraceptive use based on prior knowledge. This project was reviewed by the University of Pittsburgh Institutional Review Board and qualified for exemption.

Results

Using our electronic medical record, we initially identified 99 patient encounters. Of these, 58 patient encounters were eligible for inclusion. Reasons for exclusion included duplicate orders, patients who did not present for testing after desmopressin was ordered, patients for whom laboratory data for pre- and post-testing of at least one laboratory assay was not obtained and patients with platelet function defects. Among the 58 patient encounters reviewed, 32 patients underwent testing with intranasal desmopressin and 26 patients underwent testing with intravenous desmopressin. A majority of patients were female and of adolescent age. Hormonal contraceptive use was about twice as prevalent in the intranasal group (34% v. 19%). Overall, though, there was no significant difference between groups in terms of sex, weight, hormonal contraceptive use or hematologic diagnosis (Table 1). The two groups were significantly different in terms of mean age of patients, with patients in the IV group being younger.

We detected a statistically significant difference in the absolute increase of VWF:Ag levels following treatment, with the intravenous group showing an increase of greater magnitude than the intranasal group (1.26 U/mL vs. 0.95 U/mL). There were smaller, but not statistically significant differences, in the absolute increase of VWF:RCo levels (1.08 U/ml vs. 0.96 U/ml) and FVIII:C levels (1.55 U/ml vs. 1.32 U/ml). There were no significant differences between the intranasal and intravenous groups in terms of the relative increase above baseline (Table 2).

Mixed effects models were used to compare the improvement in assays across desmopressin groups, adjusting for differences in baseline factors such as age and oral contraceptive use. Oral contraceptive use, age and weight were not found to have a significant effect on patient

response to desmopressin and do not appear to have a confounding effect on interpreting the difference in test results based on desmopressin form (Table 3).

Discussion

In this study, we found that both intravenous and intranasal desmopressin were effective in producing a response in VWF:Ag, VWF:RCO and FVIII:C levels. The absolute increase between pre-test and post-test values of all of these assays was statistically significant, with only the absolute increase in VWF:Ag being significantly different between the intravenous group and the intranasal group.

When evaluating the response to desmopressin we typically consider a 'positive response' as generating a two-fold or greater increase in von Willebrand antigen, Ristocetin Cofactor or Factor VIII level (also described here as the relative increase in levels). Peak levels occur thirty to ninety minutes after a dose [2]. Therefore, we would expect to identify a responder in most cases by levels drawn at sixty minutes. Both the intravenous and the intranasal desmopressin groups had a mean increase above baseline that was greater than 2-fold for all three laboratory assays, with no significant difference between groups. Although we previously noted the absolute increase in von Willebrand antigen above baseline was of a greater magnitude in the intravenous group, the absolute incremental response produced by desmopressin is not often used to determine whether a patient has responded adequately. It is also unclear if this difference is clinically significant, the mean absolute increase in von Willebrand antigen in the intranasal group was 0.96 U/mL. This would be sufficient to increase von Willebrand antigen to a level appropriate for hemostasis.

Although there was a significant difference between the two groups in terms of mean age of patients, with the IV group consisting of younger patients, the mixed model analysis suggests that age is not strongly associated with test results and therefore does not appear to confound results. Perhaps younger patients were more likely to go undergo testing with IV desmopressin as it was felt they would not tolerate an intranasal form of medication. Mixed model analysis also demonstrates that weight and oral contraceptive use are not strongly associated with test results. While these factors may be important for patient care, they do not seem to necessarily bear any weight in helping clinicians predict which patients will be desmopressin responders. There may be other differentiating factors present which we have not yet identified.

At this time, there is limited information in the literature on the use of intranasal desmopressin in the pediatric population. A large study of both adult and pediatric patients looking at the use of intranasal desmopressin for control of bleeding symptoms found this form of desmopressin to be subjectively effective and was well-tolerated in the majority of patients [6]. However, objective data on response of laboratory parameters was only obtained in a small subset of patients and no comparison to intravenous desmopressin was made. Khair et al [7] also demonstrated that intranasal desmopressin appeared to be effective in a small group of pediatric patients with either hemophilia or von Willebrand disease but did not make a direct comparison to intravenous desmopressin. We did find one study which compared response to intranasal desmopressin with historic response to intravenous

desmopressin within the same small group of pediatric patients [8]. However, to our knowledge, our study is the largest to specifically compare these two forms of desmopressin in the pediatric population.

There are several limitations to our study. We believe that our study population is representative of the local population of patients with von Willebrand disease, as our hospital is a large referral center. However, some patients with suspected von Willebrand disease may have been referred to the regional Hemophilia Treatment Center for evaluation. In addition, the decision of desmopressin form to use for stimulation testing was made based on geographic location rather than in a randomized fashion. We do not believe the above factors substantially affected our results, as the only significant difference in demographic characteristics between groups was in age. Furthermore, all laboratory assays were processed in same lab, which was physically separate from both testing locations. We did have notably fewer male patients in each group, likely attributed to the fact that females are more likely to undergo investigation for a mucocutaneous bleeding disorder in relation to heavy menstrual bleeding. This difference in male subjects was seen equally in both groups. Finally, we noted that both groups had a small set of patients which met laboratory criteria for VWD. For the purposes of this study, we identified patients as having VWD versus probable VWD based upon laboratory values available in our medical record. However, for some of our patients the initial diagnostic testing was completed outside of our hospital system and results were unavailable for review. Laboratory values for Ristocetin Cofactor and von Willebrand antigen are known to fluctuate based upon a variety of factors and it is possible that a larger number of patients met laboratory criteria for VWD.

In summary, this study suggests that both intravenous and intranasal forms of desmopressin may be efficacious for stimulation testing. A shift to using intranasal desmopressin preparations when possible is desirable as it may improve patient experience as well as quality of life, including fewer trips to tertiary care centers and increased personal responsibility for disease management. Directions for future studies would include prospectively evaluating the effect of desmopressin form on effectiveness by utilizing a randomized study design. We would also be interested in learning if both forms of desmopressin are effective in other patient populations for which desmopressin is used, such as patients with hemophilia or certain platelet function defects.

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MM gathered data, analysed data and wrote the paper. NS analysed the data and critiqued the paper. JC designed the study and critiqued the paper. This project was supported in part by the National Institutes of Health through Grant Number UL1-TR-001857.

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Table 1 Demographic characteristics. Statistically significant values in bold ($p < 0.05$)

	Intranasal desmopressin (n=32)	Intravenous desmopressin (n=25)	P value
Sex			0.16
Female	24	15	
Male	8	11	
Age (years)			0.04
Mean (SD)	12.6 $\pm$ 3.8	9.8 $\pm$ 6.0	
Weight (kg)			0.27
Mean (SD)	51.1 $\pm$ 18.8	43.9 $\pm$ 29.7	
Hormonal Contraceptive Use	11	5	0.2
Diagnosis			0.86
von Willebrand Disease	8	6	
Low VWF:Ag, Positive Family History or Symptoms	24	20	

Table 2

Mean absolute increase above baseline and mean relative increase above baseline of VWF:Ag, VWF:RCo and FVIII:C levels after intranasal or intravenous desmopressin administration. N=32 in IN group, N=26 in IV group. Statistically significant values ($p<0.05$) in bold.

	VWF:Ag (U/mL)		VWF RCo (U/mL)		FVIII C (U/mL)	
	IN	IV	IN	IV	IN	IV
Absolute Increase Above Baseline						
Mean (SD)	0.95 (0.56)	1.26 (0.47)	0.96 (0.52)	1.08 (0.53)	1.32 (0.74)	1.55 (0.64)
Range	0.1-2.13	0.46-2.07	0.14-2.13	0.04-2.04	0.09-4.03	0.33-3.39
Relative Increase Above Baseline						
Mean (SD)	2.33 (0.8)	2.5 (0.61)	3 (1.18)	2.85 (0.98)	2.6 (1.16)	2.57 (1.15)
Range	1.2-4.6	1.5-4.1	1.3-5.5	1.1-4.8	0.8-7.7	0.58-7.3

Table 3

Results of Mixed Effects Model, numerical value represents the average change in laboratory assay associated with hormonal contraceptive use or with one unit increase in age or weight. Standard error in parenthesis. No values were statistically significant ($p < 0.05$).

	VWF:Ag (U/mL)	VWF:RGo (U/mL)	FVIIIc (U/mL)
N	58	58	58
Hormonal Contraceptive Use	−0.046 (0.131)	0.122 (0.126)	0.131 (0.136)
Age (years)	0.004 (0.025)	0.005 (0.024)	0.021 (0.026)
Weight (kilograms)	0.002 (0.005)	−0.003 (0.005)	−0.002 (0.005)