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Low-Dose Intranasal Desmopressin (DDAVP) for Uremic Bleeding

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Dear Sir,

In children with advanced chronic renal failure, bleeding is a frequent complication which contributes to morbidity and even mortality. In the last decade, desmopressin (1-deamino-8-*D*-arginine vasopressin; DDAVP), a synthetic analogue of antidiuretic hormone, has been used to treat uremic bleeding. The exact mechanism by which DDAVP corrects uremic bleeding is still not clear; DDAVP-induced release of large von Willebrand factor (vWF) multimers or release of serotonin from uremic platelets has been among the suggested mechanisms [1, 2]. Although DDAVP has usually been administered parenterally in uremic patients, this route of application requires a physician and is not very feasible for children. Intranasal DDAVP at high doses has also been put into use in uremic patients [3].

In the presented study, we have examined the effect of low-dose (10 and 20 μg) intranasal DDAVP (Minirin) on bleeding time, factor VIII procoagulant activity (FVIII:C), vWF, protein C (PC) activity, plasminogen activator inhibitor-3 (PAI-3), α_1-antitrypsin and thrombomodulin in our uremic children on maintenance hemodialysis. We have thus attempted to investigate the mode of action of low-dose intranasal DDAVP and clarify its action in potentiating hemostasis. The patient group consisted of 11 children hemodialyzed thrice weekly with cuprophane membranes. The age range was 12–21 years (median 16). Six of them had clinical signs of bleeding diathesis in the form of dysmenorrhea, or oral or nasal/nasopharyngeal bleeding and/or gastrointestinal bleeding, or in the form of spontaneous ecchymotic skin lesions. DDAVP was administered intranasally at a dose of 10 μg at the first phase of the study (44 h after the termination of the previous dialysis session). At the second phase of the study, 2 days later, 20 μg DDAVP was given by the same route. In only 1 patient (No. 2), who developed heparin-induced thrombocytopenia, a third dose of DDAVP was administered intravenously (0.3 $\mu g \cdot kg^{-1}$).

Table 1. Effect of low-dose DDAVP

		Dose of DDAVP		Time effect
		10 μg	20 μg	
Bleeding time, min	Before DDAVP	8.2 ± 4.8	8.3 ± 4.6	p = 0.0002
	After DDAVP	7.1 ± 4.8	6.9 ± 4.7	
	Dose effect: p = 0.49			
PC, %	Before DDAVP	73 ± 26	71 ± 21	p = 0.20
	After DDAVP	67 ± 22	70 ± 18	
	Dose effect: p = 0.83			
PAI-3, %	Before DDAVP	89 ± 26	91 ± 18	p = 0.90
	After DDAVP	90 ± 26	89 ± 21	
	Dose effect: p = 0.82			
α_1-Antitrypsin, $mg \cdot dl^{-1}$	Before DDAVP	159 ± 33	162 ± 28	p = 0.50
	After DDAVP	166 ± 46	165 ± 30	
	Dose effect: p = 0.94			

Ivy bleeding times were measured before and 2 h after DDAVP administration by a medical person who was blinded to the aim of the procedure and the medications given to the study subjects. Statistical analysis was performed by repeated measures two-way analysis of variance. In this analysis, time (before vs. after) and dose (10 vs. 20 μg) effects as within-subjects factors and also time-dose interaction were included in the model. A statistical package for social sciences (SPSS) for Windows v5.1 software was used.

In the 6 patients with bleeding diathesis, a clinical response was achieved: the abnormal bleeding subsided within 1–3 days in all and did not recur during the 2 weeks of treatment with DDAVP 20 μg daily. Mean bleeding time shortened from 8.2 ± 4.8 to 7.1 ± 4.8 min at the first stage (10 μg DDAVP) and from 8.3 ± 4.6 to 6.9 ± 4.7 min at the second stage (20 μg DDAVP; dose effect, p = 0.49; time effect, p = 0.0002; time-dose interaction, p = 0.33; table 1). The number of

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patients with bleeding time values longer than 8 min was 5 before and 3 after DDAVP administration (both 10 and 20 μg). After the first part of the study, 5 of the patients who had recurrent bleeding in the form of mild nasal/nasopharyngeal bleeding and spontaneous ecchymotic skin lesions subsequently received placebo by the same route at a dose of 20 μg. The children were blind regarding the nature of the medication and thus served as controls for themselves. The bleeding of these patients continued during the 1-week placebo treatment. Mean bleeding time values before and after placebo were 9.4 ± 3.4 and 9.2 ± 3.4 min, respectively ($p = 0.42$).

There was an increase in FVIII activity and decrease in the PC activity in patient No. 2 with heparin-induced thrombocytopenia when DDAVP was administered intravenously.

In this study, we have not been able to show any significant changes along the PC pathway at low doses of intranasal desmopressin. It does not seem possible to explain the beneficial effect of DDAVP on a placebo basis since all patients with bleeding benefited from the drug. The 5 patients who subsequently received placebo – and served as controls of themselves – did not respond clinically. Furthermore, their bleeding times, measured by a blinded person, did not shorten with placebo. Since DDAVP is known to increase platelet serotonin uptake and ATP release [2], it may be affecting platelet function, which is disordered in uremia, or other pathways may be operative at the low doses used in this study.

DDAVP is an accepted form of treatment in uremic bleeding. Mannucci et al. [1] have suggested that the appearance of larger forms of the FVIII:vWF complex, induced by DDAVP, or the release of vWF from storage sites, may be effective in promoting platelet adhesion to endothelium. DDAVP is expected to reduce PC activity which is a potent anticoagulant and this might contribute to the normalization of bleeding tendency in uremic patients and even in healthy subjects [4, 5]. Since the levels of well-known inhibitors of PC, PAI-3 and α_1-antitrypsin, did not change after DDAVP infusion, it has been suggested that the decrease in PC was not linked to the inhibitors per se [4]. There was no change in these inhibitors in our study as well.

A number of side effects are conceivable with the traditional high doses of DDAVP. The increased risk of thrombosis and accelerated atherosclerosis in uremia may be regarded as a drawback for the use of DDAVP at conventional doses [6]. Furthermore, it has been shown that children are at risk of developing severe hyponatremia after repeated infusions of DDAVP [7]. No complications of therapy were noted in any of the patients in this study.

The aforementioned increased risks of thrombosis as well as its cost are limiting factors for the use of DDAVP at high doses. Intranasal administration of 20 μg DDAVP may be an effective form of treatment in bleeding diathesis of uremic children, and it may prove successful in prophylaxis for surgical and dental procedures. Whether this dose is sufficient for more severe bleeding disorders awaits further dose-lowering studies.

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