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Subcutaneous Desmopressin (DDAVP) Shortens the Bleeding Time in Uremia

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The intravenous infusion of 1-deamino-8-D-arginine vasopressin (DDAVP) is used as a nontransfusional form of treatment in patients with congenital and acquired bleeding disorders, including patients with uremia associated with prolonged bleeding times. Since uremic patients experience minor bleeding episodes that might be self-managed at home (particularly epistaxis, gingival bleeding, and menorrhagia), we carried out a double-blind, placebo-controlled crossover study in nine uremics to evaluate whether the prolonged bleeding times could be shortened by subcutaneous injections of DDAVP. One hour after administration, the bleeding time was significantly shortened ($P < .01$) and became normal in seven of nine patients. After 4 hr, the bleeding time was still shorter than baseline ($P < .01$), but in only three patients was it still normal. There was no significant bleeding time change after placebo. When the same patients were treated with the same dose of DDAVP infused intravenously, the bleeding times were not significantly different from those measured after subcutaneous administration. Hence, subcutaneous DDAVP is an alternative method for short-term shortening of the bleeding time in uremia, at least as effective as intravenous DDAVP but with the possibility of self-administration by the patients at home.

Key words: von Willebrand factor

INTRODUCTION

The intravenous infusion of desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP), a synthetic analog of the antidiuretic hormone L-arginine vasopressin, shortens the prolonged skin bleeding times in patients with uremia (for review, see [1]). Since the prolonged bleeding time is considered the best laboratory hallmark of the bleeding tendency in uremia [2], DDAVP has been given to patients with acute and chronic renal failure to prevent bleeding before invasive procedures (biopsies and major surgery) or to stop spontaneous bleeding, with apparently good clinical results [1]. DDAVP has few side effects (mild facial flushing and headache, a 10–20% increase in pulse rate, and minor falls in mean blood pressure) [3]. Problems with fluid overload related to the antidiuretic effect of the drug have not developed so far in uremic patients [1].

For its capacity to increase factor VIII and von Willebrand factor (VWF), DDAVP has also been used as a nontransfusional form of replacement therapy in patients with congenital and acquired factor deficiencies (classic hemophilia, von Willebrand disease) [1]. In these patients, subcutaneous injections of DDAVP are at least as effective as intravenous infusions in stopping bleeding and perhaps of more practical usefulness clinically as a self-administered emergency aid [4,5]. Since uremic patients experience minor bleeding episodes that might be self-managed at home (particularly epistaxis, gingival bleeding, and menorrhagia), we carried out a double-blind, placebo-controlled crossover study to evaluate whether subcutaneous DDAVP shortened the prolonged bleeding time in nine patients with uremia. We subsequently treated the same patients with intravenous DDAVP in an open fashion to evaluate whether there

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TABLE I. Clinical and Laboratory Data in Nine Patients With Uremia and Bleeding Tendency

Patients' initials	Sex / age	Serum creatinine (μmol/liter)	Hematocrit (%)	Bleeding time (min)	Diagnosis	History of bleeding
PP	M / 28	884	20	15	Chronic glomerulonephritis	Epistaxis
VG	F / 53	973	24	11	Polycystic kidney	Gingival bleeding
MV	M / 55	1,150	23	14	Chronic glomerulonephritis	Epistaxis
ML	M / 63	1,061	22	19	Interestitial nephritis	Epistaxis
PM	M / 51	1,061	24	15	Polycystic kidney	Gingival bleeding
BE	F / 35	884	19	17	Chronic pyelonephritis	Epistaxis
MF	M / 73	1,238	18	15	Chronic glomerulonephritis	Epistaxis
CC	F / 63	1,061	21	12	Chronic glomerulonephritis	Gingival bleeding
MA	M / 35	1,150	20	18	Chronic pyelonephritis	Epistaxis

were differences in bleeding time responses between intravenous and subcutaneous DDAVP.

PATIENTS AND METHODS

Comparison of Subcutaneous DDAVP and Placebo

Nine patients (six males, three females, age range 28–73 years) with uremia due to various renal diseases with recent history of mild but recurring bleeding symptoms and skin bleeding times longer than 10 min (Table I) were fully informed of the aims and procedures involved in the experimental study, which was performed according to the Declaration of Helsinki as amended in Venice in 1983. The study was performed double blind and placebo-controlled with a crossover design. Each patient was studied twice, at least 2 weeks apart, when they received subcutaneous injections into the abdominal wall of either DDAVP (0.3 μg/kg from 1 ml ampoules containing 15 μg/ml) or identical placebo (both supplied by Ferring AB, Malmo, Sweden). The same nine patients were studied again, at least 2 weeks after the second subcutaneous injection, when they received in an open fashion 0.3 μg/kg DDAVP given by intravenous infusion in 50 ml saline over 30 min. This additional study was done before breaking the code and before the results of the controlled study were available.

Blood Collection and Bleeding Times

Blood samples were collected by venipuncture (19-gauge needles) before administration of DDAVP and then 1 hr after the intravenous infusion or subcutaneous injection was started. Citrated platelet-poor plasma (9 parts blood and 1 part 0.13 mmol/liter trisodium citrate solution) was obtained after centrifugation at 2,000*g* for 10 min and immediately frozen and stored at −70°C until assayed within 1 month. The skin bleeding times were carried out at the same time intervals as well as at 4 hr postadministration by the same investigator (G.L.V.) on the volar part of the forearm using two horizontal incisions, and the results were averaged.

Assay Methods

VWF antigen was assayed by the Laurell method [6], using a commercial rabbit anti-human VWF antiserum (Istituto Behring, Scopitto, Italy) as published [7]. The bleeding time was carried out using a commercial template method (Simplate II, General Diagnostics, Milan, Italy).

Data Analysis and Statistical Methods

The results were expressed as mean ± SD. One-way analysis of variance and Duncan's test for multiple comparisons were used to compare treatment groups. Linear regression analysis was also carried out.

RESULTS

Comparison of Subcutaneous DDAVP and Placebo (Table II)

There was no significant difference between DDAVP and placebo for mean baseline bleeding times. One hour after DDAVP, the mean bleeding time shortened significantly ($P < .01$), whereas it remained unchanged after placebo. The bleeding time become normal (i.e., in our laboratory, 7 min or less) in seven of nine patients (77%) treated with DDAVP, but in none of those treated with placebo. Four hours after DDAVP, the mean bleeding time was still significantly less than baseline ($P < .01$), but in only three of nine patients (33%) were bleeding times 7 min or less. The VWF antigen levels, measured before and 1 hr after injection, increased significantly after DDAVP ($P < .01$), but did not change after placebo (Fig. 1).

Comparison of Subcutaneous and Intravenous DDAVP (Table II)

There was no significant difference between intravenous and subcutaneous DDAVP for baseline bleeding

TABLE II. Bleeding Times (in Minutes) Before and After Subcutaneous DDAVP, Subcutaneous Placebo, and Intravenous DDAVP in Nine Patients With Uremia

Patients' initials	Subcutaneous DDAVP			Subcutaneous placebo			Intravenous DDAVP		
		After			After			After	
	Before	1 hr	4 hr	Before	1 hr	4 hr	Before	1 hr	4 hr
PP	13	*4*	9	15	12	12	15	8	9
VG	11	*5.5*	4	11	10	9	10	*4*	5
MV	14	8	9	14	11	12	12	10	10
ML	19	11	12	18	16	16	15	9	10
PM	15	*7*	10	14	12	12	16	*7*	8
BE	17	*5*	8	17	14	16	13	10	10
MF	15	*7*	*7*	14	11	11	14	*7*	6
CC	11	*4*	5	12	11	12	10	*5*	7
MA	19	*6*	9	18	16	17	17	8	10
Mean (± SD)	14.8 (3.0)	6.4* (2.2)	8.1* (2.5)	14.8 (2.5)	13.1 (2.7)	13.0 (2.7)	13.6 (2.5)	7.6* (2.1)	8.3* (1.9)

*$P < .01$ vs. before (baseline) mean values. Bleeding time values within the normal range (7 min or less) are in italics.

times. One and four hours after intravenous DDAVP, the bleeding times shortened significantly from baseline ($P < .01$), with no significant difference from the corresponding bleeding times obtained after subcutaneous DDAVP. At 1 hr, the bleeding times became normal in fewer patients after intravenous than after subcutaneous DDAVP (4/9 vs. 7/9), although this difference was lost at 4 hr (3/9 for both).

The VWF antigen levels increased significantly after intravenous DDAVP ($P < .01$), with no significant difference from the levels obtained after subcutaneous DDAVP (Fig. 1). A significant negative correlation was found between bleeding times and VWF antigen levels when values obtained before and 1 hr after DDAVP (both intravenous and subcutaneous) were pooled together ($r = .57$, $P < .001$) (Fig. 2).

Side Effects

Three patients had facial flushing after intravenous DDAVP, but none did after subcutaneous DDAVP and placebo. There was no significant difference in pulse rate and mean blood pressure among the three treatment groups.

DISCUSSION

This double-blind, placebo-controlled, crossover study clearly shows that DDAVP given subcutaneously at a dose of 0.3 μg/kg is effective in shortening or normalizing the prolonged bleeding times that occur in patients with uremia. Bleeding times shortened in all patients and became normal in about 75% of them. The shortening effect was maximal after 1 hr, but was still statistically significant after 4 hr. This pattern of results after subcutaneous DDAVP is similar to that observed after giving the same dose of intravenous DDAVP in a study carried out with a similar design [8]. Yet, in an attempt to compare more directly the bleeding time responses to subcutaneous and intravenous DDAVP, we chose to give intravenous DDAVP (0.3 μg/kg) to the same nine patients with uremia involved in the study of subcutaneous DDAVP. Patients were treated in an open fashion to avoid a fourth treatment with intravenous placebo and the associated skin bleeding times. This study design is obviously not ideal for avoiding investigator bias in performing the bleeding time. On the other hand, intravenous DDAVP was given before the code of the study of subcutaneous DDAVP was broken; therefore, the investigator was unaware of whether subcutaneous DDAVP was effective in shortening the bleeding times or to what extent shortening occurred. Our results show that subcutaneous DDAVP is at least as effective as intravenous DDAVP in shortening the bleeding time (with no more side effects) and that the time of maximal shortening after starting infusion or injection, as well as the duration of shortening, do not differ significantly between subcutaneous and intravenous DDAVP. These findings are consistent with recent observations that the bioavailability of subcutaneous DDAVP is similar to that of intravenous DDAVP because a very high proportion of the drug is absorbed [9].

The mechanisms involved in the shortening of the bleeding time induced by DDAVP are not known. VWF plasma levels are important determinants of platelet adhesion to the subendothelium because patients with VWF deficiency or dysfunction (congenital and acquired von Willebrand disease) have prolonged bleeding times. Although baseline VWF levels are normal or elevated in

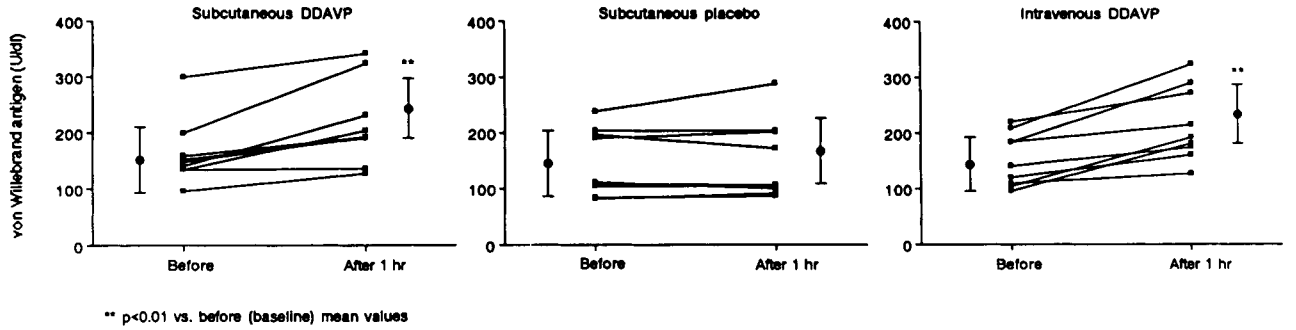

Fig. 1. VWF antigen (in U/dl) before and after subcutaneous DDAVP, subcutaneous placebo, and intravenous DDAVP in nine patients with uremia.

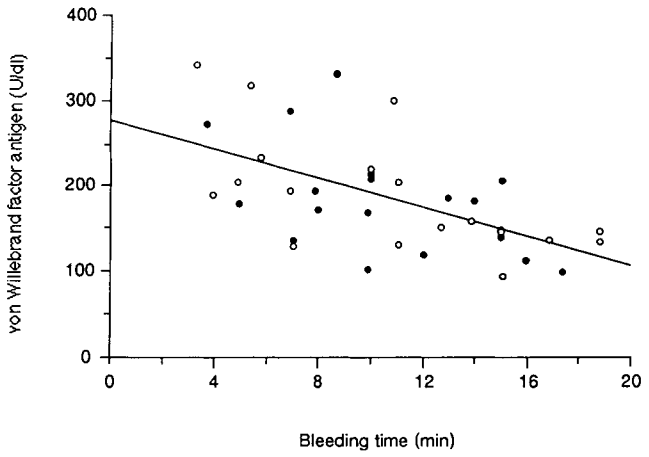

Fig. 2. Correlation between bleeding time and VWF antigen in patients with uremia before and 1 hr after subcutaneous (○) and intravenous (●) DDAVP.

patients with uremia, further elevations induced by DDAVP might enhance platelet adhesion and contribute to bleeding time shortening. This hypothesis is supported by our finding of a significant negative correlation between bleeding time and VWF levels after both subcutaneous and intravenous DDAVP (Fig. 2).

In conclusion, subcutaneous injections of DDAVP are an alternative method for short-term shortening of the bleeding time in uremics. This mode of administration might be used to treat bleeding episodes in patients with uremia, with the advantage of self-administration by the patient at home. Controlled clinical trials, however, are needed to establish firmly the clinical efficacy of DDAVP (by either route of administration) in uremic bleeding.

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