

Controlled Trial of Desmopressin in Liver Cirrhosis and Other Conditions Associated With a Prolonged Bleeding Time

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The synthetic vasopressin derivative desmopressin (DDAVP) shortens a prolonged bleeding time (BT) in patients with uremia, congenital platelet dysfunction, and von Willebrand disease. To establish the limits of the clinical usefulness of DDAVP, a controlled randomized study was carried out in 53 patients and ten volunteers with different conditions that have in common a prolonged BT. DDAVP significantly shortened the BT in 21 cirrhotics ($P < .01$), in eight patients with unclassified prolonged BT ($P < .05$) and in ten volunteers taking the antiplatelet drugs aspirin ($P < .05$) and ticlopidine. The BT changes

were not statistically significant in 15 patients with severe thrombocytopenia nor in nine with congenital platelet dysfunction, even though a few patients with storage pool deficiency responded with a marked BT shortening. Our findings indicate that DDAVP might be given when biopsies or other surgical procedures must be carried out in patients with prolonged BT. However, the compound is often ineffective in patients with thrombocytopenia or congenital platelet dysfunction.

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RECENT STUDIES have shown that the synthetic vasopressin derivative desmopressin (DDAVP) shortens the prolonged bleeding times (BT) associated with a variety of clinical disorders of primary hemostasis.¹⁻⁴ In von Willebrand disease, the most common congenital cause of prolonged BT, the effectiveness of DDAVP is clearly explained by the fact that the prolonged BT is due to low or abnormal plasma von Willebrand factor (vWF), the most important determinant of platelet adhesion to the damaged vessel wall.⁵ By releasing autologous vWF from storage sites (possibly the endothelial cells), DDAVP transiently normalizes vWF levels and shortens the BT, at least in patients with vWF that is functionally normal.¹ However, DDAVP also shortens the BT in such conditions as uremia^{2,3} and congenital and acquired platelet dysfunctions,⁴ in which no quantitative or qualitative vWF abnormality has been convincingly demonstrated. These observations, together with a recent *in vitro* study demonstrating a local hemostatic effect of the drug on the vessel wall,⁶ led us to postulate that DDAVP might have broader clinical usefulness as a primary hemostatic agent in patients with prolonged BT due to causes other than low or dysfunctional vWF. To establish the limits of the clinical usefulness of DDAVP, we have carried out a controlled study in 53 patients with different clinical conditions that have a prolonged BT in common, and in ten volunteers taking the antiplatelet drugs aspirin or ticlopidine.

MATERIALS AND METHODS

Patients. Fifty-three patients (25 men and 28 women, with a median age of 37 years; range, 15 to 65) seen at the A. Bianchi

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Bonomi Hemophilia and Thrombosis Center in Milan, Italy, or at the Department of Hematology in Salamanca, Spain, were admitted to the study on the basis of a BT of ten minutes or longer when measured before the first experimental treatment (see below). Even though the upper normal BT limit is seven minutes at both centers, an admission limit of ten minutes was chosen because we consider this value to be the clinical threshold between normal and abnormal hemostasis. Of the 53 patients admitted to the study, 21 had alcoholic or postnecrotic liver cirrhosis, diagnosed by liver tests and biopsy. Their platelet counts were normal or moderately low (median, $106 \times 10^9/L$; range, 45 to 286). Fifteen patients had severe thrombocytopenia (median platelet count, $13 \times 10^9/L$; range, 1 to 53), due to increased platelet destruction by autoantibodies in five cases and due to decreased bone marrow production in ten cases (seven had aplasia, one familial thrombocytopenia, one myeloma, one chronic lymphocytic leukemia). Nine patients belonging to different kindreds had congenital platelet dysfunction, diagnosed as delta storage pool deficiency in seven and Glanzmann thrombasthenia in two cases, according to previously described criteria.^{7,8} Finally, eight patients had prolonged BT associated with lifelong histories of bleeding but with normal platelet counts, no laboratory evidence of von Willebrand's disease, no defect in platelet aggregation or secretion, no storage pool deficiency, nor any underlying condition known to be associated with a prolonged BT. These unexplained prolonged BT might be due to vascular defects or to as yet unidentified platelet dysfunctions. We have called this patient group "unclassified prolonged BT." None of the patients had taken aspirin or other drugs that affect platelet behavior for at least ten days before the study.

We also studied six volunteers who had borderline or slightly prolonged BT due to the ingestion of 500 mg aspirin two hours before the study, and four volunteers who had very prolonged BT because they had taken a daily dose (500 mg) of the antiplatelet drug ticlopidine for six days before the study. Ticlopidine is a potent antiplatelet agent, available in Europe and presently under clinical trials in the United States and in Canada, which markedly prolongs the BT through a presently unknown mechanism.⁹ All the patients and volunteers were aware of the nature and the purpose of the study, and all gave informed consent according to the Declaration of Helsinki.

Design of the study. Patients and volunteers were randomly assigned to a single infusion of DDAVP (Valeas, Milan, Italy) or of saline, and each of them was crossed over from one treatment to the other after 20 days. After a rest period of at least 30 minutes, $0.3 \mu\text{g}$ of DDAVP per kilogram body weight was added to 50 mL of physiological saline and infused over a period of 30 minutes; physiological saline alone was infused in the same way. The study

could not be performed on a double-blind basis because DDAVP infusion can be detected by an accompanying mild facial flushing.

Blood samples were collected and plasma prepared as previously described.¹

Laboratory methods. The tests were performed in Milan and Salamanca with the same reagents, methods, and standards, except that vWF multimeric analysis was done in Milan on plasma samples kept frozen at -70°C and transported in dry ice. All tests were carried out on blood drawn before the infusion of DDAVP or saline (time 0), immediately after the infusion (time 30), and four hours after the infusion had been started (time 240).

Bleeding times were obtained with the Simplate II device (General Diagnostics, Milan, Italy). Results were expressed as the average BT from the two vertical incisions. In both laboratories, the range of normal with this method was three to seven minutes. Platelets were counted by phase-contrast microscopy. The prothrombin time (PT) was determined by using the Manchester Comparative Reagent (overseas version, Laboratori Baldacci, Pisa, Italy), and the activated partial thromboplastin time (APTT), with a commercial reagent (Automated PTT, General Diagnostics). Values of both the coagulation screening tests were expressed as ratios of patient to pooled normal plasma (obtained from 15 healthy women and 15 healthy men). Factor VIII (FVIII) was assayed by a one-stage clotting method based on the APTT.^{1,3} vWF antigen (vWF:Ag) was assayed by quantitative immunoelectrophoresis, using a commercial monospecific antiserum (Istituto Behring, Scipitto, Aquila).^{1,3} Ristocetin cofactor (RiCof) was assayed with formalin-fixed platelets.^{1,3} FVIII, vWF:Ag, and RiCof were expressed in units per deciliter, with reference to pooled normal plasma calibrated against the First International Plasma Standard for Factor VIII-related Activities (National Institute for Biological Standards, London). vWF multimers were analyzed by agarose electrophoresis in the presence of sodium dodecyl sulfate (SDS), as previously described.¹

Statistical analysis. The BT values were not normally distributed, and there were BT that did not stop after 30 minutes and were recorded as longer than 30 minutes. Hence BT values before and after DDAVP or placebo were expressed as medians and ranges. The other measurements were normally distributed, and thus were expressed as means \pm SD. Correlation coefficients were calculated

either by the Spearman *rho* test or as linear correlation coefficients (*r*).

RESULTS

An overall picture of the BT (given as medians and ranges) before and after DDAVP or saline in the patient and volunteer groups is given in Table 1. The two median BT obtained before either treatment (time 0) did not differ significantly in any of the groups.

In patients with liver cirrhosis, the prolongation of the baseline BT was unrelated to the platelet count (Fig 1) (no platelet function tests were performed). At 30 and 240 minutes after DDAVP, the median BT was significantly shorter than at time 0 ($P < .01$, Table 1). In nine of 21 patients at time 30 and in two at time 240, the BT had become shorter than ten minutes, the limit for admission to the study. Responses or non-responses to DDAVP occurred irrespective of the baseline platelet count. After saline, the median BT had not changed significantly at time 30 and at time 240 (Table 1). The BT shortened to less than ten minutes in two patients at time 30 and in five at time 240 (Fig 1). In patients with unclassified prolonged BT, the median BT became significantly shorter after DDAVP ($P < .05$ Table 1); in four of eight patients BT became shorter than ten minutes at time 30 and in three at time 240, but in none after saline (Fig 2).

In patients with thrombocytopenia, there was no significant change in the BT after either saline or DDAVP (Table 1), and the BT was shortened to less than ten minutes in only one case after saline. In the two patients with Glanzmann thrombasthenia, the baseline BT was longer than 30 minutes and remained so at all times after DDAVP or saline. In the seven patients with congenital storage pool deficiency, the median BT did not significantly change after DDAVP or saline (Table 1). After DDAVP, the BT became shorter than ten minutes in two patients at time 30 and in one at time 240, but in none after saline (Fig 3).

Table 1. Bleeding Times Before and After DDAVP or Saline Infusion in Patients With Prolonged Bleeding Times

Group	DDAVP			Saline		
	Time 0 (Before Infusion)	Time 30 (30 min After Infusion)	Time 240 (4 h After Infusion)	Time 0 (Before Infusion)	Time 30 (30 min After Infusion)	Time 240 (4 h After Infusion)
Liver cirrhosis (n = 21)	16 (10-30)	12** (6-20)	13** (5-22)	15 (9-30)	14 (8-25)	14 (7-29)
Thrombocytopenia (n = 15)	>30 (17->30)	>30 (12->30)	>30 (11->30)	>30 (12->30)	>30 (10->30)	>30 (8->30)
Storage pool deficiency (n = 7)	19 (11->30)	11 (7->30)	24 (8->30)	25 (11->30)	30 (10->30)	24 (11->30)
Unclassified prolonged bleeding time (n = 8)	17 (10->30)	11* (7->30)	12* (7->30)	16 (10->30)	16 (10->30)	15 (10->30)
Aspirin takers (n = 6)	8 (7-10)	6** (5-8)	6** (5-7)	8 (7-9)	7 (5-9)	8 (7-10)
Ticlopidine takers (n = 4)	24 (14->30)	8 (6-9)	19 (9-19)	13 (12->30)	17 (14-21)	15 (11-22)

Figures indicate median values and, in parentheses, ranges. Asterisks indicate significance of difference between post-DDAVP or -saline values and baseline values (* $P < .05$, ** $P < .01$). Significance was not evaluated for the ticlopidine group because of the small number of patients.

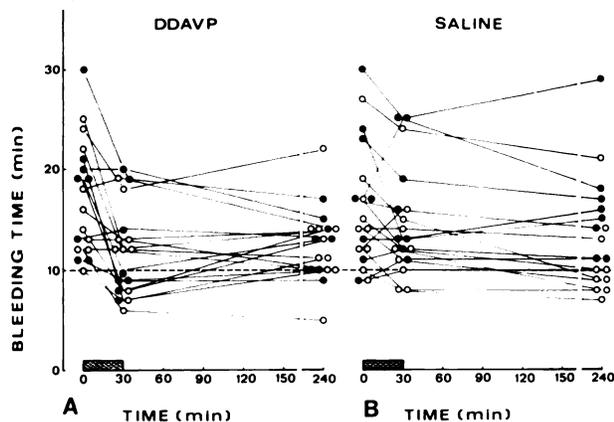


Fig 1. Changes in bleeding times before (time 0), immediately after (time 30), and 4 hours after (time 240) infusion of DDAVP (left panel) or saline (right panel) in 21 patients with liver cirrhosis. Patients with baseline platelet counts higher than $100 \times 10^9/L$ are indicated by open circles; patients with platelet counts lower than $100 \times 10^9/L$, by solid circles. The dashed horizontal line indicates a bleeding time of 10 minutes, the value for admission to the trial.

In the six volunteers who took aspirin the median BT was significantly shortened at times 30 and 240 after DDAVP ($P < 0.05$) but not after saline (Table 1 and Fig 4). Facial flushing occurred in all cases after DDAVP, whether or not they had taken aspirin. In all four volunteers who took ticlopidine, whose baseline BT were longer than those taking aspirin (Fig 4), the BT had shortened to less than ten minutes at time 30 after DDAVP but had returned to the prolonged values in three at time 240. At no time after saline did the BT shorten to ten minutes or less. Flushing occurred in all cases after DDAVP, whether or not they had taken ticlopidine. These data were not statistically analyzed because of the small number of patients.

After DDAVP or saline, all measurements other than the BT behaved in the same way in each patient or volunteer group. Hence the values for all groups were pooled and analyzed together (Table 2). After DDAVP, there were significant increases in FVIII, vWF:Ag, RiCof ($P < .001$) at

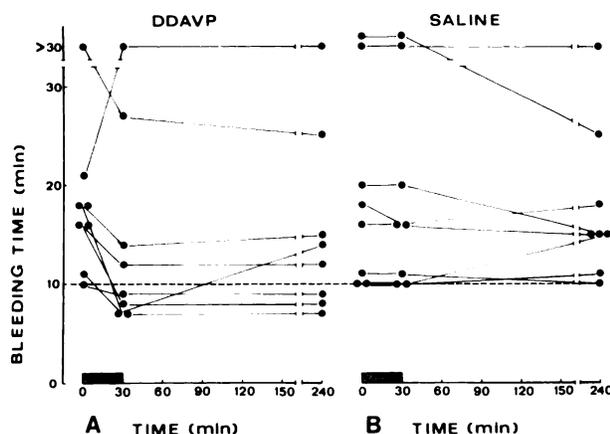


Fig 2. Changes in bleeding times in eight patients with unclassified prolonged bleeding time.

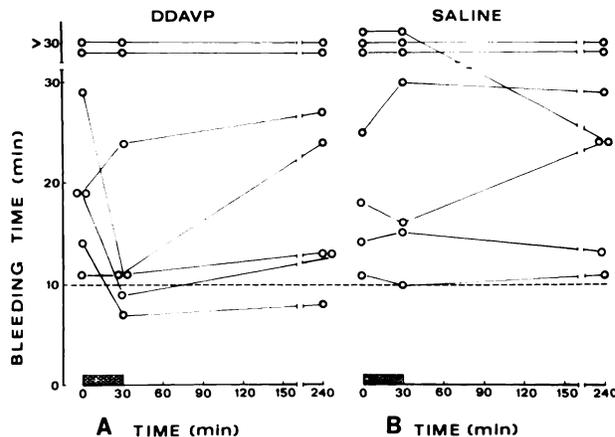


Fig 3. Changes in bleeding times in seven patients with delta storage pool deficiency.

times 30 and 240; shortening of the APTT, expressed by a lower ratio ($P < .001$), at times 30 and 240; slight prolongation of the PT expressed by a higher ratio ($P < .01$) at times 30 and 240; and no significant change in the platelet counts. No significant change in any of these was seen after saline. Correlations between the DDAVP-induced changes (differences between pretreatment and posttreatment values) in BT and in other measurements were calculated both for each patient group and for all the groups considered as a whole. No significant correlations were found (data not shown).

The multimeric structure of vWF before and after DDAVP was studied in at least two patients in each group, comparing, when available, one patient in whom the BT became shorter than ten minutes and another in whom it did not. Before DDAVP, the multimeric structure in the patients' plasma was no different from that observed in normal plasma. After DDAVP, larger vWF multimers than those present in pretreatment plasma appeared at time 30 in all patients, whether or not the BT became shorter (Fig 5). There were no changes in the multimeric structure when the patients were treated with saline.

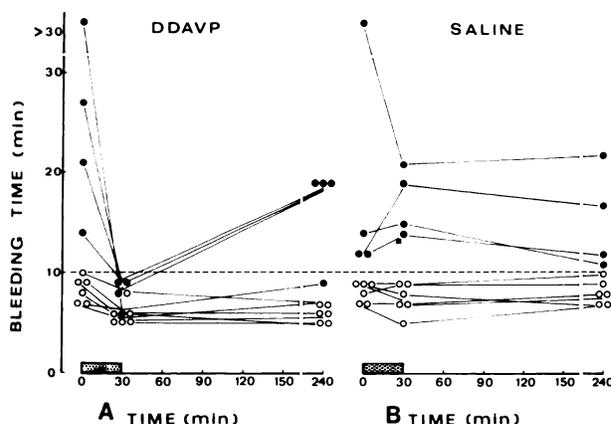


Fig 4. Changes in bleeding times in six volunteers taking 500 mg aspirin (open circles) and in four volunteers taking 500 mg ticlopidine (solid circles).

Table 2. Laboratory Measurements Before and After DDAVP or Saline Infusion

	DDAVP			Saline		
	Time 0 (Before Infusion)	Time 30 (30 min After Infusion)	Time 240 (4 h After Infusion)	Time 0 (Before Infusion)	Time 30 (30 min After Infusion)	Time 240 (4 h After Infusion)
vWF:Ag (U/dL)	252 ± 137	291 ± 112***	339 ± 126***	247 ± 129	247 ± 123	249 ± 126
RiCof (U/dL)	215 ± 168	267 ± 150***	312 ± 169***	220 ± 172	213 ± 160	216 ± 164
FVIII (U/dL)	151 ± 59	255 ± 69***	310 ± 140***	146 ± 62	143 ± 60	147 ± 58
PT ratio	1.10 ± 0.14	1.13 ± 0.15**	1.13 ± 0.15**	1.09 ± 0.12	1.10 ± 0.12	1.09 ± 0.12
APTT ratio	1.11 ± 0.25	1.02 ± 0.26***	1.00 ± 0.25***	1.11 ± 0.25	1.12 ± 0.26	1.10 ± 0.24
Platelet count (× 10 ⁹ /L)	143 ± 122	138 ± 117	140 ± 129	143 ± 116	140 ± 114	152 ± 122

Figures indicate means ± SD. Asterisks indicate significance of differences between post-DDAVP or -saline values and baseline values: ***P* < .01; ****P* < .001 (*t* test for paired samples).

DISCUSSION

The purpose of this controlled study was to see whether or not DDAVP is effective in a number of clinical situations that all have prolonged BT, the best available laboratory indication of abnormal primary hemostasis. The most significant finding was that after DDAVP, the BT became less than ten minutes in about half of the cirrhotic patients. This is the value we consider the upper clinical threshold for normal primary hemostasis. DDAVP was also effective in patients with unclassified prolonged BT and in volunteers taking the antiplatelet drugs aspirin and ticlopidine, whereas the shortening of the BT was not significant in severe thrombocytopenia or in congenital platelet dysfunction, even though three of seven patients with congenital storage pool

deficiency responded to DDAVP with a marked BT shortening.

Why the BT is prolonged in cirrhotics is not completely understood.^{10,11} Mild or moderately severe thrombocytopenia is usually present in cirrhosis and was also found in our patients, but their platelet counts were not negatively correlated with their BT. An abnormal vWF is also unlikely because patients had normal or high baseline levels of vWF:Ag and RiCof and the multimeric structure of vWF in their plasma did not differ from that of healthy subjects. Notwithstanding the present uncertainty about the causes of prolonged BT in cirrhotics, the shortening of the BT induced in about half of our patients by DDAVP indicates that this drug might be given when liver biopsies or other surgical procedures would be otherwise contraindicated by a prolonged BT. It must be emphasized, however, that the hemostatic derangement of liver disease is complex, and that the modest and short-lived shortening of the BT seen in most of the responders may not be sufficient to significantly reduce the clinical risk of hemorrhage. The APTT shortened after DDAVP but, at variance with others,¹² we have seen no shortening of the prothrombin time. Hence the hemostatic derangement of liver disease is not completely corrected by DDAVP, and only clinical experience will establish the hemostatic efficacy of the compound.

DDAVP also shortened the prolonged BT induced by the antiplatelet drugs ticlopidine and aspirin, the latter observation being in agreement with that made by Kobrinsky et al⁴ in their study of two aspirin-treated patients. It also was useful in the group of patients with prolonged BT who had no alterations in platelet function tests that could explain their deranged primary hemostasis (vascular abnormalities? unidentified platelet dysfunction?). As for cirrhotics, these effects of DDAVP might be exploited when surgical procedures must be carried out and a shortening of the BT must be obtained rapidly, but clinical experience is needed to validate this hypothesis. There is little justification for giving DDAVP to patients with thrombasthenia, in agreement with Kobrinsky et al,⁴ or to those with severe thrombocytopenia because the BT was not shortened. Unlike Kobrinsky, we did

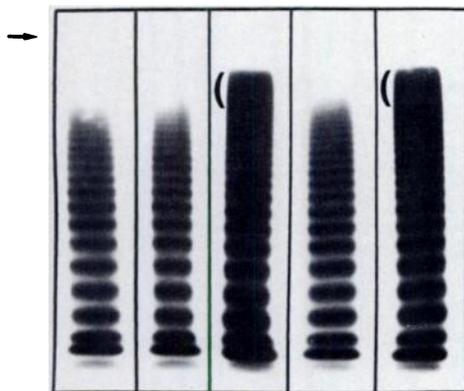


Fig 5. Autoradiograph pattern of plasma vWF electrophoresed in 1.4% high-gelling temperature agarose in the presence of SDS and detected by ¹²⁵I-labeled affinity-purified antibody. The arrow indicates the origin of the running gel and the anode is at the bottom of the gel. From left to right: normal plasma; plasma from a patient with liver cirrhosis before (bleeding time: 21 minutes) and 30 minutes after (bleeding time: 9 minutes) DDAVP; plasma from another patient with liver cirrhosis before (bleeding time: 20 minutes) and 30 minutes after (bleeding time: 20 minutes) DDAVP. The brackets indicate the large vWF multimers that appear in both plasma after DDAVP.

not find a significant shortening of the BT in patients with congenital storage pool deficiency. However, the analysis of the responses of individual patients indicates that the BT became shorter than ten minutes in two and shortened from 29 to 11 minutes in one, even though it remained prolonged in the remaining four (Fig 3). Hence it appears that in storage pool deficiency there are both responders and non-responders, and that the response cannot be predicted on the basis of criteria such as the degree of baseline BT prolongation (Fig 3) and platelet levels of serotonin and adenosine diphosphate (data not shown).

Even though this controlled study establishes more clearly the therapeutic indications and limitations of DDAVP in disorders of primary hemostasis, the mechanism of the action of the drug is still unknown. Its poor efficacy in severe thrombocytopenia indicates that some critical platelet number is necessary for the drug to be effective. Poor efficacy in thrombasthenia and, to a lesser extent, congenital storage pool deficiency would apparently indicate that the platelets must also function normally. On the other hand, DDAVP was efficacious in some but not all patients with congenital storage pool deficiency, in volunteers taking antiplatelet drugs such as aspirin and ticlopidine, both of which, and particularly the latter,^{9,13} induce severe platelet dysfunction. Even though drug-induced inhibition of vascular prostacyclin generation shortens the BT in rabbits,¹⁴ it is unlikely that, as suggested by others,¹⁵ this is a major mechanism for the DDAVP shortening effect because DDAVP shortened the BT in volunteers treated with 500 mg aspirin, a dose high enough to abolish vascular prostacyclin production.^{16,17} On the other hand, Belch et al¹⁸ have previously shown that DDAVP stimulates the production of plasma prostacyclin, suggesting that prostacyclin might cause the facial flushing seen after intravenous administration of DDAVP. We¹⁹ and others,²⁰ however, did not demonstrate any change of prosta-

cyclin after DDAVP. In agreement with Brommer et al,²¹ we have also found that aspirin intake did not abolish the flushing of the face seen after DDAVP. Hence prostacyclin has probably little to do with the effects and side effects of DDAVP. A recent study has shown that ticlopidine administration induces a thrombasthenic-like functional state in normal platelets.¹² It remains to be explained why DDAVP, which promptly shortened the prolonged BT in our volunteers taking ticlopidine, did not shorten the prolonged BT in congenital thrombasthenia.

We have previously postulated that large vWF multimers transiently released by DDAVP from cellular compartments might enhance platelet adhesion and potentiate primary hemostasis.¹ Even though this hypothesis has been subsequently corroborated by the finding of heightened platelet adhesion in normal volunteers after DDAVP,²² additional factors must be advocated to explain the hemostatic effectiveness of DDAVP because although large vWF multimers were released in all the patients we studied, the BT was not shortened in all. Other biological changes induced by DDAVP were a shortening of the APTT, previously observed by others^{4,23} and probably due to the high FVIII levels achieved; prothrombin time prolongation, probably due to plasma dilution after water retention induced by the anti-diuretic effect of the drug²⁴; whereas, unlike Kobrinisky,⁴ we saw no significant fall of the platelet count. These changes, however, seem unlikely to provide clues for the effectiveness of DDAVP because they were not correlated with BT changes and occurred in all groups, regardless of the effectiveness of DDAVP on the BT.

NOTE ADDED IN PROOF

At the time this manuscript was accepted for publication, Burroughs et al (*Br Med J* 291:1377, 1985) showed that DDAVP significantly shortened bleeding time in cirrhotics.

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