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DIABETICS DEMONSTRATE A BLUNTED VON WILLEBRAND FACTOR RESPONSE TO DESMOPRESSIN INFUSION. M.B. Grant, T. Daniels, D. Claire and R. Lottenberg, University of Florida College of Medicine, Gainesville, FL, U.S.A.

The increase in von Willebrand factor (vWF) following desmopressin (DDAVP) (1-desamino-8-D-arginine vasopressin) infusion was markedly blunted in severe hemophiliacs who had high vWF levels after treatment with vWF rich plasma concentrates. Diabetics with microangiopathy appear to have disease-induced elevation of vWF. In the current study, the vWF response to DDAVP infusion was measured in 30 diabetics (12 type I, 18 type II) and 16 controls, matched for age, sex and weight. Extent of nephropathy, macroangiopathy, and neuropathy was evaluated. Diabetic retinopathy was assessed by indirect ophthalmoscopy and fluorescein angiography (n=8 proliferative retinopathy, n=6 background retinopathy, n=16 no retinopathy). Plasma samples were collected in the supine, overnight-fasted state. DDAVP (0.3 µg/kg) was infused over 30 min and samples obtained at 0-60 min. vWF antigen was assayed by Laurell rocket electrophoresis. Tissue plasminogen activator (t-PA) activity was measured by a coupled chromogenic substrate assay. Results: Basal vWF levels for type I diabetics (124±16%, Mean±SEM) and type II (178±14%) were increased as compared to controls (94±6%), p<.05 and p<.005, respectively. vWF levels for diabetics with proliferative retinopathy (194±29%) were significantly higher than for diabetics with background retinopathy (106±13%) p<.01. Diabetics with elevated basal levels of vWF (>150%) showed less of an increase in vWF following DDAVP infusion than diabetics with normal basal levels (p<.01). The percent increase in vWF following DDAVP administration inversely correlated with basal vWF levels (type I, r=.51; p<.01 and type II, r=.46; p<.01). The basal vWF level was the significant determinant of DDAVP response, not the presence or absence of diabetic complications. Peak t-PA levels showed no difference in controls or diabetics. In contrast to the vWF response, a normal t-PA response to DDAVP infusion was observed in diabetics. Conclusion: Diabetics with microvascular complications and high circulating levels of vWF demonstrate a blunted vWF response to DDAVP. This supports the existence of a negative feedback mechanism as previously reported for the transfused hemophiliacs.

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SUCCESSFUL SURGICAL MANAGEMENT OF A PATIENT WITH COMBINED FACTOR V AND VIII DEFICIENCY WITH DDAVP + FFP. R. McKenna (1), E. R. Cole (2) and A. DOOLAS (3). Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL USA.

A 59 year-old white male with a life long history of severe bleeding following trauma or surgical procedures was documented to have a combined factor V and factor VIII-C deficiency. His baseline factor V ranged between 16% - 30% and factor VIII-C was between 20% - 30%. His APTT ranged between 50 - 56 seconds (21-31 N) with a prothrombin time activity between 33% - 40% of normal (≥ 70% N). Factor II, VII/X, X, IX, XI, XII, template bleeding time and platelet function studies were normal. There was no severe factor XIII deficiency.

Since the response of these patients to DDAVP is unknown and the patient was admitted with a large hematoma in the subolecranon bursa, DDAVP was infused in a dose of 0.5 µ g/kg body weight over 15 minutes. The baseline factor VIII-C of 20% rose to 55% at 5 minutes after termination of DDAVP and to 62% and 66% at 3 and 6 hours respectively. The factor VIII-C level dropped to 45% and 36% at 12 and 24 hours respectively after a single dose of DDAVP. As measured by a sensitive ^{125}I-fibrin assay, this dose of DDAVP caused a net rise in plasminogen activator activity of 2.43 CTA U/ml.

The patient had worn an inguinal truss for approximately 20 years for two large oblique inguinal hernias, one of which entended to the level of the mid-thigh. Pre and peri-operative management of the right inguinal herniorrhaphy consisted of DDAVP in a dose of 0.5 µg/kg Q 12 hourly for two doses, FFP at 9 ml/kg Q 12 hourly for three doses, and Amicar for 48 hours starting post-operatively. This regimen maintained the factor VIII-C at ∿ 50% with factor V between 44% - 50% for a period of three days. On the 4th post-operative day a left inguinal herniorrhaphy was accomplished with DDAVP and FFP (dosage similar to previous) administered Q 12 hourly for three doses, then once in the next 24 hours, and Amicar for three days. A 4 cm wound hematoma noted on the first day of the second surgical procedure was evacuated, and was due to the presence of a bleeder since VIII-C and V levels were higher than the values indicated on the first procedure. No red cell transfusions were given; fluids were restricted to 600 ml per day for 24 hours after the last dose of DDAVP. Successful bilateral inguinal herniorrhaphies without significant hemorrhages was achieved with exposure to a minimal volume of blood products.

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EFFECTS OF DDAVP AT COAGULATION AND FIBRINOLYTIC LEVELS : DIFFERENT MECHANISMS OF ACTION-AN EXPERIMENTAL STUDY IN THE DOG. J.M. Pina-Cabral, A. Cunha-Monteiro, M.C. Sousa-Dias and J.Aguiar-Andrade. Centro de Fisiologia da Hemostase (INIC), Dept. of Physiology, Porto Medical School, Hosp. S. João, Porto, PORTUGAL.

After the injection of DDAVP in 39 non-anesthezised dogs (0.4 µg/kg) there was an average increase of factor VIII:C activity up to 145% (p<0.0001) and of fibrinolytic potential of euglobulin precipitate (t-PA) up to 196% (p<0.0001). The injection of DDAVP was repeated in each dog of a group of good responder animals at weekly intervals , but after : -A) Pentobarbital anesthesia (30 mg/kg)- the increase of factor VIII:C was reduced from 164% to 116% (n=11; p<0.0005) and the increase in t-PA was reduced from 270% to 192% (n=11; p<0.05). -B) Injection of propranolol (1mg/kg) - the increase of factor VIII:C was reduced from 167% to 110% (n=13; p<0.0005) and there was no decrease of fibrinolytic activity, (n=13; n.s.). -C) Splenectomy-the increase of factor VIII:C was reduced from 166% to 122% (n=10; p<0.0005) and t-PA was increased from 196% to 256% (n=9; n.s.). There were no statisticaly significant differences in factor VIII:C and fibrinolytic activities after repeating only the injection of DDAVP three times in the same animal at weekly intervals (n=5; n.s.).

We conclude that the increase in F. VIII:C and fibrinolytic activities observed after DDAVP infusion are due to different mechanisms of action. On the one hand, pentobarbital anaesthesia reduced the increase of factor VIII:C and t-PA , but on the other hand , beta-blockade and splenectomy influenced differently the behaviour of both biological activities .

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CHANGES IN PLASMA t-PA, PAI AND FACTOR VIII FOLLOWING I.V. AND S.C. INJECTION OF DDAVP IN HEALTHY VOLUNTEERS. I.R. MacGregor (1), E. Roberts (1), C.V. Prowse (2), N.A. Booth (3), A. Broomhead (4) and P. Litka (4). SNBTS HQ Unit Laboratory (1) and S.E. Scotland Blood Transfusion Service, (2), Edinburgh; Department of Medicine & Therapeutics, Aberdeen University (3); Smith Kline & French Research, Welwyn Garden City, Herts, UK (4).

DDAVP is used effectively to induce a haemostatic response in certain types of haemophilia A and von Willebrands disease, but the accompanying increase in fibrinolytic activity is an unwanted effect. Here we have quantified the extent and time course of changes in t-PA, its physiological inhibitor PAI and factor VIII moieties, using functional and immunometric assays, following i.v. and s.c. injection of DDAVP 0.4 ug kg^{-1} in 6 normal volunteers in a double blind crossover study.

T-PA, factor VIII and vWF values increased after dosing and the area under the response versus time curve was higher after i.v. than s.c. injection. Conversely levels of PAI activity decreased, with lower minimum values for i.v. than s.c. and a correspondingly lower area under the response curve for the former route. In several subjects PAI activity fell to zero during the sampling period. The times to the first occurrence of maximum response were determined. The median values for factor VIII were 40 and 90 min for i.v. and s.c. respectively. For vWF they were 60 and 80 min. For t-PA activity they were 20 and 60 min indicating that the release of factor VIII and vWF was delayed compared with t-PA activity. PAI-1 antigen was assayed by ELISA to investigate clearance of PA inhibitor and was compared with changes in PAI activity during the infusion of DDAVP and after a subsequent venous occlusion.

The results indicate that fibrinolytic and haemostatic responses follow different time courses from each other, both after i.v. and s.c. administration of DDAVP, that are reproducible from subject to subject. The use of specific assays has permitted determination of the fibrinolytic response to DDAVP to be assessed in terms of changes in pro and anti-fibrinolytic components.