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HEAT-TREATED FACTOR VIII CONCENTRATES IN VON WILLEBRAND'S DISEASE AND RELATED DISORDERS: STUDIES IN PLATELET-TYPE VON WILLEBRAND'S DISEASE. Hoyu Takahashi, Wataru Tatewaki, Reizo Nagayama, Masaharu Hanano, Shin-ichiro Takizawa and Akira Shibata. The First Department of Internal Medicine, Niigata University School of Medicine, Niigata, Japan.

Cryoprecipitate has proved to correct the hemostatic defects in von Willebrand's disease (vWd). However, recent studies have revealed that transmission of the AIDS retrovirus (HIV) occurs through exposure to blood products including cryoprecipitate. Treatment with heat-treated factor VIII concentrates may have certain advantages over treatment with non-heated products, if these preparations are efficacious in vWd and related disorders. We investigated the multimeric compositoin of von Willebrand factor (vWf), contents of vWf antigen (vWf:Ag) and ristocetin cofactor activity (RCof) in the heat-treated factor VIII concentrates and cryoprecipitate, and their capacity to directly induce aggregation of platelet-type (or pseudo-) vWd platelets in vitro. The vWf multimers were visualized by a newly developed, immuno-enzymatic staining of the gel, following a discontinuous SDS-agarose gel electrophoresis. The RCof/vWf:Ag ratio was around 1.0 in cryoprecipitate, and ranged from 0.19 to 0.96 in factor VIII concentrates. Among four commercially available concentrates studied, Haemate P contained the most high-molecular-weight multimers of vWf and the highest RCof relative to vWf:Ag, and induced the aggregation of platelet-type vWd platelets at the lowest concentration. When infused into a patient with platelet-type vWd, Haemate P (14.4 units vWf:Ag/kg body weight) shortened the prolonged bleeding time and caused spontaneous platelet aggregation in vitro with a mild diminution of platelet count (from the preinfusion value of 183,000/μl to 139,000/μl at 5 minutes). These results indicate that some of the heat-treated factor VIII concentrates contain the high-molecular-weight vWf multimers and may provide a safer, yet still effective, treatment for platelet-type vWd, and possibly for various types of vWd as well.

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EFFECTS OF DDAVP INFUSION ON FVIII/vWF IN THREE CASES OF ACQUIRED TYPE II VON WILLEBRAND'S DISEASE. J. GOUDEMAND, C. CARON, B. JUDE, A. PARQUET and C. MAZURIER. Laboratoire d'Hématologie du C.H.R. et Laboratoire d'Hémostase du C.R.T.S. - LILLE - FRANCE.

The response to a single intravenous infusion of DDAVP (0.4 μg/kg) was studied in 3 patients with acquired type II von Willebrand's disease associated with monoclonal gammopathy (2 cases) or chronic lymphocytic leukaemia (1 case). The Simplate bleeding time (BT) was prolonged to 10-26 min, FVIII:C, vWF:Ag (ELISA) and vWF:RiCof activities were respectively decreased to 0.15-0.48, 0.18-0.30 and 0.06-0.48 U/ml. Circulating inhibitor to FVIII/vWF were demonstrated in the 3 cases. Plasma vWF multimeric analysis was performed by SDS-agarose electrophoresis and densitometric patterns were recorded. In that way, each well-separated multimeric unit can be expressed as a percentage of the total area under the curve representing the total vWF. Whereas the large (slower-moving) multimers (numbered 6 and more) represented 52.8-63.2 % of the total vWF in normal plasma (n = 9), they could account only for 12.5-28.7 % of the total vWF in the patients' plasma. In addition, a progressive decrease in the relative intensity of the multimers as their size increased, in a similar manner as is seen in type IIc vWD, was demonstrated. The triplet structure seen in normal plasma was undetectable in 2 patients but present in the 3rd one.

Following infusion of DDAVP, the prolonged BT was normalized for 2 hr in 2 patients and transiently shortened in the 3rd one. FVIII:C, vWF:Ag and vWF:RiCof activities were increased to normal levels and remained higher than 0.5 U/ml for respectively 4-24 hr, 3-13 hr and 2-4.5 hr. The multimeric pattern could be considered as completely normalized in 2 patients and greatly improved in the 3rd one. The triplet structure was apparent in the 3 cases. The vWF multimeric structure returned to the preinfusion pattern by 5 hr in 2 patients and approximately 10 hr in the last one. These results demonstrate that endothelial cells from these patients are able to synthesize and release vWF with a full complement of multimers. Furthermore they show that the loss of the larger vWF multimers occurs after vWF has been released into the circulation.

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HETEROGENOUS RESPONSES TO CRYOPRECIPITATE AND DDAVP IN TYPE IIA VON WILLEBRAND'S DISEASE (VWD). J. Chediak, B. Maxey, J. Eldridge, and M.C. Telfer. Joint Section of Hematology-Oncology, Michael Reese Hospital and the University of Chicago, Chicago, IL USA.

Von Willebrand's disease is an autosomal dominant disorder characterized by excessive mucocutaneous bleeding, prolonged bleeding time (BT), and reduce amounts of ristocetin cofactor activity (RiCof). The Von Willebrand factor antigen (VWF:Ag) shows either reduced amounts or no multimers (Types I and III), or a selective reduction of high molecular weight multimers (HMW) (Type IIA and IIB). Variable responses to DDAVP have been reported in IIA VWD suggesting that IIA patients (pts) are a heterogenous group. Some IIA pts may show RiCof activity after DDAVP infusion even though no HMW multimers are found.

Von Willebrand factor antigen, RiCof and BT were analyzed in five pts (2 females and 3 males) known to have Type IIA VWD. Baseline values showed marked reductions of RiCof (less than 10% of normal), BT greater than 15 minutes, faster immunoelectrophoresis of VWF:Ag and absent HMW multimers. Immunoelectrophoresis of VWF:Ag by the Laurell technique gave variable amounts ranging from 10 to 125% or normal. Three adult pts received DDAVP (Stimate) or cryoprecipitate (cryo) and the responses on abnormal parameters were assessed up to 48 hours. In two pts the BT corrected with cryo, whereas in the third patient the correction was minimal. The three pts showed a normal decay of both VWF:Ag or RiCof after cryo. However, after DDAVP the decay of VWF:Ag and RiCof was similar to that after cryo in one patient and more rapid in two patients.

In these two patients, the data would be compatible with the rapid proteolysis of endogenoue VWF released by the patient's endothelial cells, whereas the exogenous VWF given as cryo showed normal survival in the patient's blood.

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PROTEOLYTIC DEGRADATION OF VON WILLEBRAND FACTOR AFTER DDAVP ADMINISTRATION IN NORMAL INDIVIDUALS. J.Batlle (1), M.F.López-Fernández (1), C.López-Berges (1), S.D.Berkowitz (2), Z.M. Ruggeri (2) and T.S. Zimmerman (2). Dept. Hematology, Hospital Clínico, Universidad de Salamanca, Spain (1) and Dept. Basic & Clinical Research, Scripps Clinic & Research Foundation, La Jolla, CA.USA.

The infusion of 1-Deamino-8-D-Arginine Vasopressin (DDAVP) in normal individuals is followed by an increase in factor VIII/von Willebrand factor in plasma and by the appearance of larger multimers of von Willebrand factor (vWF) than those seen in the resting state. Since the larger multimers are rapidly cleared and proteolysis is known to cause disaggregation of large multimers, we evaluated the degree of vWF proteolysis after DDAVP. DDAVP was infused into eight normal adult volunteers and the relative proportions of the intact 225 kDa subunit and the 189, 176 and 140 kDa fragments were compared before and at different times after DDAVP infusion. The relative proportion of the 176 kDa fragment was increased while that of the other species was decreased, indicating that proteolytic fragmentation had occurred. However, plasmin did not appear to be responsible because the vWF fragments characteristically produced by this enzyme could not be detected. Concomitant analysis of vWF multimeric structure showed that these changes were accompanied by an increase in the relative proportion of the satellite bands suggesting that they were ptoteolytically generated. Proteolysis may explain, at least in part, rapid clearance of larger vWF multimers released by DDAVP.