

INHIBITORY EFFECTS OF ALBUMIN ON RISTOCETIN-INDUCED FIBRINOGEN PRECIPITATION. J.A. Zuhlke, J.C. Mattson and T.G. Bell. Department of Pathology, Michigan State University, East Lansing, MI.

It has been noted that ristocetin causes the precipitation of fibrinogen. In ristocetin cofactor assays, this precipitation can mask the platelet agglutination endpoint. At higher concentrations of ristocetin (>1.5 mg/ml) a heavier precipitate forms. Bovine albumin when added to the test system will inhibit this precipitation. von Willebrand's Disease (vWD) plasma was tested with varying concentrations of ristocetin and albumin. When 0, 10.1 and 13.6 mg/ml of albumin were used in the ristocetin cofactor assay (ristocetin at 1.2 mg/ml) rapid endpoints were achieved and levels of ristocetin cofactor for vWD plasma were not in the expected abnormal range. Albumin concentrations of 20 mg/ml produced low ristocetin cofactor levels for vWD plasma and normal levels for pooled normal plasma. Concentrations of bovine albumin greater than 30 mg/ml made endpoints difficult to see and greatly prolonged the time to reach the endpoint. Since higher ristocetin concentrations precipitate more fibrinogen, a studying varying ristocetin concentration was also undertaken. When 20 mg/ml of albumin was used, ristocetin in concentrations of 1.0-1.2 mg/ml produced normal activity for pooled normal plasma but low ristocetin cofactor activity for vWD plasma. Ristocetin in concentrations greater than 1.5 mg/ml resulted in normal ristocetin cofactor activity for the vWD plasma. Ristocetin at 0.5 mg/ml did not induce platelet agglutination that was detectable in this assay. Similar studies were performed using canine plasma and it was ascertained that 1.0 mg/ml of ristocetin must be used with this species because higher concentrations of ristocetin (>1.2 mg/ml) produce normal results in vWD plasma. The albumin effect in the canine assay is similar to that found in the human ristocetin assay. These data suggest that it is imperative to standardize albumin and ristocetin concentrations in ristocetin cofactor assays.

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FOUR CASES OF ACQUIRED VON WILLEBRAND'S SYNDROME ASSOCIATED WITH MONOCLONAL GAMMAPATHY. M.H. Horellou, E. Baumelou, N. Sitbon, J. Conard, J.P. Marie, J.M. Fine, N.C. Corin, R. Zittoun, M.Samama. Hotel-Dieu, Hopital Rothschild and C.N.R.S., Paris, France.

Acquired Von Willebrand syndrome is reported in four patients with monoclonal IgG: benign gammopathy in three cases, multiple myeloma in one case; to our knowledge, this last association has not been previously reported.

Coagulation abnormalities included a borderline bleeding time, a low platelet retention on glass beads, decreased levels of factor VIII coagulant activity (VIII:c), factor VIII related-antigen (VIII R:Ag) and ristocetin-induced agglutination cofactor (VIII R:Cof).

The late clinical onset, the negative family history and the immunological abnormality suggest an acquired Von Willebrand syndrome. After cryoprecipitate infusion the patients did not show the expected rise and there was no secondary increment in factor VIII:c.

Time-dependent inhibition of factor VIII R:Cof was found in one case only and was associated with qualitative abnormality of factor VIII R:Ag demonstrated by crossed-immunoelectrophoresis. It was not possible to interpretate this last test in the other cases, due to the very low level of factor VIII R:Ag. The inhibitor activity was neither found in the IgG fraction nor in the monoclonal IgG but disappeared after IgG adsorption on staphylococcal protein A.

The factor VIII abnormalities might be related to the binding and/or destruction of factor VIII by a circulating antibody, or to the adsorption of this factor on the malignant lymphocytes.

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AN ACQUIRED VON WILLEBRAND'S DISEASE WITH IgG MONOCLONAL GAMMOPATHY, NORMAL BLEEDING TIME AND POSITIVE VIIIIR:AG IN THE VASCULAR ENDOTHELIUM. A.Kimura, M.Aihara, K.Tanabe T.Momma, Y.Chiba, Y.Yoshida. First Department of Internal Medicine, Hirosaki University, Hirosaki, Japan.

A 71-year old female noticed nose bleeds a year ago and diagnosed to have an acquired von Willebrand's disease with IgG,K monoclonal gammopathy. VIII:C was of 0.10 U/ml, VIIIIR:AG and VIIIIR:WF of both below 0.05 U/ml. Bleeding time was within normal limit by both Duke's(5 min.) and Ivy's (7 min.) methods. Platelet retention rate was 10% by Bowie's method. Ristocetin induced platelet aggregation was nil at 1.2mg/ml of concentration. Serum immunoelectrophoresis showed K type IgG M-bow, but the IgG value was within normal limit (1,407 mg/dl). Bone marrow findings were normal. Over response of VIII:C following the infusion of cryoprecipitate was not seen. Her profuse epistaxis was stopped when the cryoprecipitate was administered but not the Factor VIII concentrate. Patient plasma showed an inhibitory effect to VIII:C (1.12 Bethesda unit), VIIIIR:AG and VIIIIR:WF. By immunofluorescent staining VIIIIR:AG was proven to be present in normal quantity in the vascular endothelium and platelet surface.

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EFFECT OF DDAVP IN PATIENTS WITH VON WILLEBRAND'S DISEASE AND HEMOPHILIA A. A.I. Warrier, C. Hillman and J.M. Lusher. Department of Hematology, Children's Hospital of Michigan and Department of Pediatrics, Wayne State University School of Medicine, Detroit, Michigan, U.S.A.

European investigators have reported on the efficacy of 1-deamino-9-D-arginine vasopressin (DDAVP) in von Willebrand's disease (vWD) and mild hemophilia A. We have thus evaluated the effects of a single intranasal dose of DDAVP (200ugm of the more dilute form available in the U.S.), in 12 individuals with vWD and in 4 with moderate hemophilia A. Crossed immunoelectrophoresis of VIII:Rag demonstrated normal electrophoretic mobility in each of the vWD subjects. Components of the factor VIII system (VIII:C, VIII:Rag, VIII:R Cof.) were assayed pre- and 90 and 180 minutes post-DDAVP. Each of 11 subjects with mild or moderate vWD had an increase in VIII:C activity (avg. 2X increase), 8 of 11 had an increase in VIII: R Cof, and 9 of 11 had an increase in VIII:Rag. The twelfth vWD subject, who had severe vWD, had no rise in any of these components. Of 4 vWD subjects who had pre- and post-DDAVP template bleeding times (BT) performed, the only one who had a prolonged baseline BT showed a normal BT 90 minutes post-DDAVP. One vWD subject, in whom we had documented an increase in all F. VIII components after DDAVP, later underwent dental extractions 90 minutes after DDAVP. No excessive bleeding was noted. Four individuals with moderate hemophilia A (baseline VIII:C values of 0.02-0.10 u/ml) were also studied. Three had a rise in all components of the factor VIII system post-DDAVP while the fourth did not. No undesirable side effects were noted in any of the 16 subjects who received DDAVP. We conclude that even the more dilute form of DDAVP available in the U.S., when given intranasally, results in transient improvement in selected individuals with vWD or moderate hemophilia A. This drug thus warrants further study as an alternative to blood components in the management of vWD, as well as in mild and moderate hemophilia A.