



## PIC QUESTION OF THE WEEK: 9/13/10

Q: What is von Willebrand disease and can it be caused by drugs?

A: von Willebrand disease (vWD) is a congenital bleeding disorder associated with a deficiency or defect in the function of von Willebrand *factor* (vWF). This glycoprotein is synthesized in platelet precursors and endothelial cells and binds to factor VIII. It plays a key role in platelet adhesion to damaged epithelium as well as platelet aggregation. Patients generally present with epistaxis or some type of mucocutaneous bleeding or they excessively hemorrhage after surgery or trauma. Severity of the disease is highly variable. Diagnosis is usually dependent on the level of vWF antigen and ristocetin cofactor (Rcof) activity. Desmopressin (DDAVP) concentrates of vWF and Factor VIII, and high-dose intravenous immunoglobulin have been used in the treatment of patients with vWD. A form of the disease known as acquired von Willebrand syndrome (AvWS) was identified in 1968 and a number of cases continue to be reported. In AvWS, the production of vWF is seemingly normal; however, the factor appears to be cleared more rapidly from the plasma. A number of myeloproliferative (e.g. chronic myeloid leukemia) and lymphoproliferative (multiple myeloma, non-Hodgkin lymphoma) diseases, various solid tumors, autoimmune disorders, and a small number of drugs have been associated with AvWS. The mechanisms responsible for increased clearance of vWF are variable, but probably related to the development of circulating antibody to vWF or to enhanced degradation of the glycoprotein. AvWS has rarely been associated with the administration of hydroxyethyl starch (a volume expander), ciprofloxacin, and cefotaxime. Valproic acid is the most common drug implicated in suspected cases of AvWS. This anticonvulsant has been associated with other coagulopathies including thrombocytopenia (the most frequent hematologic adverse reaction), reduced levels of vitamin K dependent clotting factors, and decreased values of fibrinogen. The mechanism by which valproic acid results in AvWS is unknown. In several reported cases, laboratory investigation revealed decreases in vWF, ristocetin cofactor activity, factor VIII, and fibrinogen. Platelet count, activated partial thromboplastin time (aPTT), and INR may be normal, especially in those with mild disease. Some authors have suggested that the increased tendency toward bleeding in children receiving valproic acid is not associated with AvWS. Regardless, it would seem prudent that children undergoing surgery while receiving valproic acid be evaluated for any evidence suggestive of possible coagulopathy.

### References:

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