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von Willebrand Disease

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Overview

Practice Essentials

Von Willebrand disease (vWD) is a common, inherited, genetically and clinically heterogeneous hemorrhagic disorder caused by a deficiency or dysfunction of the protein termed von Willebrand factor (vWF). Consequently, defective vWF interaction between platelets and the vessel wall impairs primary hemostasis. (See Etiology and Workup.)

vWF, a large, multimeric glycoprotein, circulates in blood plasma at concentrations of approximately 10 mg/mL. In response to numerous stimuli, vWF is released from storage granules in platelets and endothelial cells. It performs two major roles in hemostasis. First, it mediates the adhesion of platelets to sites of vascular injury. Second, it binds and stabilizes the procoagulant protein factor VIII (FVIII). (See Etiology.)

vWD is divided into three major categories, as follows:

- Type 1 – Partial quantitative vWF deficiency
- Type 2 – Qualitative vWF deficiency
- Type 3 - Total vWF deficiency

vWD type 2 is further divided into four variants (2A, 2B, 2N, 2M), based on characteristics of dysfunctional vWF. These categories correspond to distinct molecular mechanisms, with corresponding clinical features and therapeutic recommendations. (See Etiology, Workup, and Treatment.) In a review of 670 French families with von Willebrand Disease, the distribution of VWD types was as follows[1] :

- Type 1 – 25%
- Type 2 – 66%
- Type 3 – 8%
- Unknown type – 1%

The main treatment options for patients with vWD are desmopressin (DDAVP), recombinant vWF, and vWF/factor VIII (vWF/FVIII) concentrates. In addition, antifibrinolytic drugs (ie, aminocaproic acid, tranexamic acid) can be used orally or intravenously to treat mild mucocutaneous bleeding. See Treatment and Medication.

For discussion of vWD in children, see Pediatric Von Willebrand Disease.

Patient education

Patients should be instructed about their coagulation disorder and be aware of the conditions in which prophylactic therapy is highly recommended. Patient education information is available online through the following organizations:

- American Society of Hematology
- Centers for Disease Control and Prevention
- Mayo Clinic
- National Heart, Lung, and Blood Institute
- National Hemophilia Foundation (includes printable brochure)

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Etiology

In the great majority of cases, vWD is an inherited condition. The vWF gene is located near the tip of the short arm of chromosome 12. The gene is composed of 52 exons and spans a total of 180kb of the human genome; therefore, it is similar in size to the FVIII gene. Expression of the vWF gene is restricted to megakaryocytes, endothelial cells, and, possibly, placental syncytiotrophoblasts. A partial, nonfunctional duplication (pseudogene) is present on chromosome 22.

vWF exists as a series of multimers varying in molecular weight between 0.5-kd (dimer) and 20 million kd (multimer). The building blocks of multimers are dimers, which are held together by disulfide bonds located near the C-terminal end of each subunit.[2]

vWD type I

vWD type I causes a mild to moderate quantitative deficiency of vWF (ie, about 20-50% of normal levels). In individuals with vWF levels < 0.3 IU/mL, type I is usually inherited in autosomal dominant fashion; in those with levels >0.3 IU/mL mutations show variable penetrance.[3]

vWD type II

vWD type II is due to qualitative vWF abnormalities and is subdivided into types IIA, IIB, IIN, and IIM. vWD type IIA, the most common qualitative abnormality of vWF, is associated with selective loss of large and medium-sized multimers. Most cases have autosomal dominant inheritance.[3]

vWD type IIB characterized by the loss of large multimers occurs through a mechanism distinct from that of type IIA. Observations to date have identified a critical region of vWF involved in the binding of vWF to the platelet receptor glycoprotein Ib (GpIb). Each of the identified single amino acid substitutions is thought to result in a gain of function, leading to spontaneous binding of vWF to platelets.

Normally, plasma vWF is inert in its interaction towards platelets until it encounters an exposed subendothelial surface. vWF binding to collagen and/or other ligands within the injured vessel wall presumably results in a secondary conformational change, which then facilitates binding to the GpIb receptor.

In vWD type IIB, the mutant vWF spontaneously binds to GpIb in the absence of subendothelial contact. The large multimers have the highest affinity for GpIb and are rapidly cleared from the plasma along with the bound platelets, resulting in thrombocytopenia and the characteristic loss of large multimers.

vWD type IIN, sometimes referred to as vWD Normandy (after the province of origin of one of the first families identified with the disease), is characterized by a defect residing within the patient's plasma vWF that interferes with its ability to bind FVIII. This has important implications in the differential diagnosis of hemophilia. Most patients are compound heterozygotes with a vWF null allele.[3]

vWD type IIM (for multimer) involves qualitative variants with decreased platelet-dependent function not resulting from absence of high–molecular weight multimers. Type IIM vWD can result from a variety of mutations and is heterogeneous. In a study of 14 patients with vWD type IIM, the consistent findings were significant prolongation in PFA-100 and greatly reduced or absentristocetin-induced platelet aggregation and vWF ristocetin cofactor.[4]

vWD type III

Patients with vWD type III, a severe, quantitative deficiency associated with very little or no detectable plasma or platelet vWF, have a profound bleeding disorder. vWD type III appears to result from the inheritance of a mutant vWF gene from both parents. In the most straightforward model, vWD type I would simply represent the heterozygous form of vWD type III; however, inheritance patterns indicate greater complexity.

vWD type III is much rarer than the predicted frequency of 1 case per 40,000 persons based on this model, instead having a frequency closer to 1 case per 1 million persons. Although few mutations have been identified in families with pure vWD type I, some vWD type I cases have been suggested to be due to a mutant vWF subunit that interferes in a dominant, negative way with the normal allele, accounting for the autosomal dominant inheritance.

The discovery of a deletion of vWF (c.221-977_532 + 7059del [p.Asp75_Gly178del]) in 7 of 12 white patients with vWD type III from 6 unrelated families, and its absence in 9 Asian patients, led Sutherland et al to develop a genomic deoxyribonucleic acid (DNA)–based assay for the deletion of vWF exons 4 and 5.[5] This deletion was also found in 12 of 34 vWD type I families and was associated with a specific vWF haplotype, which the investigators noted may indicate a possible founder origin. Additional studies demonstrated the presence of the mutation in other patients with type I vWD and in a family that expressed both type I and type III vWD.[5]

Sutherland et al reported the c.221-977_532 + 7059del mutation as a novel cause of type I and type III vWD and suggested that screening for this mutation in other type I and type III vWD patient populations may clarify its contribution to vWD that arises from quantitative vWF deficiencies.[5]

Acquired vWD

Acquired vWD is a rare disorder that results from the development of antibodies to vWF. Acquired vWD may arise from a variety of mechanisms—including lymphoproliferative, cardiovascular, and myeloproliferative diseases[6] —and typically resolves with treatment of the cause.[3]

For example, acquired vWD may occur in patients with hypothyroidism; these cases are typically mild to moderate and improve with restoration of euthyroidism.[7] Acquired vWD has also been reported as a cause of postoperative bleeding in patients with congenital heart disease, especially those with complex defects and Eisenmenger syndrome.[8] The narrowed pulmonary vasculature in idiopathic pulmonary arterial hypertension has also been identified as a cause of acquired vWD.[9]

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Epidemiology

Clinically significant vWD affects approximately 125 persons per million population, with severe disease affecting approximately 0.5-5 persons per million population. Reports from screenings of unselected individuals indicated a higher prevalence of vWD abnormalities, ie, close to 1% of the population.

Sex- and age-related demographics

Males and females are affected equally by vWD. However, the phenotype may be more pronounced in females, because of menorrhagia and the greater visibility of bruises.[10]

In the great majority of cases, vWD is an inherited condition. Bleeding-related symptoms may occur at a young age, even just after or during birth. Some reports have suggested a decreased bleeding tendency as patients age.

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Prognosis

For most affected individuals, vWD is a mild, manageable bleeding disorder in which clinically severe hemorrhage manifests only in the face of trauma or invasive procedures. However, significant variability of symptomatology exists among family members.

In individuals with vWD types II and III, bleeding episodes may be severe and potentially life threatening. Individuals with type III disease who have correspondingly low FVIII levels may develop arthropathies, as more commonly seen in hemophilia A patients with comparably decreased FVIII levels.

Levels of vWF normally increase with age. However, Sanders and colleagues found that although vWF levels increased with aging in patients with type I vWD, elderly patients with type I reported no change in their pattern of bleeding did not change. In patients with type II vWD, vWF levels did not increase with aging, and eldelry patients reported significantly more bleeding symptoms.[11]

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Presentation

History

The most common signs of von Willebrand disease (vWD) include nosebleeds and hematomas. Prolonged bleeding from trivial wounds, oral cavity bleeding, and excessive menstrual bleeding are common. Gastrointestinal bleeding rarely occurs. Other manifestations include the following[12, 13] :

- Easy bruising - Common but nonspecific
- Prolonged bleeding - After minor trauma to skin or mucous membranes
- Severe hemorrhage - After major surgery; less common
- Delayed bleeding - May occur up to several weeks after surgery
- Heavy bleeding - Common after tooth extraction or other oral surgery, such as tonsillectomy and adenoidectomy
- Menorrhagia - Common presenting complaint in women
- Exacerbation of bleeding symptoms - After ingestion of aspirin
- Amelioration of bleeding symptoms with use of oral contraceptives

Pediatric-specific bleeding that may occur in children with vWD include the following[14] :

- Umbilical stump bleeding
- Cephalohematoma
- Cheek hematoma
- Conjunctival bleeding
- Post-circumcision bleeding
- Post-venipuncture bleeding

Patients with possible vWD should be asked about any family or personal history of bleeding problems. Any use of medications that might affect coagulation should also be elicited.[12]

Bleeding assessment tools

Bleeding assessment tools (BATs) have been developed to allow clinicians to objectively assess bleeding symptoms in patients with vWD. BAT scores may also help predict bleeding risk in patients with vWD.[15, 16] The International Society on Thrombosis and Haemostasis (ISTH) developed and endorsed a single BAT (ISTH-BAT), to standardize reporting of bleeding symptoms for use in adult and pediatric populations.[17, 15] BATs should always be complemented by coagulation screening tests.[15]

A practical disadvantage of existing BATs is that they must be administered by a physician or other properly trained health professional. Consequently, Deforest and colleagues have developed and validated a self-administered BAT for vWD. Their Self-BAT generated bleeding scores comparable BS to those of ISTH-BAT and proved reliable and effective screening tool for assessment of a possible bleeding disorder, particularly in women.[18]

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Physical Examination

Physical examination findings are usually normal. However, patients may show physical sequelae, such as bleeding or bruises. The examiner should note the size, location, and distribution of any ecchymoses, hematomas, or petechiae, and should assess for evidence of risks of increased bleeding, such as the following[12] :

- Jaundice or spider angiomata
- Splenomegaly
- Arthropathy
- Joint and skin laxity
- Telangiectasia

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Diagnostic Considerations

Conditions to consider in the differential diagnosis of von Willebrand disease (vWD) include the following:

- Hemophilia A
- Hemophilia B
- Bernard-Soulier syndrome
- Platelet function defects
- Antiplatelet drug ingestion
- Fibrinolytic defects

- Platelet-type (or pseudo) vWD
- Acquired vWD

Differential Diagnoses

- Factor X Deficiency
- Factor XI Deficiency
- Hemophilia A

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Workup

Workup

Approach Considerations

Laboratory studies are directed towards documenting a deficiency of von Willebrand factor (vWF).[12, 13, 19] Levels of vWF vary with physiologic stress; in particular, plasma levels increase with estrogens, vasopressin, growth hormone, and adrenergic stimuli. Thus, vWF levels may intermittently be normal in patients with von Willebrand disease (vWD), and measurements should be repeated to confirm abnormal results.

Repeating tests at intervals of more than 2 weeks is advisable to confirm or definitively exclude the diagnosis of vWD. Optimally, testing should occur at a time remote from events that may raise vWF levels, such as pregnancy, infection, surgery, and strenuous exercise.

Screening tests typically include the following:

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Factor VIII coagulant activity
- Ristocetin cofactor (RCoF) activity
- Concentration of vWF antigen (vWF:Ag)

Levels of vWF correlate with ABO blood type. Individuals with type O blood normally have the lowest levels of vWF, approximately 50-75% of the vWF levels found in persons with other blood types. vWF levels should be compared with an ABO blood group type–specific range from the laboratory where the test is performed.

Genetic analysis can aid diagnosis of vWD type. Newer techniques, such as next-generation sequencing, have the capacity to analyze several genes simultaneously when necessary and to identify exon deletions and duplications, which makes it possible to identify causative vWF defects in more patients than previously. Examples include discrimination of possible type 2N vWD from mild hemophilia A, discrimination of type 2B vWD from platelet-type vWD, and prenatal diagnosis of type 3 vWD.[20]

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Evaluation of vWF Level and Function

vWF Activity

vWF activity (the binding of VWF to platelet glycoprotein Ib [GPIb]) has traditionally been assessed by ristocetin cofactor (RCoF) activity. In this test, ristocetin is added to a suspension of washed formalin- or paraformaldehyde-fixed platelets in the presence of the patient's plasma (as a source of vWF). The rate of aggregation is then measured using an aggregometer, a device specifically designed to monitor this activity.

The test for RCoF activity is good for evaluating vWF function, although results are difficult to standardize and the test is difficult to perform. Thus, the validity of test results should be verified when the test is performed at centers with personnel who are not accustomed to performing this test.

Normal RCoF values are 50-200 IU/dL. A level below 30 IU/dL is considered definitive for vWD, although levels of 30-50 IU/dL may be found in some patients with type 1 or 2 vWD.[12]

Newer vWF activity assays use gain-of-function GPIbα mutants that bind vWF without the need for ristocetin. This provides better precision and a lower limit of detection. These assays avoid the falsely low readings than can occur with ristocetin-dependent methods in patients with some common vWF polymorphisms that do not cause bleeding.[21, 22]

vWF:Ag

This assay is usually performed (with rabbit antibody to vWF) using either a quantitative immunoassay or an enzyme-linked immunosorbent assay. A discrepancy between the vWF:Ag value and RCoF activity suggests a qualitative defect that should be further investigated by characterization of the vWF multimeric distribution. As with RCoF, a vWF:Ag level below 30 IU/dL is considered diagnostic of vWD, but levels of 30-50 IU/dL may be found in some patients with type 1 or 2 vWD.[12]

Bleeding Time, PT, and aPTT

Bleeding time

Historically, the template bleeding time was a test used to help diagnose vWD. However, this test is subject to wide variation and, with the availability of tests that provide more specific results, is not currently essential for making the diagnosis.

A prolonged bleeding time is not specific for vWD and does not help to predict whether patients without a bleeding disorder will have problematic bleeding during surgery. The test is difficult to perform, and results are difficult to confirm (ie, poor reproducibility); results frequently are normal in patients with vWD type I.

PT and aPTT

The aPTT is mildly prolonged in approximately 50% of patients with vWD. The prolongation is secondary to low levels of FVIII because one of the normal functions of vWF is to protect FVIII from degradation.

The PT should be within reference ranges. Prolongations of both the PT and the aPTT signal a problem with acquisition of a proper specimen or the presence of a disorder other than or in addition to vWD.

Workup by Type

vWD type 1

vWD type 1 can be diagnosed in a patient with significant mucocutaneous bleeding, laboratory test results compatible with vWD type 1, and a positive family history for vWD type 1. However, these criteria may be impossible to satisfy in many patients for various reasons. Therefore, physicians must acknowledge this diagnostic uncertainty and should not deny patients treatment, especially when patients' laboratory test results are compatible with vWD type 1 and the patients have either a significant history of mucocutaneous bleeding or a positive family history for vWD type I.

A less common problem is the misdiagnosis of vWD type 1 in patients who actually have a qualitative defect. The results of screening tests recommended for patients with vWD type 1 often show proportionally decreased RCoF activity and vWF:Ag in patients with vWD type 2B, although classic teaching is that a discrepancy should exist between the 2 tests. In this scenario, ristocetin-induced platelet aggregation test results should demonstrate an exaggerated affinity of the mutant vWF for platelets in the presence of ristocetin.

vWD type 2

Disproportionately low RCoF activity relative to vWF:Ag may reflect a decreased affinity of vWF for platelets. The most common cause of such loss of function is the absence of hemostatically effective large vWF multimers, characteristic of vWD type 2A. This subtype is diagnosed based on the combination of markedly reduced RCoF activity and compatible multimer gel analysis results.

In type 2B, brisk platelet agglutination occurs at low concentrations of ristocetin that have little or no effect on platelet-rich plasma from normal controls. Similar results are seen in one extremely rare disease, platelet-type vWD. In platelet-type vWD, mutations in platelet GpIb cause a phenotype similar to that of vWD type IIB.

vWD type 2M includes variants in which binding to platelets is impaired but the vWF multimer distribution is normal. Screening laboratory test findings are similar to those found in vWD type 2A, but multimer gel analysis results show that large multimers are present.

In vWD type 2N, the platelet-dependent functions of vWF are preserved, but FVIII levels are low (often < 10%). This condition is an autosomal mimic of hemophilia A, and a careful family history helps to distinguish the 2 disorders.

Multimeric examination of vWF is particularly important in the diagnosis of vWD type 2. Results from this laboratory test reveal the multimeric distribution of vWF, thus allowing classification of type 2 disease based on the specific absence of large multimers (type 2B) or both intermediate and large (type 2A) multimers.

vWD type 3

This is a recessive disorder in which vWF protein is virtually undetectable. The absence of vWF causes a secondary deficiency of FVIII and a subsequent severe combined defect in blood clotting and platelet adhesion. Results from screening assays show both absent or severely decreased RCoF activity and vWF:Ag in addition to a prolonged aPTT.

Low vWF

Guidelines from the National Institutes of Health and the United Kingdom recommend that the term "low vWF" rather than vWD be used to designate patients with an appropriate bleeding history and RCoF/vWF:Ag levels of 30-50 IU/dL.[12, 3] Such patients may nevertheless be candidates for treatment to increase vWF levels when they are at risk for bleeding.[12]

Testing for Therapeutic Options

A laboratory evaluation of a patient's response to administrations of desmopressin (DDAVP) is commonly performed to assess whether or not a patient can receive this product either therapeutically or prophylactically before surgery.

Perform a laboratory evaluation to rule out whether the patient has vWD type 2B prior to testing, in patients with risk factors for thrombotic complications, because case reports suggest this drug may be contraindicated in this setting.

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Treatment

Approach Considerations

The main treatment options for patients with von Willebrand disease (vWD) are desmopressin (DDAVP), recombinant von Willebrand factor (rVWF), and von Willebrand factor/factor VIII (vWF/FVIII) concentrates. DDAVP is a synthetic analogue of the antidiuretic hormone vasopressin; it has enhanced antidiuretic activity and no pressor activity related to vasopressin. Recombinant von Willebrand factor is indicated for on-demand treatment of minor or major hemorrhage in adults with vWD.[23] Purified plasma-derived concentrates of vWF/FVIII are used for treatment of bleeds and for surgical prophylaxis when DDAVP is ineffective or contraindicated.[3, 12]

Recombinant von Willebrand factor (Vonvendi) was approved by the US Food and Drug Administration (FDA) in December 2015. Approval was based on a phase 3 trial that showed that rVWF was safe and effective in treating 192 bleeds in 22 patients with vWD and stabilized endogenous FVIII:C levels. Control of bleeding was rated good or excellent, with excellent control in 96.9% (119 of 122 minor bleeds, 59 of 61 moderate bleeds, and 6 of 7 major bleeds). A single infusion was effective in 81.8% of bleeds.[23]

In addition, antifibrinolytic drugs (ie, aminocaproic acid, tranexamic acid) can be used orally or intravenously to treat mild mucocutaneous bleeding. Topical agents (eg, fibrin sealants) may be considered as optional adjunctive therapy for dental surgery and for surface wound bleeding that is unresponsive to drugs and concentrates; however, the safety of these agents remains unconfirmed.[12]

Platelet transfusions may be helpful in some patients with vWD (eg, type 3) to control bleeding that is refractory to other therapies.[12] Cryoprecipitate and fresh frozen plasma contain functional von Willebrand factor (vWF) but should be avoided if at all possible because of the potential transmission of viral disease. An additional drawback of fresh frozen plasma is the large infusion volume most often required.[12, 13]

For prophylaxis in major surgery or for treatment of serious bleeding episodes, rVWF (with or without FVIII) or vWF-containing factor VIII (FVIII) concentrates are the treatment of choice. However, a hematologist experienced in the management of bleeding disorders should be consulted prior to all surgical/dental procedures.

In extremely rare cases, vWD patients who receive FVIII concentrates as prophylaxis for surgery may experience venous thromboembolic complications. A literature review by Franchini et al found only 11 reported cases, most of which involved orthopedic procedures. Nevertheless, these authors advise that the need for thromboprophylaxis with vWF/FVIII concentrates in patients with vWD who undergo major surgery should be individually assessed, after a careful risk/benefit analysis.[24]

vWF in pregnancy

During pregnancy, the vWF level increases in most patients with non–type 3 vWD. Thus, in patients with functionally normal vWF, labor and delivery usually proceed normally.

However, patients with type 2 disease may experience hemorrhagic problems. In particular, patients with type 2B may experience thrombocytopenia due to the increased plasma levels associated with abnormal vWF. All patients should be monitored for excessive bleeding, particularly during the first week post partum.

Deterrence

Advise patients to avoid aspirin-containing compounds. In addition, patients should be wary of any physical activity associated with an increased risk of hemorrhage.

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Type I von Willebrand disease

DDAVP is the treatment of choice for individuals with vWD type I. The infusion of DDAVP into healthy individuals and individuals with vWD type 1 results in a rapid increase in circulating levels of vWF:Ag and FVIII and RCoF activity.

Typically, a maximal rise of vWF and FVIII is observed in 30-60 minutes. The typical maximal rise is 2- to 4-fold for vWF and 3- to 6-fold for FVIII. Additionally, hemostatic levels of both factors are usually maintained for at least 6 hours.

DDAVP can be administered not only through intravenous infusion but also via a highly concentrated nasal spray; 300 mcg intranasally produces levels comparable to those observed with an intravenous infusion. Intranasal treatment is particularly useful for home therapy of menorrhagia and recurrent epistaxis.

DDAVP regimens are not standardized. A review by Neff notes the following[25] :

- Dosing DDAVP at 24 hour intervals may reduce the risk of side effects without significantly compromising vWF activity/FVIII:C levels; most treatment centers will not prescribe more than three doses at this frequency
- Standard intravenous and subcutaneous DDAVP doses are 0.3 µg/kg, but for patients over 50 kg, a fixed dose of 15 µg may provide acceptable efficacy with less risk of serious side effects

Fluid retention and hyponatremia are common complications of DDAVP therapy. Consequently, most treatment centers recommend weight-based fluid restriction, particularly in patients undergoing surgery, along with monitoring of serum sodium levels in children younger than 2 years and in patients receiving repeated doses of DDAVP.[3, 25]

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Type 2 von Willebrand disease

Responses to DDAVP are variable in patients with type 2 disease; some patients respond while others should receive vWF concentrates.[25] United Kingdom guidelines recommend performing a trial infusion of DDAVP in patients with type 2A, 2M, and 2N vWD and measuring vWF antigen, vWF activity, and FVIII at baseline, 30–60 min, and 4–6 h.[3]

Many individuals with vWD type 2A have a response to DDAVP, with peak vWF and FVIII levels at 30-60 minutes. This is similar to responses observed in patients with vWD type 1. However, rapid loss of vWF, FVIII, and particularly ristocetin cofactor (RCoF) activity occurs as the high-molecular-weight multimers are degraded, with return to baseline levels at 4 hours post infusion. Although the response is transient, it may be adequate therapy in certain clinical situations.

DDAVP trials may be contraindicated in patients with type 2B, because of thrombocytopenia and possible thrombotic complications. DDAVP is usually not effective in patients with type 2M and is rarely effective in patients with type 2N.

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Type 3 von Willebrand disease

Individuals with vWD type 3 have a virtually complete deficiency of vWF. Thus, DDAVP, which causes the release of stored vWF, has no effect in patients with this disorder.

The treatment of choice for patients with vWD type 3 (as with other vWD types unresponsive to DDAVP) is rVWF (with or without FVIII)[23] or virus-inactivated, vWF-containing FVIII concentrates that contain a near-normal complement of high-molecular-weight vWF multimers.[26] Most experience reported in the literature has been with the use of Humate-P, a plasma-derived product of intermediate purity. Two other FVIII concentrates, Alphanate and Koate-HP, have been reported to be effective in the treatment of vWD. Too little vWF is present in monoclonally purified FVIII concentrates and recombinant FVIII concentrates to allow their use in the treatment of vWD.

Alloantibody formation occurs in 10-15% of patients with type 3 disease. Therefore, the possibility of this complication must be managed appropriately, because patients are at increased risk for life-endangering anaphylactic reactions to vWF-FVIII preparations. With hemostatic stress in emergency situations, infusion of FVIII preparations devoid of vWF, while adjusting for the markedly decreased FVIII half-life, may be necessary.

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Medication

Medication Summary

The two principal drug categories used in the treatment of von Willebrand disease (vWD) are nontransfusional compounds (eg, desmopressin [DDAVP], antifibrinolytics) and transfusional compounds. Whenever possible, avoid transfusions.

DDAVP is the treatment of choice for individuals with vWD type 1. Responses to DDAVP are variable in patients with type 2 disease. Individuals with vWD type 3 have a virtually complete deficiency of vWF; therefore, because DDAVP acts by releasing stored vWF, the drug has no effect in type 3 disease.

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Coagulation Factors

Class Summary

Replacing coagulation factors are essential to successfully managing bleeding episodes.

von Willebrand factor, recombinant (Vonvendi)

Recombinant von Willebrand factor that promotes platelet aggregation and platelet adhesion on damaged vascular endothelium. It is indicated for on-demand treatment and control of bleeding episodes in adults aged 18 years or older with von Willebrand disease.

Antihemophilic factor/von Willebrand factor complex (Alphanate, Humate P, Wilate)

When DDAVP cannot raise the vWF level to hemostatically acceptable levels, a blood product containing vWF may be required. VWF, a protein found in normal plasma, is necessary for clot formation; when administered, it can temporarily correct coagulation defects of patients with classic hemophilia (hemophilia A), in whom a deficiency of FVIII exists. The specific activity of different brand products varies. Humate-P and Alphanate are products containing both FVIII and vWF. The dose depends on the patient's weight, the severity of hemorrhage, the severity of deficiency, the presence of inhibitors, and the desired FVIII level.

The clinical effect on the patient is the most important determinant of therapy. When inhibitors are present, dose requirements are extremely variable and are determined by clinical response. The length of treatment and the loading dose depend on the extent and location of the hemorrhage.

Alphanate is indicated for the prevention of excessive bleeding for surgical and/or invasive procedures in vWD when desmopressin is either ineffective or contraindicated. It is not indicated for patients with severe vWD (ie, type III) who are undergoing major surgery.

Humate-P is indicated for the treatment and prevention of spontaneous and trauma-induced bleeding episodes for patients with mild to moderate or severe vWD.

Antifibrinolytics Agents

Class Summary

Antifibrinolytics may be used to prevent the breakdown of formed blood clots in order to temper hemorrhage. These agents block the formation of plasmin. They may be used to manage mucosal bleeding, particularly in the nasopharynx and in the gastrointestinal and genitourinary tracts. Antifibrinolytics are most often used concomitantly with other medications for dental extractions and oral surgery.

Aminocaproic acid (Amicar)

Aminocaproic acid inhibits fibrinolysis via the inhibition of plasminogen activator substances and, to a lesser degree, through antiplasmin activity. Its main disadvantage is that thrombi that form during treatment are not lysed, and its effectiveness is uncertain. Aminocaproic acid has been used to prevent the recurrence of subarachnoid hemorrhage.

Tranexamic acid (Cyklokapron, Lysteda)

Tranexamic acid is an alternative to aminocaproic acid. It inhibits fibrinolysis by displacing plasminogen from fibrin.

Vasopressin-Related

Class Summary

These agents improve platelet function in qualitative disorders.

Desmopressin (DDAVP, Stimate)

Desmopressin is the treatment of choice for individuals with vWD type I. It causes a rapid (about 30 min; peaks in 90-120 min), 3- to 5-fold increase in the release of vWF and FVIII from endothelial cells.

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Estrogens

Class Summary

Estrogen may be helpful in reducing menorrhagia. Even in type III disease, in which case vWF and FVIII levels are not necessarily increased, estrogen may mediate changes in the endometrium that lessen menstrual bleeding severity.

Ethinyl estradiol and levonorgestrel (Levora, Nordette, Lutera, Trivora)

Ethinyl estradiol reduces the secretion of luteinizing hormone and follicle-stimulating hormone from the pituitary by decreasing the amount of gonadotropin-releasing hormones.

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Questions & Answers

Overview

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