VON WILLEBRAND DISEASE

Type 1 — Partial quantitative deficiency of vWF. Autosomal dominant disorder, but only a minority of persons with a nonfunctional vWF allele have bleeding symptoms.

Type 2 — Qualitative abnormalities of vWF.

Type 2A — Abnormal assembly of high-molecular-weight vWF multimers. Autosomal dominant.

Type 2B — An abnormal (increased) binding of vWF to platelets, causes depletion of high-molecular-weight vWF multimers and thrombocytopenia. Autosomal dominant.

Type 2M — Abnormal (decreased) binding of vWF to platelets, but with normal vWF multimer distribution. Autosomal dominant.

Type 2N — Abnormal (decreased) binding of vWF to factor VIII, causing low plasma factor VIII levels. Autosomal recessive.

Type 3 — Virtually complete deficiency of vWF. Autosomal recessive (but most carriers do not manifest the abnormalities of type 1 disease).

Pseudo-von Willebrand disease (platelet-type vWD)
Abnormal platelet GP Ib-IX-V with increased affinity for large vWF multimers. Phenotype indistinguishable from type 2B disease.

TYPICAL LAB FINDINGS

TYPICAL LABORATORY FINDINGS IN VWD VARIANTS

Type	vWF: Ag	vWF: RCof	F VIII	RIPA	Multimer pattern
1	↓	↓	↓	↓	All sizes present or uniformly ↓
2A	↓	↓↓	↓ or NL	↓	Absence of large & intermediate forms
2B	↓	↓↓	↓ or NL	↑	Absence of large forms
2M	↓	↓	↓ or NL	↓	All sizes present
2N	NL	NL or ↓	↓↓	NL	All sizes present
3	↓↓↓↓	↓↓↓↓	↓↓↓↓	N/A	Absence of all vWF

vWF = von Willebrand Factor
FVIII = Factor VIII level
Ag = antigen
RCof = ristocetin cofactor activity
RIPA = ristocetin-induced platelet agglutination. Concentration of ristocetin at which platelets aggregate.

References: Federici AB and Mannucci PM. *Ann Med* 2007;39:346 – 58 and Kitchens. Consultative Hemostasis and Thrombosis. Second Edition; Saunders Publishing; 2007:103.

Last Updated on June 3, 2009

TREATMENT OF BLEEDING EPISODES IN VON WILLEBRAND DISEASE

Type	Initial Treatment	Alternative Options
1	Desmopressin	Antifibrinolytics; estrogens; vWF/FVIII concentrates
2A	vWF/FVIII concentrates	Desmopressin for mild bleeding
2B	vWF/FVIII concentrates	
2M	Desmopressin	vWF/FVIII concentrates
2N	Desmopressin	vWF/FVIII concentrates
3	vWF/FVIII concentrates	Desmopressin, platelet concentrates
3 with alloantibodies	Recombinant FVIII	Recombinant FVIIa
vWF = von Willebrand Factor FVIII = Factor VIII FVIIa = Activated Factor VII		

Reference: Adapted from Federici AB and Mannucci PM. *Ann Med* 2007;39:346-58

Desmopressin (DDAVP) 0.3 mcg/kg q12-24 hrs IV or SQ Daily for 2 days

Factor VIII Concentrate with von Willebrand Factor (See Table Below)

NOTE: Expert opinion and review articles suggest variety of doses. After the loading dose, further dosing should be based on Factor VIII levels or preferably ristocetin cofactor activity if available.

FACTOR VIII CONCENTRATE WITH VON WILLEBRAND FACTOR (SEE NOTE ABOVE)		
Classification	**Hemorrhage**	**Dosage (IU vWf:Rcof/kg)**
Type 1		
Mild Baseline vWF:Rcof activity typically >30% of normal (i.e.,> 30 IU/dL)	Major	Loading: 40 to 60 IU/kg Then 40 to 50 IU/kg every 8 to 12 hrs for 3 days to keep the nadir level of vWF:Rcof greater than50% of normal (i.e., greater than 50 IU/dL) Then 40 to 50 IU/kg daily for a total of up to 7 days
Moderate or Severe Baseline vWF:Rcof activity typically <30% of normal(i.e., <30 IU/dL)	Minor	40 to 50 IU/kg (1 or 2 doses)
	Major	Loading: 50 to 75 IU/kg Then 40 to 60 IU/kg every 8 to 12 hrs for 3 days to keep the nadir level of vWF:Rcof greater than 50% of normal (i.e., greater than 50 IU/dL) Then 40 to 60 IU/kg daily for a total of up to 7 days
Type 2 (all variants) and Type 3		
	Minor	40 to 50 IU/kg (1 to 2 doses)
	Major	Loading: 60 to 80 IU/kg Then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of vWF:Rcof greater than 50% of normal (i.e., greater than 50 IU/dL) Then 40 to 60 IU/kg daily for a total of up to 7 days.

Reference: Mannucci PM. *N Engl J Med* 2004;351:683 - 94.

COAGULATION PRODUCTS

DESMOPRESSIN
(DDAVP®)

I. MECHANISM OF ACTION
Synthetic analogue of arginine vasopressin. Increases levels of vWF and Factor VIII through release from endogenous reservoirs, but not increased synthesis. Expected increase in levels is 3-5 fold baseline. Mechanism of efficacy in other inherited and acquired platelet disorders is less certain, but may be due to enhanced exposure if platelet vWF to GIIB/IIIA on platelet surface. Vasopressin like mechanisms not covered in this monograph.

II. PHARMACOKINETICS
A) Administered in nasal, oral, or in parenteral forms.
B) Distribution of the drug is unknown. Unknown whether it crosses the placenta.
C) Peak activity after IV dosing occurs 90 minutes to 2 hours. Increase in Factor VIII activity is noted after 30 minutes.
D) Peak activity after nasal dosing is within 40-45minutes. Increase in Factor VIII is noted 30 minutes after dose.
E) Half-life is 3-4 hours.
F) Bioavailability of oral dose is about 5% and 16% compared to intranasal and IV dosing.

III. DOSAGE AND ADMINISTRATION
A) Intravenous dosage is 0.3mcg/kg IV. Repeat doses are usually given in 8-24 hours. A dose of 25 mcg is typically used.
B) Nasal dosage: Adults >50 kg: One spray (150 mcg/0.1 mL) in each nostril. Adults < 50 kg, adolescents, children, and infants ≥ 11 months: A single 150 mcg intranasal spray. Repeat doses are usually given in 8-24 hours.
C) Tachyphylaxis occurs with repeated dosing. May continue dosing for 2 – 3 days.
D) No dose adjustment needed for renal or hepatic dysfunction.
E) Administer 0.5 – 2 hours prior to procedure.

IV. TOXICITY
A) Hyponatremia leading to water intoxication, seizures, and/or coma can occur, especially in elderly or pediatric patients.
B) The most common adverse reactions to nasal or parenteral desmopressin are mild facial flushing and headache.
C) Tachyphylaxis (tolerance) is more common if doses of desmopressin are administered more frequently than every 48 hours.
D) Anaphylactoid reactions have been reported.
E) Transient elevated hepatic enzymes up to ≤ 1.5 times the upper limit of normal occur and they typically return to normal with continued desmopressin treatment.

V. CLINICAL MONITORING
A) Monitoring of Factor VIII levels in hemophilia after a single dose is recommended prior to clinical use in order to determine efficacy.
B) Monitoring of bleeding time or PFA in patients with platelet dysfunction after a single dose is recommended prior to clinical use to determine efficacy, although this lab parameter may not fully correct.
C) Serum sodium and blood pressure should also be monitored.

AMINOCAPROIC ACID
(AMICAR®)

I. MECHANISM OF ACTION
Binds to lysine-binding sites within the plasminogen/plasmin molecule interfering with the ability of plasmin to lyse fibrin clots. Does not alter the concentration of clotting factors. May suppress chymotrypsin proteolytic enzymes and antigen-antibody reactions. Diminishes tuberculin reaction in those sensitive to tuberculin.

II. PHARMACOKINETICS
A) Administered topically, orally or in parenteral forms.
B) Rapidly absorbed after oral administration with peak plasma concentrations attained in less than 2 hours.
C) Eliminated primarily by the kidney, but dose reductions not needed in renal failure.
D) Elimination half-life is 2 hours.

III. DOSAGE AND ADMINISTRATION
A) Oral dose is 5 grams PO the first hour, followed by 1—1.25 grams/hour PO for 8 hours or until a therapeutic response is achieved. The maximum dosage is 30 grams/day.
B) Intravenous loading dose is 4—5 grams IV over 1 hour, followed by a continuous infusion at 1 gram/hour IV for 8 hours or until therapeutic response is achieved.
C) For the prophylaxis or treatment of oral bleeding following dental extraction in hemophiliacs, rinse with 5 ml (1.25 g) aminocaproic syrup for 30 seconds. This procedure should be repeated every 4 hours until the bleeding is controlled.
D) For hemorrhagic cystitis, a continuous bladder irrigation with 20 mg/100 mL of saline until 24 hours after the urine becomes clear has been used.

IV. TOXICITY
A) Inhibition of spontaneous fibrinolysis, presenting the possibility of a thrombotic event. There have been reports of thrombosis following use of aminocaproic acid, but a causal relationship is uncertain. **This drug is contraindicated for genitourinary tract bleeding if an upper tract source is possible.** Consult with GU service prior to use.
B) Hypotension and sinus bradycardia.
C) CNS effects including dizziness, headache, tinnitus, and delirium. Seizures have also been reported.
D) Rhabdomyolysis.
E) GI symptoms including abdominal pain, diarrhea, and nausea/vomiting.
F) Hemophilia patients receiving aminocaproic acid after dental surgery have reported ejaculation dysfunction (dry ejaculation).

V. CLINICAL MONITORING
A) Monitoring is primarily through clinical response of decreased bleeding.
B) No routine coagulation or fibrinolytic parameters are usually tested. Conceivably a thromboelastogram would show decreased fibriniolysis.

DRUGS DESIGNED TO AFFECT PLATELET AGGREGATION

DRUG	SITE OF ACTION	ROUTE	HALF-LIFE	METABOLISM	ANTIDOTE	STOP BEFORE PROCEDURE
Aspirin*	COX 1-2	PO	20 minutes	Hepatic	None	7 days
Dipyridamole	Adenosine	PO	40 minutes	Hepatic	None	24 hours
Clopidogrel	ADP	PO	7 hours	Hepatic	None	5 days
Ticlopidine	ADP	PO	4 days	Hepatic	None	10 days
Abciximab	GPIIb-IIIa	IV	30 minutes	Renal	None	72 hours
Eftifibatide	GPIIb-IIIa	IV	2.5 hours	Renal	None	24 hours
Tirofiban	GPIIb-IIIa	IV	2 hours	Renal	Hemodialysis	24 hours

COX = cyclooxygenase enzyme

ALL: No PT/PTT prolongation. Monitor platelets periodically.
*__Aspirin__: Irreversibly acetylates and blocks the platelet COX enzyme complex, leading to inactivation of TXA2 in platelets and megakaryocytes.
Since only 10% platelet pool replenished daily, a daily ASA permanently blocks platelet COX
Takes 5-6 days for 50% of platelets to return to function.
GP IIb-IIIa: Final common pathway for platelet aggregation. Inhibition of fibrinogen and vWF to platelets like Glanzmann's thrombasthenia.

Reference: Roberts HR, Monroe DM, Escobar MA. *Anesthesiology* 2004;100:722 – 30. Adapted from Table 3.

NSAIDs EFFECT ON PLATELET AGGREGATION

DRUG	SITE OF ACTION	ROUTE	HALF-LIFE*	STOP BEFORE PROCEDURE
Piroxicam	COX 1-2	PO	50 hours	10 days
Indomethacin	COX 1-2	PO/PR	5 hours	2 days
Ketorolac	COX 1-2	PO/IV	7 hours	2 days
Ibuprofen	COX 1-2	PO	2 hours	1 days
Naproxen	COX 1-2	PO	13 hours	2 days
Diclofenac	COX 1-2	PO	2 hours	1 days
Celecoxib/Rofecoxib	COX 2	PO	10-17 hours*	None

COX = cyclooxygenase enzyme
*Half-life increases with dose size

ALL: Competitive, rev inhibitors of COX activity by 70-90%.
Liver metabolism.
No antidote.
No PT/PTT prolongation.

Reference: Roberts HR, Monroe DM, Escobar MA. *Anesthesiology* 2004;100:722 – 30. Adapted from Table 4.