How to Reverse an Antithrombotic Agent

The authors review options and precautions to consider when you need to restore hemostasis in a patient receiving an anticoagulant, antiplatelet, or fibrinolytic agent who is getting into trouble with bleeding or an elevated INR.

By Maria Neuner, MD, and Jonathan Davis, MD

A stable patient with a supratherapeutic international normalized ratio (INR) level and a hemorrhaging patient on clopidogrel both present the acute care provider with the same difficult challenge: determining the most appropriate way to reverse an antithrombotic medication.

The ubiquity of antithrombotic agent use and the range of serious health problems that call for it are sobering things to stop and think about. We have patients with atrial fibrillation or venous thromboembolism taking anticoagulants such as warfarin and enoxaparin, patients with a history of acute coronary syndromes (ACS) or cerebrovascular disease on antiplatelet agents such as aspirin and clopidogrel, patients being treated with fibrinolytics for acute myocardial infarction or (in carefully selected cases) a cerebrovascular accident, and more. Given the high-risk nature of many of these conditions, it is essential for us to have a solid understanding of the actions of antithrombotic agents and of what is involved in reversing them.

>>FAST TRACK<<

Hemostasis has three key components: platelets, the plasma coagulation cascade, and the blood vessel wall (endothelium).

COMPONENTS OF HEMOSTASIS

Familiarity with the process of intrinsic hemostasis by endogenous prothrombotic and antithrombotic mechanisms is fundamental to understanding antithrombotic medication reversal. Hemostasis has three key components: platelets, the plasma coagulation cascade, and the blood vessel wall (endothelium). Primary hemostasis (Figure 1) involves the formation of a "platelet plug" at the site of blood vessel injury. Platelets are activated and form a plug to initially halt bleeding. Platelet adhesion occurs through their binding to exposed subendothelial von Willebrand factor.

Secondary hemostasis (Figure 2) stabilizes the initial platelet plug through fibrin deposition. Fibrin results from the plasma coagulation cascade. Thrombin converts soluble fibrinogen to insoluble fibrin, which cements and stabilizes the plug.

The principal endogenous antithrombotic mechanisms include antithrombin III, protein C, protein S, and the plasmin system. Antithrombin III neutralizes most of the enzymes in the coagulation cascade, particularly thrombin. Proteins C and S work together to inactivate certain procoagulant factors, and plasmin converts fibrin to its degradation products.

ANTITHROMBOTICS AND THEIR OPPONENTS

Antithrombotic medications can be divided into three principal categories: anticoagulants, antiplatelet agents, and fibrinolytics (Table 1). Antithrombotic medications work by blocking endogenous prothrombotic pathways (warfarin, for example, antagonizes the carboxylation of vitamin K–dependent factors) or by accentuating endogenous antithrombotic pathways (heparin, for example, accentuates the effects of antithrombin III).

Dr. Neuner is chief resident and Dr. Davis is associate program director and associate professor in the department of emergency medicine at Georgetown University and the Washington Hospital Center Emergency Medicine Training Program in Washington, DC.

The various available "reversal" agents share a common characteristic: they are prothrombotic in nature. Prothrombotic agents include blood products and medications, either of which may exert their effects on primary or secondary hemostatic pathways (Table 2). The blood products carry the potential for bloodborne pathogen transmission. Although more detailed information regarding transfusion medicine is beyond the scope of this article, it is important to recognize that platelets, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), and cryoprecipitate are all derived from donated human blood. Factor VIIa, on the other hand, is a recombinant product, and thus classified as a medication for the purpose of this discussion.

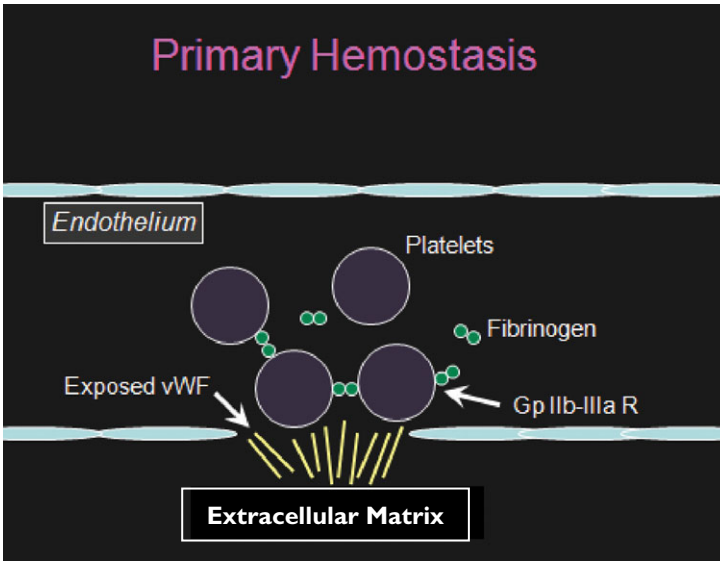

FIGURE 1. Primary Hemostasis. The intrinsic hemostatic response to blood vessel injury begins with the formation of a plug as platelets bind to exposed subendothelial vWF.

vWF = von Willebrand factor; GP IIb-IIIaR = glycoprotein receptor

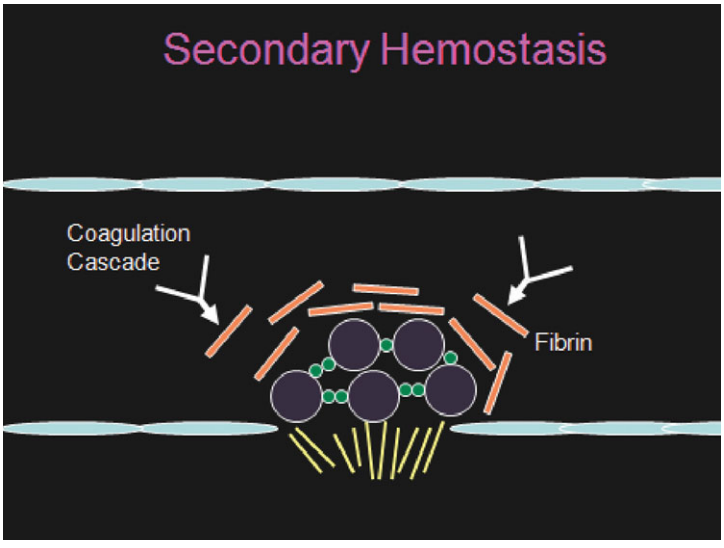

FIGURE 2. Secondary Hemostasis. As the hemostatic response continues, the plasma coagulation cascade leads to the production of insoluble fibrin that cements and stabilizes the platelet plug.

REVERSAL STRATEGIES FOR SPECIFIC AGENTS

Management of antithrombotic medication toxicity requires varying management strategies depending on several factors, including the mechanism of action of each antithrombotic medication involved.[1,2] In the following sections, antithrombotic reversal will be discussed both generally and in terms of case-based scenarios. Anticoagulant reversal, specifically vitamin K antagonists and heparins, will be addressed first, followed by antiplatelet agent reversal, fibrinolytic reversal, and reversal of the newer (alternative) antithrombotic medications.

Vitamin K antagonists. Warfarin is an agent that inhibits the activation of factors II, VII, IX, and X.[3] Although there is a paucity of outcomes-based literature on this topic, the American College of Chest Physicians (ACCP) has published specific consensus recommendations regarding the reversal of vitamin K antagonists.[4] The reversal of warfarin coagulopathy involves three principal measures: discontinuing the warfarin, administering vitamin K, and consideration of factor replacement with FFP, PCC, or recombinant factor VIIa (rFVIIa).

The underlying indication for the patient's antithrombotic therapy must be reviewed prior to any decision about warfarin reversal. For instance, reversal would increase a patient's risk of thromboembolic complications if the purpose of the warfarin is to help maintain a mechanical heart valve. If atrial fibrillation is the indication, warfarin reversal will raise the risk of mural thrombus and consequent

TABLE 1. Commonly Used Antithrombotic Agents

Drug class	Acts on	Examples
Anticoagulants		
vitamin K antagonists	II, VII, IX, X	warfarin
heparins	Xa, others	UFH, LMWH
pentasaccharides	Xa	fondaparinux, indraparinux
direct thrombin inhibitors	II	argatroban, bivalirudin, lepirudin
Antiplatelet agents		
NSAIDs	prostaglandin	aspirin
thienopyridines	ADP	clopidogrel, ticlodipine
pyrimido-pyrimidine	cAMP	dipyridamole
glycoprotein IIb/IIIa receptor antagonists		eptifibatide, tirofiban, abciximab
Fibrinolytics		
plasminogen activators		alteplase, reteplase, tenecteplase

UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; NSAIDs = nonsteroidal anti-inflammatory drugs; ADP = adenosine diphosphate; cAMP = cyclic adenosine monophosphate

ischemic stroke. A careful risk-benefit analysis must be undertaken on a case-by-case basis. In certain instances the decision is made easier due to one of two relatively firm indications for warfarin reversal: serious or life-threatening hemorrhage or the need for invasive procedures. A softer indication is correction of a supratherapeutic INR level in a mildly symptomatic (limited to nuisance-level bleeding) or entirely asymptomatic patient.

>>FAST TRACK<<

The underlying indication for the patient's antithrombotic therapy must be reviewed prior to any decision about warfarin reversal.

Scenario 1: An asymptomatic elderly female patient with a supratherapeutic INR level (INR = 12) who is referred by her primary care provider for evaluation.

Mildly symptomatic or asymptomatic patients with elevated INR need frequent monitoring in the short term, followed by an adjustment in warfarin dosage. The ACCP's management recommendations, including those on the dosing of vitamin K, differ depending on the degree of deviation from the therapeutic target range for INR. If the patient's INR is between 3 and 5, a single dose of warfarin should be withheld; between 5 and 9, one or two doses should be withheld and 1 to 5 mg of oral vitamin K should be considered; and if the INR is above 9, warfarin should be stopped and 2.5 to 5 mg of oral vitamin K considered.[4] Oral vitamin K given according to these guidelines will significantly reduce INR within 24 to 48 hours.

Scenario 2: A patient with a supratherapeutic INR on warfarin (INR = 4.6) with an active lower GI bleed and associated vital sign abnormalities (mild tachycardia, borderline hypotension).

Patients with serious or life-threatening bleeding need more aggressive reversal of their coagulopathy. Recommendations include withholding warfarin therapy, giving intravenous vitamin K (up to 10 mg slow infusion), and supplementing these interventions with FFP, PCC, or rFVIIa, depending on the urgency of the situation.[5] In patients with life-threatening

bleeding (such as intracranial hemorrhage), there may not be enough time to wait for FFP to be thawed and delivered from the blood bank. In addition, the amount of FFP required to fully correct the INR is considerable and may take hours to infuse. Therefore, guidelines recommend bypassing FFP for other alternatives, such as rFVIIa or PCC. It is important to note, however, that both rFVIIa and PCC have been associated with an increased risk of thromboembolic events, which must be weighed in the overall risk-benefit equation when contemplating their use.

The delayed and unpredictable response to both subcutaneous and intramuscular administration of vitamin K makes those routes inappropriate for anticoagulant reversal. Adequate effects are typically achieved within 24 hours when the vitamin is administered orally, or within 12 hours when it is given intravenously. For asymptomatic (or mildly symptomatic) patients, it is best to start with lower oral doses. The effects of vitamin K can overcorrect the INR or last for a longer period than desired (warfarin "resistance"), particularly with higher doses, and may last up to 7 days.

Intravenous vitamin K has long been shunned by health care providers because of its association with anaphylactic reactions. Although controlled data are lacking, a large case series demonstrated a lower rate of serious allergic reactions—approximately 3 per 10,000 doses—than is generally appreciated.[6] Interestingly, reactions may in fact be related to the pharmaceutical vehicle and not to the vitamin itself. Emergency medicine textbooks typically advocate a conservative approach to the use of intravenous vitamin K, recommending it for use only in patients with life-threatening bleeding, suicidal vitamin K antagonist ingestion, or "super-warfarin" poisoning, as in rodenticide ingestion.

Overall, the risks associated with intravenous vitamin K have been exaggerated. With this said,

TABLE 2. Prothrombotic Agents

	Reversal agent	Mechanism of action	Typical adult dosage*
Medications			
1° hemostasis	dDAVP	releases vWF	0.3 µg/kg IV
2° hemostasis	vitamin K	rejuvenates factors II, VII, IX, X	varies
	protamine	reverses heparin	50 mg IV maximum
	rFVIIa	activates coagulation cascade	30 µg/kg IV (range 15-90 µg/kg)
	aminocaproic acid/ tranexamic acid	antifibrinolytic	variable
Blood products			
1° hemostasis	platelets	supplies platelets	1 unit (apheresis) *or* "6 pack" IV
2° hemostasis	FFP	supplies clotting factors	5-15 mL/kg IV
	PCC	supplies factors II, VII, IX, X	20-50 IU/kg IV
	cryoprecipitate	supplies factor VIII, vWF, and fibrinogen	10 units IV

*These are general guidelines, as dosing for antithrombotic agent reversal has not been firmly established.
dDAVP = deamino-D-arginine vasopressin (desmopressin); vWF = von Willebrand factor; IV = intravenously; rFVIIa = recombinant factor VIIa; FFP = fresh frozen plasma; PCC = prothrombin complex concentrate

practitioners experienced in administering intravenous vitamin K recommend a very slow, dilute, controlled infusion (1 mg per hour), despite the maximum infusion rate of 1 mg per minute recommended in the medication package insert, because the risks, although very rare, are real.

>>FAST TRACK<<

Intravenous vitamin K has long been shunned by health care providers because of its association with anaphylactic reactions.

In patients with serious bleeding, 5 to 15 mg/kg IV FFP should be administered.[7,8] In the average adult, this amounts to approximately 3 to 4 units of FFP. There is no additional benefit to be gained from exceeding this recommended dose. Rather, infusing more FFP increases the potential for volume overload. The treatment may need to be repeated in cases of persistent coagulopathy despite initial interventions aimed at reversal.

The use of PCC can be considered for the treatment of hemophilia in patients who have developed inhibitors to single-factor concentrates. The concentration of vitamin K–dependent factors is 25 times higher in PCC than in FFP (and therefore the volume needed for effect is much less). This is not always a practical option, however, because PCC is not uniformly available "on demand" in the United States.

When there is not enough time for the thawing of FFP to treat life-threatening hemorrhage and PCC is unavailable, the use of rFVIIa should be considered as its effects are immediate.[9] The typical recommended dose of rFVIIa in this setting is anywhere from 15 to 90 µg/kg IV. Administration leads to a burst of thrombin generation at sites of vessel injury. The use of rFVIIa is associated with theoretical and anecdotal benefits,

but since outcomes-based data are lacking, a trial of more "traditional" therapies (vitamin K, FFP) is typically indicated first.[10] As a general rule, rFVIIa should be reserved for use as a rescue agent in patients with serious or life-threatening bleeding complications of antithrombotics for whom conventional therapies have failed or are unavailable.

Heparin. Heparins bind and activate antithrombin III, which in turn inactivates factors Xa and IIa. The half-life of unfractionated heparin (UFH) is 30 to 150 minutes, and the level of anticoagulation can be followed with the activated partial thromboplastin time (aPTT). Low-molecular-weight heparins (LMWH) inactivate factor Xa primarily. Reversing anticoagulant effects of heparins involves two principal strategies: allowing the anticoagulant effect to dissipate over time or protamine administration. Low-molecular-weight heparins present a special circumstance, as there is no proven, reliable method for their reversal.

Scenario 3: A patient who receives UFH for treatment of a recurrent deep venous thrombosis and develops coffee-ground emesis following heparin bolus.

Directed treatment of the bleeding source and waiting for the effects of heparin to simply dissipate on its own represent the most straightforward approach to this problem. Alternatively, protamine sulfate may be given. Protamine is a basic protein that binds to heparins, forming a stable salt. It should be administered cautiously, with a maximum intravenous dose of 50 mg over 10 minutes. Protamine is dosed in direct proportion to the amount of heparin received (1 mg protamine for every 100 U of heparin administered in the preceding few hours). The risks of protamine include allergic phenomena, as well as the potential for platelet aggregation, which may cause either bleeding (reduced number of functional platelets) or thrombosis.

There is currently no reliable antidote available for LMWH. Given its comparatively long half-life,

discontinuation is a less attractive reversal option for LMWH. Similarly, protamine is less reliable for LMWH as compared with UFH. Fortunately, however, bleeding complications related to LMWH are infrequent. One important exception is patients with underlying renal disease, who are more prone to LMWH-related bleeding complications than are those with normal renal function.

Antiplatelet agents. There are no formal guidelines and limited data regarding optimal strategies for reversing antiplatelet agents. Available options include discontinuing the antiplatelet medication, administering desmopressin (deamino-D-arginine vasopressin [dDAVP]), and transfusing platelets. In addition, there is a potential role for rFVIIa in this setting. If you have time and the patient does not have life-threatening bleeding, discontinue the antiplatelet medication and consider dDAVP at a dose of 0.3 µg/kg IV (approximately 20 µg for an adult patient). In the case of serious or life-threatening bleeding, administer dDAVP, transfuse platelets, and if all else fails, consider the use of rFVIIa as a rescue agent in the direst situations.

Fibrinolytic agents. In patients with massive bleeding, hemodynamic compromise, or intracranial hemorrhage following fibrinolytic administration, all anticoagulant, antiplatelet, and fibrinolytic medications should be immediately discontinued. In addition, give medication-specific reversal agents based on the antithrombotics that are "on-board" at the time. The central strategy for reversal of fibrinolytic agent–related bleeding involves preservation of fibrin. Cryoprecipitate may be utilized to replenish fibrinogen stores (particularly when fibrinogen levels are less than 100 mg/dL), and FFP may be administered to replete all coagulation factors (which fuels the conversion of fibrinogen to fibrin). Antifibrinolytic agents such as aminocaproic acid serve as an additional option but are rarely utilized in this setting.

>>FAST TRACK**<<**

The central strategy for reversal of fibrinolytic agent–related bleeding involves preservation of fibrin.

Alternative antithrombotic agents. The search for novel antithrombotic agents has made great strides in recent years. Two new antithrombotic classes include the factor Xa inhibitors and the direct thrombin inhibitors (DTIs). Fondaparinux, a factor Xa inhibitor, has begun to take on a role in the management of ACS. In addition, argatroban and bivalirudin are DTIs being used in ACS patients undergoing interventional procedures. Currently there are no specific antidotes for bleeding in patients receiving these medications. There is some literature to support the use of rFVIIa in patients with complications while on these medications, but further investigation is needed.

KNOW YOUR ARSENAL

Antithrombotic agents are ubiquitous and are utilized in the treatment of many high-risk conditions. Anticoagulants, antiplatelet agents, and fibrinolytics all carry the potential for bleeding complications. With knowledge regarding the arsenal of available reversal agents and strategies, the emergency practitioner is armed with the essential tools to safely and effectively manage bleeding complications of antithrombotic medications. □

REFERENCES

1. Cruickshank J, Ragg M, Eddey D. Warfarin toxicity in the emergency department: recommendations for management. *Emerg Med (Fremantle).* 2001;13(1):91-97.
2. Kessler CM. Urgent reversal of warfarin with prothrombin complex concentrate: where are the evidence based data? *J Thromb Haemost.* 2006;4(5):963-966.
3. Hirsh J, Fuster V, Ansell J, Halperin JL; American Heart Association/American College of Cardiology. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol.* 2003;41(9):1633-1652.
4. Ansell J, Hirsch J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians. Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133:6(suppl):160S-198S.
5. Schulman S, Bijsterveld NR. Anticoagulants and their reversal. *Transfus Med Rev.* 2007;21(1):37-48.
6. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K1): a 5-year retrospective review. *Ann Allergy Asthma Immunol.* 2002;89(4):400-406.
7. American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anethesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology.* 2006;105(1):198-208.
8. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol.* 2004;126(1):11-28.
9. Ingerslev J, Vanek T, Culic S. Use of recombinant factor VIIa for emergency reversal of anticoagulation. *J Postgrad Med.* 2007;53(1):17-22.
10. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation Factor VIIa. *JAMA.* 2006;295(3):293-298.