Anticoagulation Reversal

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KEYWORDS

• Anticoagulant reversal • Novel oral anticoagulants • Warfarin • Heparin
• Prothrombin complex concentrate • Idarucizumab

KEY POINTS

- Four-factor prothrombin complex concentrate was designed specifically for the reversal of warfarin-associated coagulopathies.
- Reversal of heparin's anticoagulant effect may be achieved through the administration of protamine sulfate.
- Idaricuzimab is the Food and Drug Administration–approved agent for the reversal of the direct thrombin inhibitor, dabigatran.
- The use of 4-factor prothrombin complex concentrate is recommended by the American College of Cardiology and the Hemostasis and Thrombosis for the reversal of factor Xa inhibitor anticoagulation. Andexanet alfa may be considered for use in patients experiencing life-threatening or uncontrolled bleeding secondary to rivaroxaban and apixaban. Trials of the factor Xa reversal agent, aripazine are underway.
- Current guidelines for the reversal of antiplatelet therapy are lacking.

INTRODUCTION

In the United States, anticoagulant therapy is indicated for the prophylaxis and treatment of thromboembolic disorders.[1] Today, vitamin K antagonists, heparin, low-molecular-weight heparins, direct thrombin inhibitors (DTIs), and factor Xa inhibitors, are commonly used. With nearly 30 million prescriptions for warfarin written annually,[1] and more than 2.3 million individuals taking novel oral anticoagulants,[2] the clinician must be equipped with a strategy to address the most common complication of these therapies: bleeding.

THE CLOTTING CASCADE

The reversal of anticoagulation requires an understanding of the clotting cascade, a complex physiologic process used to maintain homeostasis between clot formation and degradation. In the setting of vascular endothelial injury, clot formation begins

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with primary hemostasis. During primary hemostasis, platelets bind damaged endothelium via an interaction between a glycoprotein (GP IIbIIIa) and von Willebrand factor.[3] Through platelet activation and degranulation, additional platelets are recruited to the site of injury, thereby forming a platelet plug.[3] The efficacy of the platelet plug in achieving hemostasis is a function of platelet quantity and quality. These platelet characteristics may vary according to patient comorbidities (bleeding diathesis, advanced renal disease, etc) and pharmaceutical therapy (eg, nonsteroidal antiinflammatory drugs or aspirin).[3,4]

After primary hemostasis, secondary hemostasis begins with activation of the clotting cascade. During secondary hemostasis, activated factor Xa catalyzes the conversion of prothrombin to thrombin (factor IIa). Thrombin, in turn, catalyzes the conversion of fibrinogen to fibrin.[5] Ultimately, fibrin is responsible for cross-linking and strengthening the platelet plug. The process of secondary hemostasis depends on the quantity of functional clotting factors, and their successful activation.[5]

In terms of laboratory analyses, platelet function tests and platelet aggregation assays may be used to assess primary hemostasis; however, many of these studies are time consuming and poorly standardized, limiting their clinical usefulness in the emergency setting.[4] Bleeding time is no longer used clinically. The process of secondary hemostasis is measured using prothrombin time (PT), International Normalized Ratio (INR; extrinsic and common pathways; factors II, VII, X), and activated partial thromboplastin time (aPTT; intrinsic and common pathways; all factors except factor VII).[3]

REVERSAL OF WARFARIN

In the United States, warfarin (Coumadin; Bristol-Myers-Squibb, NY) is indicated for the prophylaxis and treatment of venous thromboembolism, pulmonary embolism (PE), thromboembolic complications associated with atrial fibrillation or cardiac valve replacement, and for reduction of mortality risk secondary to emboli after myocardial infarctions (MIs) and cerebrovascular accidents. Warfarin is a vitamin K antagonist, inhibiting the hepatic enzyme vitamin K epoxide reductase, thereby limiting the synthesis of factors II, VII, IX, and X, and the anticoagulant proteins C and S. Therapeutic doses of warfarin decrease the total amount of each active vitamin K–dependent clotting factor by approximately 30% to 50%.[6] As mentioned, the PT and INR are measures of the extrinsic pathway of the coagulation cascade and are, therefore, used to monitor the anticoagulant effect of warfarin.[7]

The reversal of warfarin centers on immediate and sustained therapy. Immediate reversal is attained through the employment of prothrombin complex concentrates (PCC) and fresh frozen plasma (FFP), and sustained reversal is achieved through vitamin K administration.

Prothrombin Complex Concentrates

In the United States, PCCs are available in 3- and 4-factor preparations. Bebulin (BDI Pharma, Inc, SC) or Profilnine-SD (Grifols Inc, Spain) are 3-factor concentrates that contain factors II, IX, X, and minimal amounts of factor VII.[8] The 3-factor concentrates are approved by the US Food and Drug Administration (FDA) for the treatment of bleeding events in individuals with hemophilia B (factor IX deficiency).[9,10] In 2009, Holland and colleagues[11] published data regarding the off-label use of Profilnine for the reversal of warfarin in patients with bleeding (n = 29) or at high risk for bleeding (n = 11). Three-factor PCC alone (25 international units per kilogram [IU/kg] and 50 IU/kg doses) lowered the INR to less than 3 in 50% and 43% of patients, respectively,