Monitoring and Reversal of Oral Anticoagulation in Hospitalized Patients

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KEYWORDS

• Anticoagulation • Reversal of anticoagulation • Warfarin • Vitamin K
• Fresh frozen plasma • Prothrombin complex concentrates
• Direct thrombin inhibitors • Factor Xa inhibitors

HOSPITAL MEDICINE CLINICS CHECKLIST

1. There is a large population of patients who require anticoagulation for stroke and venous thromboembolism (VTE) prevention and treatment.
2. Warfarin was the only available oral anticoagulant until the past decade. Fluctuations in international normalized ratio (INR) are common, and management of a supratherapeutic INR depends on degree of elevation and presence of bleeding (American College of Chest Physicians [ACCP] CHEST guidelines in 2012).
   a. INR 4.5 to 10 with no bleeding: no vitamin K.
   b. INR greater than 10 with no bleeding: oral vitamin K.
   c. Warfarin-associated major bleeding: 4-factor (4F) prothrombin complex concentrate (PCC) + vitamin K IV.
3. Over the past decade, 2 new classes of oral anticoagulation have been introduced: direct thrombin inhibitors (DTIs) and factor Xa inhibitors.
4. The only orally available DTI is dabigatran.
   a. Dabigatran cannot be easily monitored and has rapid onset of action with half-life of 12 hours to 17 hours.
   b. Idarucizumab is an approved reversal agent for patients with severe bleeding.

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5. Factor Xa inhibitors that are currently available are rivaroxaban, apixaban, and edoxaban.
   a. Factor Xa inhibitors have each been proved noninferior to warfarin in the prevention and treatment of stroke and VTE.
   b. There is currently no available reversal agent; however, 2 are in development.
   c. In cases of severe bleeding, 4-F PCC can be administered; however, the evidence for the use of 4-F PCC is lacking.
6. Review safety considerations for each oral anticoagulant to guide selection of an anticoagulant for special patient populations.

BACKGROUND

Indications for anticoagulation are varied and include a wide range of diagnoses. Most common indications for anticoagulation include pulmonary embolism (PE), deep vein thrombosis (DVT), atrial fibrillation, mechanical heart valves and inherited thrombophilias, such as antiphospholipid syndrome. Warfarin, one of the most widely prescribed medications, is notoriously onerous to monitor and dosing can be difficult due to a long list of food and drug interactions. In the year 2004 alone, there were approximately 31 million outpatient prescriptions dispensed for warfarin, and this number was on the rise compared with prior years.[1] In making a decision about anticoagulation, the risks of potential bleeding need to be weighed in reference to the benefits of anticoagulation. Often, this requires a nuanced discussion between patients and their providers, especially as age and medical comorbidities may alter both the risk of thrombosis and risk of bleeding. In the past decade, new anticoagulants and reversal agents have become more prevalent. These agents, including DTIs and factor Xa inhibitors, may be preferable to warfarin, because they do not require monitoring and their dosing level does not fluctuate. For this reason, they have become recommended as a first-line therapy for treatment, prevention, and secondary prevention of VTE. Unlike warfarin, however, these drugs cannot be monitored and are not well studied in certain patients with comorbid conditions, such as severe liver or kidney disease. Additionally, the ability to reverse the effect of agents is currently limited.

Among hospitalized patients who are anticoagulated, bleeding is a frequent concern. Often, patients on anticoagulation are admitted to the hospital for unrelated reasons, and changes in medications may result in disruption of appropriate anticoagulation. Additionally, the need for urgent or emergent procedures may require rapid reversal of anticoagulation. This article focuses on the factors involved in monitoring and reversing anticoagulation among hospitalized patients.

OVERVIEW OF COAGULATION CASCADE

The coagulation cascade, which is initiated with tissue injury, has been well studied and is well understood. The cascade includes both intrinsic and extrinsic pathways, both of which lead to clot formation. Warfarin interacts with several coagulation factors, whereas the newer agents specifically target 1 step in the pathway. See **Fig. 1** for visual display of coagulation cascade and drug target sites.