Warfarin Associated Coagulopathy: Reversal Options and Practical Considerations for the Pharmacist

1. In the clotting cascade, which factor leads directly to the activation of platelets?

A. Thrombin***
B. Vitamin K
C. Factor Xa
D. Fibrinogen

Answer: A

A final step in the clotting cascade is the direct activation of platelets by thrombin, also known as factor IIa. Thrombin also converts fibrinogen to fibrin and participates in several other coagulation-related reactions.

2. Which of the following describes the mechanism of action of warfarin:

A. Inhibition of activated prothrombin complex concentrate (aPCC)
B. Inhibition of cytochrome P450 (CYP)4F2
C. Inhibition of tissue factor
D. Inhibition of vitamin K epoxide reductase***

Answer: D

Warfarin inhibits vitamin K epoxide reductase, the enzyme that converts vitamin K epoxide to vitamin K. Vitamin K plays a critical role in the hepatic production of the vitamin K-dependent clotting factors II, VII, IX, and X.
3. Which one of the following patients would have an increased risk of warfarin-associated bleeding:

A. A patient who has a history of stable international normalized ratios (INRs)
B. A patient who has an INR of 3.5
C. A patient who is also taking an antiplatelet agent
D. A patient who is 47 years old

Answer: C

Several risk factors increase the risk of bleeding with warfarin therapy: high intensity anticoagulation (INR > 4.0), age of 65 years or older, history of highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, anemia, malignancy, trauma, renal impairment, certain genetic factors, the concomitant use of drugs that impede hemostasis such as antiplatelet agents, and a long duration of warfarin therapy.

4. How long does it take to reach a steady state of anticoagulation with warfarin?

A. 4 to 6 hours
B. 13 to 48 hours
C. 2 to 3 days
D. 5 to 7 days

Answer: D

The onset and duration of action of the anticoagulant effect of warfarin is influenced by the elimination half-life of clotting factors II, VII, IX, and X. It takes approximately 5 to 7 days to reach a steady state of anticoagulation after warfarin therapy is initiated or after dosing changes, and the same amount of time for the drug’s effects to disappear after stopping therapy.
5. Which one of the following patients would be a candidate for intravenous administration of vitamin K monotherapy:

A. A patient with emergency bleeding
B. A patient with an INR of 4.5 and no active bleeding
C. A patient with an INR of 6 and active bleeding***
D. A patient with an INR of 11 and no active bleeding

**Answer:** C

In patients who are bleeding (regardless of the INR), 5 to 10 mg of IV vitamin K via slow infusion and withholding warfarin are recommended. Vitamin K monotherapy is inadequate in the setting of emergency bleeding because the onset of action of anticoagulant reversal is 6 to 8 hours.

6. Which of the following is TRUE regarding fresh frozen plasma (FFP):

A. FFP can be used alone to reverse warfarin anticoagulation
B. FFP is immediately available for use in urgent settings
C. FFP produces normalization of INR in less than 10 minutes
D. FFP is administered in large volumes***

**Answer:** D

**Rationale:** Large volumes of FFP are required to normalize the INR, often 400 mL or more. The time to correct INR after FFP ranges from 13 to 48 hours. The need for thawing can delay therapy and is an obstacle to its use when urgent treatment is needed. FFP is usually used in combination with Vitamin K in clinical practice and the quality of evidence supporting its
effectiveness for the treatment of warfarin-induced bleeding is very limited; FFP alone is not recommended for routine reversal of warfarin anticoagulation.

7. Which one of the following is not a potential complication of prothrombin complex concentrate (PCC) products:

A. Venous thromboembolism
B. Decreased hemoglobin***
C. Intravascular coagulation
D. Myocardial infarction

Answer: B

PCC treatment has been associated with thrombotic complications, including venous thromboembolism, disseminated intravascular coagulation, microvascular thrombosis, and myocardial infarction. While the overall risk of thromboembolic events with PCC products is low, it is deemed clinically relevant. A prospective study demonstrated that PCC-4 treatment led to a cessation of hemoglobin decline.

8. Based on American College of Chest Physician (ACCP) guidelines, which of the following approaches is preferred for reversal of warfarin anticoagulation in a patient requiring urgent surgery:

A. No therapy is needed; simply hold warfarin until after surgery
B. Vitamin K 5-10 mg intravenous (IV) + PCC-4***
C. Vitamin K 5-10 mg IV + FFP
D. Vitamin K 2.5 mg orally
Answer: B

In warfarin-treated patients who require surgery within 24 hours, a two-drug combination of vitamin K 5-10 mg slow IV injection plus (1) PCC-4, (2) rFVIIa, or (3) aPCC will likely be effective for lowering the INR. FFP is not recommended when urgent reversal is needed, because of the delay in therapy required for thawing and for screening and typing the patient’s blood, the potential for adverse reactions, and the slower onset of INR correction.

9. What one of the following is the only product that is approved by the U.S. Food and Drug Administration (FDA) for the reversal of warfarin anticoagulation:

A. rFVIIa
B. KCentra***
C. FEIBA
D. Autoplex T

Answer: B

Currently, KCentra is the only agent approved by the FDA for warfarin reversal. KCentra is a PCC-4 product that is administered based on INR and patient body weight.

10. GH is a man, 67 years of age, who has been taking warfarin for approximately 3 months. His INR is 8. He is in no acute distress and shows no signs or symptoms of active bleeding. Which of the following strategies would be appropriate to reduce the INR to therapeutic levels for this patient:

A. Withhold warfarin until the INR returns to therapeutic levels***
B. Administer oral vitamin K 2-2.5 mg
C. Administer intravenous vitamin K 5 to 10 mg

D. Administer 1 L of FFP

**Answer: A**

Rationale: The American College of Chest Physicians does not recommend the routine use of vitamin K for the reversal of warfarin in patients with an INR of 4.5 to 10 and no bleeding because clinical studies have demonstrated that there is no benefit to this approach. Rather, warfarin should be withheld until the INR decreases back to therapeutic levels for these patients.