Anticoagulant-related Bleeding: An Update for Pharmacists

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be better able to:

1. Describe the incidence of warfarin-related bleeding events;
2. Develop a treatment plan for a patient with elevated international normalized ratio (INR) without bleeding;
3. Develop a treatment plan for a patient with warfarin-related bleeding;
4. Differentiate 3-factor and 4-factor prothrombin complex concentrate (PCC) products;
5. Identify contraindications, precautions, and adverse effects of the 4-factor PCC product; and
6. Summarize the evidence for bleeding related to non-warfarin oral anticoagulants.

Post-Test/Rationale

1. A 54-year-old male presents to the Emergency Department and is diagnosed with an intracranial hemorrhage. He was taking warfarin for atrial fibrillation prior to admission. His past medical history also includes hypertension, gout, and esophageal reflux. His current medications include colchicine, warfarin, hydrochlorothiazide, and metoprolol. Which portion of the patient’s history increased his risk for a warfarin-associated bleeding event?

   A. Age
   B. Male gender
   C. History of hypertension***
   D. Metoprolol use

Correct answer: C
Risk factors for warfarin-associated hemorrhage include age older than 65 years; previous history of gastrointestinal bleed, atrial fibrillation, and hypertension; high-intensity anticoagulation (prolonged prothrombin time or supratherapeutic international normalized ratio); and the use of antiplatelets or non-steroidal anti-inflammatory drugs.

2. Which is TRUE concerning warfarin-related bleeding?

   A. The incidence of bleeding is inversely related to the intensity of anticoagulation
   B. The risk of bleeding is highest in the first year of anticoagulation***
   C. Patients with a low socioeconomic status have a low risk of bleeding events
   D. Bleeding can be immediately stopped with the use of vitamin K

Correct answer: B
The incidence of bleeding is directly related to the intensity of anticoagulation. Patients with a low socioeconomic status have an increased risk of bleeding. Vitamin K can take up to 24 hours to completely reverse the effects of warfarin.

3. Which is TRUE regarding recombinant factor VIIa (rFVIIa)?

   A. Infusion of rFVIIa abolishes the protective effect of warfarin
B. The use of rFVIIa as monotherapy is sufficient for emergent warfarin reversal
C. rFVIIa has a high incidence of DVT when combined with 3-factor prothrombin complex concentrates (PCC)***
D. The use of rFVIIa as a reversal agent is associated with a shorter length of hospital stay than the use of 4-factor PCC

Correct answer: C
The length of hospital stay is longer with rFVIIa than with 4-factor PCC. Infusion of prothrombin (not factor VII) abolishes the protective effect of warfarin. Monotherapy with rFVIIa is generally insufficient and requires large amounts of fresh frozen plasma to resolve a bleeding event.

4. Increases in prothrombin time and related international normalized ratio during the first few days of warfarin therapy are primarily due to the reduction of which clotting factors?
   A. Factor II and factor X
   B. Factor VII and factor X
   C. Factor II and factor IX
   D. Factor VII and factor IX***

Correct answer: D
Changes in prothrombin time/international normalized ratio during the first few day of warfarin therapy are primarily due to reductions in factor VII, which has a half-life of 6 hours, and factor IX, which has a half-life of 24 hours.

5. The international normalized ratio goal in patients receiving warfarin therapy for high-risk conditions such as antiphospholipid syndrome with prior venous thromboembolism is:
   A. 0.9 to 1.1
   B. 2.0 to 3.0***
   C. 2.5 to 3.5
   D. 3.0 to 4.0

Correct answer: B
For patients with antiphospholipid syndrome with prior arterial or venous thromboembolism, warfarin therapy should be implemented with a goal international normalized ratio range of 2.0 to 3.0.

6. Which therapy for warfarin-related bleeding is approved by the U.S. Food and Drug Administration for the urgent reversal of vitamin K antagonists in adult patients with acute major bleeding?
   A. 4-factor prothrombin complex concentrate (PCC) ***
   B. Fresh frozen plasma
   C. 3-factor PCC
   D. Warfarin cessation

Correct answer: A
A 4-factor PCC (Kcentra) is approved for urgent reversal of vitamin K antagonists in adult patients with acute major bleeding.

7. Prothrombin complex concentrates vary in their concentration of which clotting factor?
   A. Factor II
   B. Factor VII***
   C. Factor IX
   D. Factor X

Correct answer: B
All prothrombin complex concentrates (PCCs) contain a mixture of factors II, VII, IX, and X and proteins C and S. The concentrations of factor VII vary between 3-factor and 4-factor PCCs: 3-factor PCC contains minimal factor VII and 4-factor PCC contains therapeutic concentrations of factor VII.

8. Which warfarin-related bleeding therapy is available in both oral and parenteral dosage forms?
   A. Prothrombin complex concentrates
   B. Fresh frozen plasma
   C. Phytonadione***
   D. Idarucizumab

Correct answer: C
Phytonadione can be administered orally or parenterally. All other choices are only administered parenterally.

9. Compared to fresh frozen plasma (FFP), which is an advantage of prothrombin complex concentrates (PCCs)?
   A. FFP requires thawing time, but PCCs do not require thawing time
   B. FFP can take up to 1 hour to prepare and administer, but PCCs can be administered immediately
   C. FFP often requires the administration of large volumes, but PCCs can be administered in small volumes
   D. All of the above***

Correct answer: D
FFP needs to be cross-matched prior to administration, which can be a lengthy process. PCCs do not require thawing time, which can lead to quicker administration compared to FFP. PCCs can be administered in small volumes.

10. Which agent is specifically indicated for reversal of bleeding associated with the target-specific oral anticoagulant dabigatran?
    A. Phytonadione
    B. 3-factor prothrombin complex concentrate (PCC)
    C. Idarucizumab***
D. 4-factor PCC

Correct answer: C
Idarcizumab is approved by the U.S. Food and Drug Administration as a reversal agent for dabigatran.