Available Strategies to Reverse Anticoagulant Medications

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Objectives

• Describe the pharmacological agents and therapeutic strategies available for use in patients who experience major bleeds
• Discuss the risk and limitations of current agents available for reversal
• Construct treatment plans to manage severe bleeds in a patient’s anticoagulation therapy

Disclosure

Anuja Rizal and I have no actual or potential conflict of interest associated with this presentation

Background

• Anticoagulation is the cornerstone of treatment for thrombosis and thromboembolic complications
• In the United States, over six million patients are on anticoagulation therapy
• Evidence is limited on the management of bleeding and reversal of anticoagulation therapy
  – Reversing therapy is a risk (thrombosis) versus risk (bleeding) decision
  – Involves fully informed clinical decision making

Reversal Decision Pathway

1. Assess Bleeding
2. Determine Anticoagulation Therapy
3. Rapid Laboratory Testing

Assess Bleeding Severity

**Major**
• Hemodynamically unstable
• Bleeding in an anatomically critical location
• Requires transfusion
  – ≥ 2 units of RBCs
• Decrease of hemoglobin
  – ≥ 2 g/dL drop in Hgb

**Non-major**
• All other bleeding not classified as major
• Patient may require intervention or hospitalization
Assess Bleeding Symptoms

Determine Anticoagulation Therapy

- Medication Reconciliation
  - Dose of medication
  - Timing since last administered
  - Monitoring parameters
  - Use of additional anticoagulants/anti-platelet agents

Rapid Laboratory Testing

Knowledge Check!

- A patient comes into the Emergency Department with a BP of 93/67, abdominal distention and recently was started on anticoagulation therapy
  - What steps would you take to triage this patient?
  - What acronym can you use to remember the decision pathway?
  - What laboratory values would be important to order?
**Reversal Agents**

**Non-Specific**
- Fresh Frozen Plasma (FFP)
- PCC
- aPCC
- rFVIIa
- Hemodialysis

**Specific**
- Idarucizumab (Praxbind)
- Andexanet Alfa (Andexxa)
- Vitamin K (Phytonadione)
- Protamine
- Ciraparantag (Arize-PK977)

**Non-Specific Reversal Agents**

**Fresh Frozen Plasma (FEP)**
- **Indication:** alternative reversal agent for patients on warfarin when preferred agents are unavailable
- **Mechanism of action:** direct plasma transfusion
- **Dosing:** Depends upon the patient’s size and clinical situation. The typical 70 kg adult dose is 4 to 6 units (approximately 15 mL/kg) infused at 10mL/min
- **Caution:** hypervolemia with PE or cardiac failure, disease transmission, transfusion reactions associated with antibody generation, higher incidence of thrombosis
- **Contraindications:** not indicated for volume expansion only, not recommended as a protein or fibrinogen source

**3 Factor Prothrombin Complex Concentrate (PCC) Profilnine®**
- **Indication:** reversal in patients with severe, life-threatening bleeds or need for urgent and invasive surgery when other agents are not available
- **Mechanism of action:** replaces deficient coagulation factors II, IX and X
- **Dosing:** Dosing is individualized based on severity of factor IX deficiency, extent and location of bleeding and clinical status; factor IX 1 unit/kg will increase the plasma factor IX level by 1%
  - **Onset and Duration:** raises factor IX levels 20-30% (moderate bleeding) or 30-50% (major bleeding) every 16 to 24 hours, continued until hemostasis is achieved
- **Caution:** antibody formation, hypersensitivity reactions, thrombotic events
- **Contraindications:** none listed in manufacturer’s labeling

**4 Factor Prothrombin Complex Concentrate (PCC) Octaplex® KCentra®**
- **Indication:** reversal in patients with severe, life-threatening bleeds or need for urgent and invasive surgery
  - Warfarin; associated with 1.4% increase in thrombotic events
  - DOACs; used off-label; rivaroxaban, edoxaban, and apixaban
- **Mechanism of action:** replaces coagulation factors II, VII, IX and X and protein C and S
  - **Onset:** rapid decline within 10 minutes
  - **Duration:** ~6 to 8 hours
- **Contraindication:** hypersensitivity to concentrate, history of heparin induced thrombocytopenia
- **US Boxed Warning:** administration of prothrombin complex concentrate (PCC) may predispose the patient to thromboembolic complications
**Anti-inhibitor Coagulant Complex (aPCC) FEIBA®**

- **Indication:** for reversal in in hemophilia A and B patients with uncontrolled bleeding, used off-label or oral anticoagulation associated bleeding
- **Mechanism of action:** replaces coagulation factors II, VII (activated and more potent), IX and X
  - **Onset:** within 15 to 30 minutes
  - **Duration:** ~ 8 to 12 hours
- **Contraindications:** hypersensitivity to FEIBA or its components, disseminated intravascular coagulation (DIC), acute thrombosis or embolism
- **US Boxed Warnings:** thromboembolic events, especially following doses >200 units/kg/day; monitor patients for signs and symptoms of thromboembolic events
- **Warnings:** anaphylaxis and hypersensitivity reactions may occur

**Anti-inhibitor Coagulant Complex (aPCC) FEIBA®**

- **Indication:** promoting hemostasis through the extrinsic pathway of the coagulation cascade
- **Mechanism of action:** vitamin K-dependent glycoprotein promotes hemostasis through intrinsic pathway
  - **Onset varies:** administration required every 2 hours until hemostasis is achieved
  - **Duration:** ½ life ~2 to 3 hours
- **Contraindications:** none listed in manufacturer’s labeling
- **US Boxed Warning:** serious thromboembolic events are associated with use, monitor patients for signs and symptoms of thrombosis
- **Warning:** antibody formation, hypersensitivity reactions

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**Hemodialysis**

- Reversal of dabigatran is associated with life-threatening bleeding
  - Dabigatran: protein bound ~35%
  - Hemodialysis removes up to 68% of dabigatran DOAC activity
- Edoxaban is protein bound (~50%)
  - However, trials did not demonstrate hemodialysis as an effective method for removal

**Specific Reversal Agents**
Vitamin K (Phytonadione)

- **Mechanism of Action:**
  - [Diagram showing the metabolic pathway of Vitamin K (Phytonadione)]
  - This includes the conversion of precursor prothrombin to biologically active prothrombin, oxidative deactivation to Vit K (epoxide), and reductase to Vit K (reduced). Warfarin inhibits this conversion.

- **Indication:** reverse elevated INRs associated with active bleeding episodes on vitamin K antagonists; warfarin (Coumadin, Jantoven)

  - **Onset**
    - PO 6 to 10 hours
    - IV 1 to 2 hours

- **Duration**
  - SC and IM not recommended

- **US Boxed Warning:** Fatal hypersensitivity reactions have occurred with parenteral use. Avoid IV and IM administration unless subcutaneous administration is not feasible and the serious risk is justified.

- **Route of Administration Dosing**
  - PO: 1 to 10 mg
  - IV: Infusion 1 to 10 mg in NE or D5W over 30 minutes

- **Caution/Warnings**
  - Infuse at maximum rate of 1 mg/min
  - Rapid IV push can cause hypotension or anaphylaxis

- **Monitor**
  - BP, INR, active bleeding

- **Contraindications**
  - Hypersensitivity to phytonadione or any component of the formulation

Protamine

- **Indication:** reverses enoxaparin

  - **Mechanism of action:** In the presence of LMWH, protamine incompletely reverses the antifactor-Xa activity of LMWH

- **Dosage**
  - Enoxaparin Last Administered Dose
    - Previous 8 hours: 1 mg IV protamine sulfate/1 mg of enoxaparin
    - >8 hours ago or if aPTT remains prolonged: 0.5 mg IV of protamine/1 mg of enoxaparin

Protamine Sulfate

- **Indication:** reverses unfractionated heparin and enoxaparin, dalteparin, tiazaparin, nadroparin

  - **Mechanism of action:** protamine given in the presence of heparin or LMWH forms a stable salt bond and the anticoagulant activity of both drugs is nullified

  - **Dosage**
    - Heparin Last Administered Dose
      - Immediate: 1 mg to 1.5 mg IV protamine sulfate/100 units of heparin
      - 30 to 60 min: 0.1 to 0.15 mg IV protamine sulfate/100 units of heparin
      - >2 hours: 0.25 to 0.375 mg IV protamine sulfate/100 units of heparin
      - Unknown: 25 mg to 50 mg IV single dose
    - Enoxaparin Last Administered Dose
      - Previous 8 hours: 1 mg IV protamine sulfate/1 mg of enoxaparin
      - >8 hours ago or if aPTT remains prolonged: 0.5 mg IV of protamine/1 mg of enoxaparin
### Protamine

- **Dosing dalteparin, tinzaparin, nadroparin**
  - **Onset**: ~5 minutes
  - **Duration**: ½ life ~7 minutes
- **Warnings/Precautions**:
  - Heparin rebound
  - Hypersensitivity reactions
  - Have epinephrine available, consider co-administration with diphenhydramine or hydrocortisone
  - Infusion reactions can cause severe hypotensive and anaphylactic-like reactions
- **Contraindications**: hypersensitivity to components


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### Idarucizumab (Praxbind)

- **Warning/Precautions**
  - Hereditary fructose intolerance, thromboembolic risk; dabigatran can be reinitiated 24 hours after administration if appropriate
  - Hypersensitivity reactions
  - Thromboembolic risk
- **Contraindications**
  - None listed in manufacturer’s labeling


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### Andexanet Alfa (Andexxa)

- **Warning/Precautions**
  - Anti-factor Xa activity re-elevation
  - Thromboembolic and ischemic risks
  - >10% Immunologic antibody development, infusion related reaction
  - 1 to 10% DVT, stroke, MI, cardiac failure, UTI, pneumonia, acute respiratory failure
- **Contraindications**
  - None listed in manufacturer’s labeling

Ciraparantag (Aripazine-PER977)

- Direct sequestering of heparin, direct factor Xa and thrombin inhibitors
- Small synthetic water-soluble molecule
- Forms strong ionic, noncovalent bonds and large complex molecules that bind anticoagulation agents
- Under evaluation in Phase II clinical trials
  - FDA fast-tracked

Managing Major Bleeding

- Anticoagulants and antiplatelet agents should be held
- Airway and IV access secured
- Obtaining and administering reversal agents must not delay resuscitation and local hemostatic measures
  - Volume resuscitation
  - Pressure/Packing
  - Supportive measures (blood product transfusion when appropriate)

Resumption of Anticoagulation

- Benefits of resuming anticoagulation vs. the risk of recurrent bleeding
- Risk assessment of recurrent thrombosis
  - Utilize guidelines based on underlying indication for anticoagulation
  - Assess specific risk patient factors
    - Site of bleeding
    - Past medical history
    - Clotting disorders, etc.

Conclusion

- Evidence is limited on the reversal of anticoagulation agents
  - Many agents are available and pharmacist are a key promoter for the right reversal agent for the correct anticoagulation agent
  - Each agent comes with risks and limitations that are important to inform the patients and providers
- Utilize this presentation when developing treatment plans to manage severe bleeds

Knowledge Check!

- A 87 yo male reports to the anticoagulation clinic. You see him on a monthly basis as his INR is always within goal of 2-3. Today is the day after St. Patrick’s Day. He reports of increased alcohol intake yesterday, and his INR comes back at 3.8. How will you manage this patient?
  - Assess patients bleeding
  - Hold Warfarin dose x 1
  - Counsel on signs and symptoms of bleeding
  - Follow up with patient within the week

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Knowledge Check!

- A 76 yo female reports to the anticoagulation clinic with complaints of abdominal pain and distension. He reports feeling dizzy and weak the past 24 hours and has apparent tachypnea. His INR comes back at 4.7, what is your clinical suspicion, how should you proceed?

Knowledge Check!

- A 76 yo female reports to the clinic with complaints of abdominal pain and distension. He reports feeling dizzy and weak the past 24 hours and has apparent tachypnea. His INR comes back >4 and is unable to be detected on a POCT. What is your clinical suspicion, how should you proceed?
  - Immediately refer to the Emergency Room
  - Intravenous INR draw
  - High clinical suspicion for intra-abdominal bleed
  - Select appropriate agent based on agents available at your institution

Knowledge Check!

- A 54 yo male is hospitalized status post coronary artery bypass grafting (CABG)
  - Heparin infusion at 1200 u/hr is administer for 3 hours
  - Patient begins complaining of lower extremity swelling and pain
  - A Doppler is ordered to rule out DVT and extremity bleeding is suspected
  - The provider wants to reverse the heparin, what do you recommend?

Knowledge Check!

- The provider wants to reverse the heparin, what do you recommend?
  - Stop heparin drip
  - Recommend Protamine 1mg/100 units of heparin
    - 1200 units heparin x 3 hours = 3,600 units / 100 units
    - 36mg of Protamine
  - If bleeding persists consider another dose of protamine
  - Monitor for signs and symptoms of thrombosis

Knowledge Check!

- A 67yo male comes into the Emergency Department at 10:36am on Rivaroxaban 20mg nightly for nonvalvular atrial fibrillation. Upon CT scan, the patient shows evidence of an intracranial hemorrhage. Assuming the patient took the medication last night and all available reversal agents are available at your institution, what medication and dose would you recommend as the most effective agent?
  - KCentra 1500 units IV once
  - Andexxa 400 mg IV bolus followed by 4 mg/minute IV infusion for up to 120 minutes
  - Vitamin K 10mg IV once
  - Protamine 10mg

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Applying your knowledge

• Utilize the information provided for reversal of anticoagulation therapy to construct treatment plans and manage severe bleeds at your institution

Thank you for your attention!

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Please see "Direct Oral Anticoagulants and Factor IIa and Xa Inhibitors" CE presentation for additional information on Oral Anticoagulants