What a Blood Bath! Andexxa® Makes a Splash! Current Trends in Anticoagulation Reversal

Marianela Robainas
South Miami Hospital, MarianelaR@baptisthealth.net

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What a Blood Bath! Andexxa® makes a Splash! Current Trends in Anticoagulation Reversal

Marianela Robainas, PharmD
PGY-1 Pharmacy Resident
South Miami Hospital
Baptist Health of South Florida
Objectives

- Discuss various pharmacological management options for anticoagulation reversal

- Review andexanet alfa (Andexxa®) prescribing information and examine its role in the management of anticoagulation reversal

- Describe the role of the pharmacist in the management of anticoagulation reversal
Anticoagulants are important for preventing and treating blood clots but are associated with an increased risk of bleeding.

In 2013 and 2014, warfarin was responsible for:
- 32% of estimated emergency room visits for all adverse drug events (ADEs) among older adults
- 36% of emergent hospitalizations for all ADEs among older adults
- Warfarin, rivaroxaban, and dabigatran were in the top 10 most common causes of ADEs resulting in emergency department visits

In 2017:
- Bleeding from oral anticoagulants resulted in approximately 235,000 emergency department visits
- Direct Oral Anticoagulants (DOACs) contributed to approximately 40% of estimated oral anticoagulant bleeding visits
Anticoagulation Reversal Considerations

- Risks versus benefits
- Indication and mechanism of action
- Patient’s presentation
- Severity of bleeding
- Available agents currently on the market
## Anticoagulation Agents and Antidotes

<table>
<thead>
<tr>
<th>Agent</th>
<th>Antidotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Vitamin K, Prothrombin Complex Concentrate (PCC)</td>
</tr>
<tr>
<td>Unfractionated Heparin (UFH)</td>
<td>Protamine, PCC</td>
</tr>
<tr>
<td>Low Molecular Weight Heparin (LMWH)</td>
<td>Protamine, PCC</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>PCC</td>
</tr>
<tr>
<td>Direct Thrombin Inhibitor (DI)</td>
<td>Idarucizumab, PCC</td>
</tr>
<tr>
<td>• Dabigatran</td>
<td></td>
</tr>
<tr>
<td>Oral Factor Anti-Xa Inhibitors</td>
<td>Andexanet Alfa*, PCC</td>
</tr>
<tr>
<td>• Apixaban</td>
<td></td>
</tr>
<tr>
<td>• Rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>• Edoxaban</td>
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</tbody>
</table>

*Andexanet alfa is only approved for the reversal of apixaban and rivaroxaban*
Clotting Cascade
PCC (KCENTRA®)

- FDA indication: urgent reversal of vitamin K antagonist therapy in adult patients with
  - Acute major bleeding or
  - Need for an urgent surgery/invasive procedure

- Mechanism of action: rapidly increases plasma levels of the vitamin K dependent factors II, VII, IX, X, as well as Proteins C and S

- Intravenous administration: administer intravenously through a separate infusion line; no blood should enter the syringe, due to fibrin clot formation

- PCC is contraindicated in patients with:
  - Known anaphylaxis to PCC or any components including heparin, factors II, VII, IX, X, proteins C and S, antithrombin III, or human albumin
  - Disseminated intravascular coagulation
  - Known heparin-induced thrombocytopenia

Kcentra (prothrombin complex concentrate human) [prescribing information]. Kankakee, IL: CSL Behring; October 2018.
Idarucizumab (Praxbind®)

- **FDA indication:** reversal of dabigatran in adult patients
  - For emergency surgery/urgent procedures
  - In life-threatening or uncontrolled bleeding

- **Mechanism of action:** humanized monoclonal antibody fragment that binds to dabigatran and its metabolites with higher affinity

- **Intravenous administration:** two consecutive infusions or a bolus injection

- **Adverse reactions:**
  - Thromboembolic risk
  - Hypersensitivity reactions
  - Risk of serious adverse reactions in patients with hereditary fructose intolerance due to sorbitol excipient
Protamine

- FDA indication: treatment of heparin overdose
- Mechanism of action: neutralizes heparin by forming a stable salt
- Intravenous administration: slow infusion
- Box warning:
  - Severe hypotension
  - Cardiovascular collapse
  - Non-cardiogenic pulmonary edema
  - Catastrophic pulmonary vasoconstriction
  - Pulmonary hypertension

Protamine [prescribing information]. Lake Zurich, IL: Fresenius Kabi; December 2016.
# Coagulation Laboratory Tests

<table>
<thead>
<tr>
<th>Agent</th>
<th>Baseline Parameters</th>
<th>Monitoring Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>CBC</td>
<td>INR, PT</td>
</tr>
<tr>
<td>UFH</td>
<td>CBC</td>
<td>aPTT, INR</td>
</tr>
<tr>
<td>LMWH</td>
<td>CBC, Scr</td>
<td>Anti-Xa Assay</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>CBC, Scr</td>
<td>Anti-Xa Assay</td>
</tr>
<tr>
<td>Direct Thrombin Inhibitor (DI) • Dabigatran</td>
<td>CBC, Scr, Tbili, albumin, INR</td>
<td>aPTT, TT</td>
</tr>
<tr>
<td>Oral Factor Anti-Xa Inhibitors • Apixaban</td>
<td>CBC, Scr, Tbili, albumin, INR</td>
<td>Anti-Xa Assay</td>
</tr>
<tr>
<td>• Rivaroxaban</td>
<td></td>
<td></td>
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<tr>
<td>• Edoxaban</td>
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</tr>
</tbody>
</table>

CBC: Complete blood count, Sr: Serum creatinine, Tbili: Total bilirubin, INR: International normalized ratio, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, TT: Thrombin time, Anti-Xa Assay: Anti-factor Xa

Assessment of Anticoagulation Related Bleeding

- History and physical examination
- Vital signs
- Laboratory tests
- Time of last dose of anticoagulant
- Intentional or unintentional overdose
- Severity of bleeding
- Medications
Major Bleeding Definition

- At least one of the following factors:

<table>
<thead>
<tr>
<th>Criteria for Major Bleeding</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical Site</strong></td>
<td></td>
</tr>
<tr>
<td>- Hemorrhage</td>
<td></td>
</tr>
<tr>
<td>- Intracranial</td>
<td></td>
</tr>
<tr>
<td>- Spinal</td>
<td></td>
</tr>
<tr>
<td>- Thoracic</td>
<td></td>
</tr>
<tr>
<td>- Bleed that compromises organ function</td>
<td></td>
</tr>
<tr>
<td><strong>Hemodynamic Instability</strong></td>
<td></td>
</tr>
<tr>
<td>- SBP &lt;90 mmHg</td>
<td></td>
</tr>
<tr>
<td>- Decrease in SBP &gt;40 mmHg</td>
<td></td>
</tr>
<tr>
<td>- MAP &lt;65 mmHg</td>
<td></td>
</tr>
<tr>
<td>- Additional clinical signs and other markers of poor organ perfusion can aid in the evaluation</td>
<td></td>
</tr>
<tr>
<td><strong>Overt Bleeding</strong></td>
<td></td>
</tr>
<tr>
<td>- Decrease in hemoglobin ≥2 g/dL</td>
<td></td>
</tr>
<tr>
<td>- Administration of ≥2 units of packed RBCs</td>
<td></td>
</tr>
</tbody>
</table>

SBP: Systolic blood pressure, MAP: Mean arterial pressure, RBC: Red blood cell
Guideline Recommendations

**Bleeding Considered Major**
Is the bleed at a critical site or life threatening?

**Yes**
- Stop oral anticoagulant
- If patient is on warfarin, give 5-10 mg IV vitamin K
- Manual compression
- Supportive care
- Discontinue antiplatelet agent
- Assess comorbidities that contribute to bleeding
- Surgical management of bleeding site
- **Suggest administering reversal agent**

**No**
- Stop oral anticoagulant
- If patient is on warfarin, give 5-10 mg IV vitamin K
- Manual compression
- Supportive care
- Discontinue antiplatelet agent
- Assess comorbidities that contribute to bleeding
- Surgical management of bleeding site
**Bleeding Considered Non-major**

Does the bleed require hospitalization, surgical/procedural intervention, or transfusion?

- **Yes**
  - Stop oral anticoagulant
  - If patient is on warfarin, give 2-5 mg IV vitamin K
  - Manual compression
  - Supportive care
  - Discontinue antiplatelet agent
  - Assess comorbidities that contribute to bleeding
  - Consider surgical management of bleeding site

- **No**
  - Consider continuing oral anticoagulant
  - Manual compression
  - Supportive care
  - If patient is on antiplatelet therapy, assess for discontinuation
  - Assess comorbidities that contribute to bleeding
  - Determine if anticoagulant dosing is appropriate
• **Warfarin**
  - Administer 4Factor–prothrombin complex concentrate (4F-PCC) weight based dose
    - INR 2-4: 25 units/kg
    - INR 4-6: 35 units/kg
    - INR >6: 50 units/kg
  - Or low fixed-dose option
    - Any major bleed: 1,000 units
    - Intracranial hemorrhage: 1,500 units
  - If 4F-PCC not available, use plasma 10-15 ml/kg
DI (dabigatran)

- Administer idarucizumab IV 5 g
- If unavailable, administer 4F-PCC or activated prothrombin complex concentrate (aPCC) 50 units/kg IV
- Consider activated charcoal for known recent ingestion (within 2-4 hours)

Factor-Xa Inhibitor (apixaban, edoxaban, rivaroxaban)

- Administer 4F-PCC 50 units/kg IV
- If unavailable, aPCC 50 units/kg IV
- Consider activated charcoal for known recent ingestion (within 2-4 hours)
UFH
- IV protamine can rapidly reverse anticoagulant effects of heparin
- 1 mg of protamine will neutralize approximately 100 units of heparin
- Patient’s dose largely depends on heparin dose and duration of infusion

LMWH
- IV protamine can also reverse LMWH
- LMWH given within 8 hours: protamine administered in a dose of 1 mg per 100 anti-Xa units of LMWH (maximum single dose: 50 mg)

Fondaparinux
- Fondaparinux does not bind to protamine
- If uncontrollable bleeding occurs, PCC could be used at a dose of 50 units/kg IV
Andexanet Alfa (Andexxa®)
Mechanism of Action

- Coagulation factor xa (recombinant), inactivated-zhzo (modified Fxa decoy proteine) exerts its procoagulant effect by binding and sequestering the Fxa inhibitors with strong affinity and overcoming the competition.

- Another procoagulant effect is its ability to bind to and inhibit the activity of tissue factor pathway inhibitor, which increases tissue factor-initiated thrombin generation.
FDA Indication

- Andexanet alfa
  - Reversal of apixaban or rivaroxaban
  - Life-threatening or uncontrolled bleeding
  - Major bleeding defined as:
    - Occurring in a critical site
    - Hemodynamic compromise
    - Decrease in hemoglobin ≥2 g/dL
    - Requiring transfusion
### Dose and Administration

<table>
<thead>
<tr>
<th>Factor Xa Inhibitor</th>
<th>Dose</th>
<th>&lt;8 hours or Unknown</th>
<th>≥8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>≤10 mg</td>
<td>Low dose</td>
<td>LOW DOSE</td>
</tr>
<tr>
<td></td>
<td>&gt;10 mg or unknown</td>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>≤5 mg</td>
<td>Low dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5 mg or unknown</td>
<td>High dose</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial IV Bolus</th>
<th>IV Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>400 mg</td>
<td>4 mg/min for up to 120 minutes</td>
</tr>
<tr>
<td></td>
<td>Target rate 30 mg/min</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>800 mg</td>
<td>8 mg/min for up to 120 minutes</td>
</tr>
<tr>
<td></td>
<td>Target rate 30 mg/min</td>
<td></td>
</tr>
</tbody>
</table>
True or False?

If a patient took rivaroxaban 20 mg at least 12 hours ago, the patient should receive andexanet alfa high dose.
Answer

If a patient took rivaroxaban 20 mg at least 12 hours ago, the patient should receive andexanet alfa high dose

FALSE
Reconstitution

- Determine total number of vials needed

- Reconstitution instructions
  - 100 mg vial: 10 ml sterile water
  - 200 mg vial: 20 ml sterile water
  - Final concentration: 10 mg/ml

- Powder must completely dissolve

- Infusion requires a 0.2 or 0.22 micron in-line polyether sulfone or equivalent low protein binding filter

- Reconstituted product is a clear to slightly yellow solution
Stability

- **DO NOT SHAKE** solution as it could lead to foaming

- Vial is stable at room temperature for 24 hours

- After reconstitution in an IV bag: stable at room temperature for 8 hours

- Doesn’t contain preservatives
Adverse Reactions

>10%:
- Immunologic: Antibody development (6% to 17%)
- Miscellaneous: Infusion-related reaction (18%)

1% to 10%:
- Cardiovascular: Deep vein thrombosis (6%), ischemic stroke (5%), acute myocardial infarction (3%), pulmonary embolism (3%), cardiogenic shock (2%), cardiac failure (1%)
- Genitourinary: Urinary tract infection (≥5%)
- Respiratory: Pneumonia (≥5%), acute respiratory failure (1%)
True or False?

Andexanet alfa dosing is guided by administration time and dose of the factor Xa inhibitor.
Answer

Andexanet alfa dosing is guided by administration time and dose of the factor Xa inhibitor.
Warning and Precautions

- No contraindications

WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS

See full prescribing information for complete boxed warning

Treatment with ANDEXXA has been associated with serious and life-threatening adverse events, including: (5.1)

- Arterial and venous thromboembolic events
- Ischemic events, including myocardial infarction and ischemic stroke
- Cardiac arrest
- Sudden deaths

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.
Special Populations

- **Pregnancy**: No adequate controlled studies
- **Lactation**: No information regarding presence in human milk
- **Pediatrics**: No safety or efficacy information
- **Geriatrics**: No observed differences in safety and efficacy in geriatric patients in the ANNEXA-4 trial
Resuming Anticoagulation

- Risks versus benefits
- Severity and location of the bleed
- Indication
- Timing
- Re-evaluate dose
- Consider patient’s comorbidities
- Comprehensive medication review
True or False?

There are no risks associated withandexanet alfa following its administration
Answer

There are no risks associated with andexanet alfa following its administration
Clinical Trials

- Approved under accelerated approval based on the change from baseline anti-factor Xa in healthy volunteers
- Efficacy and safety was established in a phase III trial for apixaban and rivaroxaban in ANNEXA-A and ANNEXA-R
- ANNEXA-4: multinational, single arm, open label phase IIIb/IV study
  - Ongoing trial, preliminary results are published
ANNEXA-A and ANNEXA-R

- **Purpose:** Establish the efficacy and safety of andexanet alfa for the reversal of anticoagulation with apixaban or rivaroxaban in older healthy volunteers.

- **Patient population:** Healthy older volunteers were given apixaban 5 mg twice daily or rivaroxaban 20 mg daily.

- **Intervention:** For each factor Xa inhibitor, a two-part randomized placebo-controlled study was conducted to evaluate andexanet alfa administered as a bolus or as a bolus plus a 2-hour infusion.

- **Outcome:** The mean percent change in anti-factor Xa activity from baseline.

Trial Results

- **Apixaban**
  - Anti–factor Xa activity was reduced by 94% among those who received an andexanet alfa bolus (24 participants), as compared with 21% among those who received placebo (9 participants) (P<0.001)
  - Unbound apixaban concentration was reduced by 9.3 ng/ml versus 1.9 ng/ml (P<0.001)
  - Thrombin generation was fully restored within 2 to 5 minutes in 100% versus 11% of the participants (P<0.001)
Trial Results

- **Rivaroxaban**
  - Anti–factor Xa activity was reduced by 92% among those who received an andexanet alfa bolus (27 participants), as compared with 18% among those who received placebo (14 participants) (P<0.001)
  - Unbound rivaroxaban concentration was reduced by 23.4 ng/ml versus 4.2 ng/ml (P<0.001)
  - Thrombin generation was fully restored in 96% versus 7% of the participants (P<0.001)
  - Effects were sustained when andexanet alfa was administered as a bolus plus an infusion

ANEXXA-4

Purpose: to assess the efficacy and safety of andexanet alfa in patients with acute major bleeding occurring while taking a factor Xa inhibitor

Inclusion criteria
- ≥18 years old
- Acute major bleeding
- Received one of the following within 18 hours: apixaban, rivaroxaban, edoxaban, or enoxaparin at a dose ≥ 1 mg/kg/day

Patients were enrolled from April 2015 through May 2018
- From July 2016 through August 2017, only patients with intracranial hemorrhage were enrolled
- After August 2017, patients with all types of bleeding except visible, musculoskeletal, or intraarticular bleeding were enrolled
Outcomes:

- Percent change in anti-factor Xa activity after andexanet alfa treatment
- Percentage of patients with excellent or good hemostatic efficacy at 12 hours after the end of the infusion

Bleeding: predominantly intracranial (in 227 patients [64%]) or gastrointestinal (in 90 patients [26%])
Results

- **Apixaban**
  - Median anti–factor Xa activity decreased from 149.7 ng/ml at baseline to 11.1 ng/ml after the andexanet alfa bolus (92% reduction; 95% confidence interval [CI], 91 to 93)

- **Rivaroxaban**
  - Median value decreased from 211.8 ng/ml to 14.2 ng/ml (92% reduction; 95% CI, 88 to 94)

- **Enoxaparin**
  - Median value for anti–factor Xa activity decreased from 0.48 IU/ml at baseline to 0.15 IU/ml at the end of the bolus administration (75% reduction; 95% CI, 66 to 79)

- Excellent or good hemostasis occurred in 82% of patients

- Safety outcomes (within 30 days): death occurred in 49 patients (14%) and a thrombotic event in 34 patients (10%)
Patient Counseling

- **Purpose of medication**

- **Inform patients that reversing factor Xa inhibitor therapy increases the risk of thromboembolic events**
  - Arterial and venous thromboembolic events, ischemic events, cardiac events, and sudden death were observed within 30 days following andexanet alfa administration

- **Signs and symptoms of deep venous thromboembolism or pulmonary embolism**
Future Agents for Anticoagulation Reversal

- **Cirapratang (Aripazine®)**
  - Phase II trial
  - Broad-spectrum reversal agent
  - Mechanism of action: binds through ionic charge interactions and removes anticoagulant from its target
  - Reversal includes: factor Xa inhibitors, DI, UFH, and LMWH

- **Andexanet alfa (Andexxa®)**
  - Phase II trial for the reversal of apixaban, rivaroxaban, and edoxaban in healthy Japanese and Caucasian patients
Pharmacist Role

- Evaluates patient’s presentation
- Ensure appropriate agent and dose
- Monitor for adverse effects
- Monitor laboratory markers and patient’s hemodynamic stability
- Medication history
- Restart anticoagulation therapy when appropriate
Questions?
References

19. Praxbind injection (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; April 2018.