Anticoagulation reversal in the era of the non-vitamin K oral anticoagulants

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4/27/19
Disclosure Statement

• Nothing Financial
• Nonfinancial
  • Some of the medications today will be discussed for non-FDA approved indications.

• For simplicity of this CE activity, the trade names will be utilized; no specific product endorsement is implied.
  • Praxbind (idarucizumab)
  • Andexxa (andexanet alfa)
  • FIEBA (anti-inhibitor coagulant complex)
  • Kcentra (prothrombin complex concentrate)
Learning Objectives

1. At the end of this presentation, pharmacists will be able to compare and contrast the available agents for emergent reversal of oral anticoagulants.

2. At the end of this presentation, pharmacists will be able to discuss the pros and cons of adding Andexxa® (andexanet alfa) to formulary.

3. At the end of this presentation, pharmacy technicians will be able to assist in medication procurement and sterile compounding.
Pre-test Questions

1. Which of the following statements is correct?
   A. The GI tract is the most common site of anticoagulant bleeding
   B. ICH carries a low 30-day mortality with most survivors having full functional recovery
   C. Idarcucizumab can be used to reverse Xa inhibitors
   D. All of the above are correct?

2. A 45 YO male taking apixaban 10mg PO BID (0900 & 2100) for DVT arrives unresponsive at noon. Head CT reveals ICH. What is the correct reversal and dose?
   A. Vit K 10mg SQ
   B. Andexxa 400mg bolus, then infusion 480mg at 4mg/min
   C. Andexxa 800mg bolus, then infusion 960mg at 8mg/min
   D. Idarucizumab 2.5g push times 2 doses

3. True or False: Andexxa can be shaken to decrease dissolve time?
A physician wants to reverse the effects of an OAC:

- Intervention: What is my role?
- Assess the situation
  - Medication history
  - Goals
- What do I have available to me?
- Situation and Setting dependent
- How fast can lab or imaging results be available?
Effects of DOACs on Coagulation Labs

Effects of Common DOACs on Coagulation Labs

- Dabigatran TT, dTT, ECT, ECA
- Dabigatran aPTT
- Dabigatran PT
- Rivaroxaban Anti-Xa
- Rivaroxaban PT
- Rivaroxaban aPTT
- Apixaban Anti-Xa
- Apixaban PT
- Apixaban aPTT

Insensitive | Quantifiable | Know it's there

What is a bleed?

- Decrease in Hemoglobin of at least 2 g/dL or Hct of 4% from normal limits
- Requiring blood transfusion products
- Life-threatening based on physician discretion
Well, we're both fruit.
Pradaxa (dabigatran)

- **Praxbind (idarucizumab)**\(^1,2\)
  - 5 GM (2 separate 2.5 GM doses no more than 15 minutes apart)
  - Onset/hemostasis: minutes to median 11 hours
  - Duration: usually 24 hours

- **Dialysis**
  - 60% removed in 2-3 hours

- **FEIBA (aPCC)**\(^3\)
  - 25 - 50u/kg

- **Kcentra (4 factor PCC)**\(^4\)
  - Eerenberg et al.
  - 50u/kg

- **TXA**
Warfarin

- FFP
- rFVIIa
- Profilnine (3 factor PCC)
- Profilnine + FFP
- Profilnine + rVIIa
- FEIBA
- Kcentra (4 factor PCC)
  - 25-50 units/kg based on INR and wt
  - Fixed dose
3 Factor PCC in Warfarin reversal

- **Plus FFP**
  - Holland et al. (2009)\(^6\)
  - Excluded ICH patients
    - Retrospective case series
  - Duplaga (2013)\(^7\)
    - Time to reversal
    - Retrospective cohort study patients with ICH

- **Plus rFVIIa**\(^5\)
  - Time to reversal
  - Increased thrombosis

- **No direct comparisons to 4 factor PCC**
  - Retrospective cohort study (Barton 2018)\(^8\)
4 Factor PCC in Warfarin reversal

- **FIEBA**
  - Wojcik et al.\(^9\)
  - 500 units \(<\ INR\ >5\ 1000\ units\)
  - More thrombotic??

- **Kcentra**
  - INR: 2 - \(<\ 4\ 25u/kg\) INR: 4 – 6 35u/kg INR: >6 50u/kg
  - Sarode et al.\(^10\)
Fixed dose Kcentra in Warfarin reversal

- Khorsand et al.\textsuperscript{11}
  - 28 studies, 15 different protocol
  - Based on wt, wt & INR, wt, INR & target INR, doctor discretion, fixed dose
  - No evidence that one strategy is superior
- Klein et al.\textsuperscript{12}
  - N=39, retrospective cohort
  - 1500 units
  - 1,500 units
  - 2,500 units for ICH
- Air Ambulance
<table>
<thead>
<tr>
<th>Population Characteristics</th>
<th>Treatment Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication (%)</td>
<td>Initial INR median, range</td>
</tr>
<tr>
<td>Intracranial Bleed 35%</td>
<td>Dose (units) median, range</td>
</tr>
<tr>
<td>GI bleed 35%</td>
<td>Dose (units/kg) median, range</td>
</tr>
<tr>
<td>Preop reversal 15%</td>
<td>Repeat INR median, range</td>
</tr>
<tr>
<td>other 19%</td>
<td>Appropriate dose % 85%</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Vit k admin appropriately (%) 92%</td>
</tr>
<tr>
<td>Warfarin 54%</td>
<td>Addition of FFP 12%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety and Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic event within 7 days (n)</td>
<td>1</td>
</tr>
<tr>
<td>ICU LOS (days) median, range</td>
<td>2 (0-15)</td>
</tr>
<tr>
<td>Hospital LOS (days) median, range</td>
<td>4 (1-33)</td>
</tr>
<tr>
<td>Mortality (n)</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to PCC (min) median, range</td>
<td>190 (55-616)</td>
</tr>
<tr>
<td>Door to INR result (min) median, range</td>
<td>37 (15-94)</td>
</tr>
<tr>
<td>Order to admin (min) median, range</td>
<td>56 (24-255)</td>
</tr>
<tr>
<td>Dose to repeat INR (min) median, range</td>
<td>190 (32-960)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost Considerations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent Dose (units)</td>
<td>cost ($)</td>
</tr>
<tr>
<td>Kcentra (PI) 2500 (median)</td>
<td>4000</td>
</tr>
<tr>
<td>Kcentra (all fixed) 1600 (median)</td>
<td>2560</td>
</tr>
<tr>
<td></td>
<td>$25,440</td>
</tr>
</tbody>
</table>
Factor Xa inhibitors

- **Kcentra**
  - Zahir et al\textsuperscript{13}
  - 50 units/kg
  - Fixed dose???

- **FEIBA**
  - Limited data to support, risk for thrombosis
  - 25 – 50 Units/kg

- 3 Factor PCC + rFVIIa or FFP
  - NO DATA TO SUPPORT – THEORETICAL

- **Andexxa**
ANDEXXA Has 2 Regimens Specific to FXa Inhibitors Used and Time of Last Dose

- **≥8 Hours** since last dose of rivaroxaban or apixaban
- **<8 Hours** since last dose of rivaroxaban or apixaban
- **Unknown** administration (dose/time) of rivaroxaban or apixaban

### ANDEXXA STANDARD DOSE
- rivaroxaban ≤10 mg OR apixaban ≤5 mg

### ANDEXXA HIGH DOSE
- rivaroxaban >10 mg OR apixaban >5 mg

**Syringe size and SWFI volume for ANDEXXA reconstitution**

<table>
<thead>
<tr>
<th>Vial strength</th>
<th>Syringe size</th>
<th>SWFI volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>10 mL</td>
<td>10 mL</td>
</tr>
<tr>
<td>200 mg</td>
<td>20 mL</td>
<td>20 mL</td>
</tr>
</tbody>
</table>

- Gently swirl each vial until complete dissolution of cake or powder occurs—avoid prolonged or vigorous agitation
- **DO NOT SHAKE** the vials as it can lead to foaming
- Dissolution time for each vial is approximately 3-5 minutes
## Andexanet Alfa or PCC4 for Reversal of Bleeding Associated with Xa-inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>ANNEXA-4 (n=67)</th>
<th>Majeed et al (n=84)</th>
<th>Schulman et al (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal agent</td>
<td>Andexanet alfa</td>
<td>PCC4</td>
<td>PCC4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>77.1±10.0</td>
<td>75.0±10.9</td>
<td>76.9±10.4</td>
</tr>
<tr>
<td>ICH</td>
<td>42%</td>
<td>70%</td>
<td>55%</td>
</tr>
<tr>
<td>Time since last dose (hours)</td>
<td>R 12.8±4.2</td>
<td>12.5 (9-16)</td>
<td>16.9 (12-21)</td>
</tr>
<tr>
<td></td>
<td>A 12.1±4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effectiveness for CNS bleeds</td>
<td>16 (80%)</td>
<td>43 (73%)</td>
<td>25 (76%)</td>
</tr>
<tr>
<td></td>
<td>excellent or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>12 (18%)</td>
<td>3 (4%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Death</td>
<td>10 (15%)</td>
<td>27 (32%)</td>
<td>9 (14%)</td>
</tr>
</tbody>
</table>
Both PCCs have not been evaluated for effect on anti-factor Xa levels and bleeding/hematoma expansion.
Andexxa Considerations

- Surgery
  - Rebound anti-xa levels 2-4 hours post infusion
- Outside hospital transfer s/p PCC treatment
- Xa other than apixaban or rivaroxaban
- Thrombosis
- Compounding
  - Vial size, tubing
- Cost/Return Policy
  - NTAP
- Restrict use/ CYA
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