Emergent Reversal of Novel Oral Anticoagulants

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Learning Objectives

• Pharmacists
  – Describe characteristics of novel oral anticoagulants (NOACs).
  – Interpret the NOACs effect on coagulation assays.
  – Discuss the pharmacologic reversal of NOACs during life-threatening bleeding.
  – Discuss the NOAC antidotes in the pipeline.

• Technicians
  – Discuss the role of pharmacologic reversal of NOACs in management of patients with life-threatening bleeding.
No conflicts of interest to disclose.
Oral Anticoagulants

- Vitamin K antagonists (VKAs)
  - Warfarin
- Direct thrombin inhibitor (DTI)
  - Dabigatran
- Factor Xa inhibitors
  - Rivaroxaban
  - Apixaban
  - Edoxaban

Novel Oral Anticoagulants (NOACs) =
Direct Oral Anticoagulants (DOACs) =
Target Specific Oral Anticoagulants (TSOACs)
NOACs

• Advantages
  – Predictable pharmacokinetics
  – Rapid onset of action
  – Comparable safety and efficacy

• Challenges
  – Bleeding risks
  – Lab monitoring
  – Emergent reversal
## Pharmacokinetics of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6%</td>
<td>60-80%</td>
<td>50-85%</td>
</tr>
<tr>
<td><strong>Time to peak</strong></td>
<td>1-2 hours</td>
<td>2-4 hours</td>
<td>1-3 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Conjugation; no CYP involvement</td>
<td>CYP 3A4</td>
<td>CYP 3A4</td>
</tr>
<tr>
<td><strong>Renal Excretion</strong></td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
</tr>
</tbody>
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## Metabolism of NOACs

<table>
<thead>
<tr>
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<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
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</thead>
<tbody>
<tr>
<td>Renal Impairment</td>
<td>6-fold higher exposure when CrCl 10-30 mL/min</td>
<td>1.6 fold higher exposure when CrCl 15-29 mL/min</td>
<td>1.44 fold higher exposure when CrCl 15-29 mL/min</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>N/A</td>
<td>2.3 fold increase exposure in Child-Pugh B</td>
<td>N/A</td>
</tr>
<tr>
<td>Age</td>
<td>30% increase in trough concentrations in age &gt;75</td>
<td>Mean AUC 1.5 fold higher in age &gt;65</td>
<td>Mean AUC 1.3 fold higher in age &gt;65</td>
</tr>
</tbody>
</table>

Clinical Lab Monitoring of NOACs

• Prolonged aPTT (activated partial thromboplastin time)
  – May indicate an anticoagulant effect of dabigatran
  – Normal aPTT may exclude anticoagulation
  – Can be insensitive to FXa inhibitors: not recommended for routine monitoring

• Prolonged PT (prothrombin time)
  – May indicate an anticoagulant effect of the FXa inhibitors, rivaroxaban>apixaban,edoxaban
  – Normal PT may exclude significant drug levels of rivaroxaban

Clinical Lab Monitoring of NOACs

• TT (thrombin time)
  – Most sensitive test for dabigatran
  – dTT (dilute thrombin time) quantifies dabigatran drug levels

• Anti-FXa chromogenic assay
  – Recommended for rivaroxaban, apixaban, and edoxaban

Important Note:
Validation required and not universally available. Often with delayed turnaround time that diminishes usefulness in emergent situations.

*Ask the patient*
Strategies for Anticoagulation Reversal

• Ideally managed by pre-determined institutional guidelines

• Influenced by
  – Pharmacology of specific agent
  – Urgency of clinical situation
  – Severity of bleeding
Strategies for Anticoagulation Reversal

- All strategies preceded by appropriate supportive and symptomatic treatment
- Observation and withholding anticoagulation
- Administering a specific reversal agent if one is available
- Administration of supplemental clotting factors either via fresh frozen plasma (FFP) or prothrombin complex concentrates (PCCs)
- Administration of prohemostatic agents such as activated prothrombin complex concentrated (aPCC or FEIBA) or reconstituted factors VIIa (rFVIIa)
Supportive Measures

• Minor bleeds
  – Temporary discontinuation of anticoagulation for several doses

• Significant bleeds may require:
  – Local management
  – Volume resuscitation
  – Consideration of red blood cell and platelet transfusion

• Role of oral activated charcoal

• Role of hemodialysis
Fresh Frozen Plasma

• Not used to reverse anticoagulant effects of NOACs
• May be used a plasma expander
• PCCs preferred over FFP if replacement of coagulation factor is required
Prothrombin Complex Concentrates (PCCs)/
activated Prothrombin Complex Concentrates (aPCCs)

• PCCs
  – Plasma-derived products that contain 3 or 4 clotting factors in addition to variable amounts of heparin and proteins C & S
  – Unactivated 4-factor PCC: Kcentra®
  – Vitamin K + Kcentra® in warfarin reversal

• aPCCs
  – A.k.a. factor VIII inhibitor bypassing activity
  – Contains mostly activated factor VII along with mainly unactivated factors II, IX, and X
  – Activated 4-factor PCC: FEIBA®
Recombinant Activated Factor VII

• rFVIIa: Novoseven®

• In vitro and ex vivo studies demonstrate variable efficacy to reverse coagulation parameters attributable to NOACs

• No clinical trials investigating NOAC reversal with rFVIIa
<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>aPCC (FEIBA&lt;sup&gt;®&lt;/sup&gt;)</th>
<th>PCC (Kcentra&lt;sup&gt;®&lt;/sup&gt;)</th>
<th>rFVIIa (Novoseven&lt;sup&gt;®&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to effect</strong></td>
<td>Hours</td>
<td>Peak effect in 15-30 mins</td>
<td>~10 mins</td>
<td>~10 mins</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>All factors; limited thrombosis risk</td>
<td>Rapid; small volume; provides factor VII</td>
<td>Rapid; small volume; provides factor VII</td>
<td>Rapid; small volume; without infection risk</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Risk of fluid O/L; Prep delay; infectious risk; ABO matching; infusion reactions</td>
<td>Increased thrombotic complication risk greatest with activated factors</td>
<td>Thrombotic complications; contraindicated in HIT</td>
<td>Increased thrombotic complication risk greatest with activated factors</td>
</tr>
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Efficacy Results

• Some but limited data with safety and efficacy

• Increased risk of thrombotic complications
  – Higher with activated factors

• Reserved for patients taking NOACs who present with life-threatening bleeding despite general supportive measures or who require emergency surgery
Idarucizumab (Praxbind®)

- Specific reversal agent for dabigatran
- Chemical Structure: humanized monoclonal antibody fragment
- Binding: noncompetitive binding to dabigatran
- Onset: <5 mins
- Half-life: initial 47 mins; terminal 10.3 hrs
- Elimination: renal
- Dosing: 5 g (2.5 g x 2 doses)
Approaches to Reversal

• First steps to severe and life-threatening hemorrhage:
  – Addressing hemodynamic stability
  – Immediate discontinuation of anticoagulation
  – Consider activated charcoal based on time since ingestion
  – Obtain stat labs
  – Screening

• Administer hemostatic agent of choice or specific reversal agent if indicated
<table>
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<th>Dosing</th>
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<tr>
<td><strong>Unactivated 4-factor PCCs (Kcentra®)</strong></td>
<td>50 IU/kg; maximum 5,000 IU</td>
</tr>
<tr>
<td><strong>aPCCs (FEIBA®)</strong></td>
<td>50-100 units/kg; maximum 200 units/kg daily</td>
</tr>
<tr>
<td><strong>rFVIIa (Novoseven®)</strong></td>
<td>90 µg/kg</td>
</tr>
<tr>
<td><strong>idarucizumab (Praxbind®)</strong></td>
<td>5 g</td>
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The Future…
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<tr>
<th></th>
<th>Andexanet alfa</th>
<th>Ciraparantag</th>
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<tr>
<td><strong>Target Anticoagulants</strong></td>
<td>Oral FXa inhibitors, LMWHs, fondaparinux</td>
<td>Oral FXa inhibitors, dabigatran, LMWHs, fondaparinux, UFH</td>
</tr>
<tr>
<td><strong>Structure Type</strong></td>
<td>Modified recombinant FXa protein</td>
<td>Synthetic small molecule</td>
</tr>
<tr>
<td><strong>I.V. Dosage</strong></td>
<td>For apixaban: 400 mg bolus → 4 mg/min cont. inf. x 2 hr</td>
<td>Undetermined</td>
</tr>
<tr>
<td></td>
<td>For rivaroxaban: 800 mg bolus → 8 mg/min cont. inf. x 2 hr</td>
<td></td>
</tr>
<tr>
<td><strong>Common Adverse Effects</strong></td>
<td>Mild-moderate infusion reactions</td>
<td>Transient mild perioral and facial flushing; distortion of sense of taste</td>
</tr>
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In Development: Andexanet alfa

• Specific reversal agent for oral FXa inhibitors, LMWHs, fondaparinux

• Binding: competitive binding to direct FXa inhibitors or to indirect FXa inhibitor-activated thrombin

• Onset: 2 mins

• Half-life: terminal 6 hrs

• Elimination: not reported
In Development: Ciraparantag

- Specific reversal agent for oral FXa inhibitors, dabigatran, LMWHs, fondaparinux, and UFH
- Binding: covalent hydrogen bonding
- Onset: 5-10 mins
- Half-life: Duration of action 24 hrs
- Elimination: not reported
Conclusions

• No guidelines for the emergent reversal of oral anticoagulants

• Additional studies needed to evaluate effectiveness and thrombotic risk of factor replacement

• Newly developed and in-development specific reversal agents give potential for consistent and effective treatment and management options
Self-Assessment

• LB 78 yo F presents to ED with ICH and last dose of dabigatran 8 hours ago. CrCl=25, prolonged aPTT and TT.

• What is the preferred reversal agent for LB?

A. Kcentra®
B. Feiba®
C. Vitamin K
D. Idarucizumab (Praxbind®)
Self-Assessment

• TB 55 yo F presents to ED with moderate GIB and last dose of rivaroxaban 36 hours ago. Hx of CHF. Normal PT. CrCl=98, Hgb=6.8. BP 86/58

• What is an appropriate initial treatment for TB?

A. Feiba®

B. Supportive measures and address hemodynamic stability

C. FFP

D. Idarucizumab (Praxbind®)
Self-Assessment

• TL 66 yo M presents to ED with ICH and last dose of apixaban 10 hours ago. CrCl=29, prolonged PT.

• What is an appropriate treatment for TB?

A. Feiba®
B. Supportive measures and address hemodynamic stability
C. FFP
D. Idarucizumab (Praxbind®)
References


Cleveland Clinic

Every life deserves world class care.