Emergency Operations and the New Anticoagulants* - What to Do?

*TSOACs=Target Specific Oral AnticoagulantS

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I have no conflicts of interest

New Target Specific Oral Anticoagulants

<table>
<thead>
<tr>
<th>Target</th>
<th>Dabigatran Pradaxa*</th>
<th>Rivaroxaban Xarelto*</th>
<th>Apixaban Eliquis*</th>
<th>Edoxaban Not approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td>7</td>
<td>80</td>
<td>66</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Factor Xa</td>
<td>12-14</td>
<td>9-13</td>
<td>8-15</td>
<td>9-11</td>
</tr>
<tr>
<td>Factor Xa</td>
<td>80</td>
<td>33</td>
<td>40</td>
<td>35-39</td>
</tr>
<tr>
<td>Factor Xa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>2</td>
<td>2-4</td>
<td>1-3</td>
<td>1-2</td>
</tr>
<tr>
<td>Renal (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage</td>
<td>Once Daily</td>
<td>Twice daily</td>
<td>Twice Daily</td>
<td>Once Daily</td>
</tr>
<tr>
<td>Antidote</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DDI</td>
<td>Pgp</td>
<td>CYP3A4, Pgp</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Monitoring</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CYP Met (%)</td>
<td>None</td>
<td>32</td>
<td>15</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Target specific oral anticoagulants [TSOACs], Relative bioavailability in humans, Pgp=P-glycoprotein, Tmax=time to maximum absorption, NR=not reported, #=Fixed dosing

• Advantages
  - Rapid onset/offset of action [short T½]
  - Easier use perioperatively
  - Bridging unnecessary
  - No need for routine laboratory monitoring
  - Fewer drug interactions
  - Lack of dietary interactions
  - Less ICH

• Disadvantages
  - Inability to monitor with routine laboratory tests
  - Lack of reversibility
  - No current antidote
  - Expensive
  - Risk for bleeding from certain sites (GI)
  - Other side effects, e.g. dyspepsia (dabigatran, ?MI)
  - Adherence?
  - Renal clearance
Perioperative Management TSOACs
Normal renal function

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<tr>
<th>Agent</th>
<th>Recommended minimum interval between last dose and procedure</th>
<th>Laboratory tests to detect residual anticoagulant effect</th>
<th>Postprocedure initiation of medication</th>
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<tr>
<td>Dabigatran</td>
<td>T½ = 14-17 h, CrCl ≥ 50 mL/min</td>
<td>Hold for 24 h in low bleed risk; hold for 2-4 days in moderate to high bleed risk</td>
<td>Thrombin time</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>T½ = 8-9 h, CrCl &gt; 60 mL/min</td>
<td>Hold for 24 h in low bleed risk and 48 h in mod to high bleed risk</td>
<td>Anti-factor Xa, Prothrombin time [APTT]</td>
</tr>
<tr>
<td>Apixaban</td>
<td>T½ 7-8 h, CrCl &gt; 60 mL/min</td>
<td>Hold for 24 h in low bleed risk and 48-72 h for mod to high bleed risk</td>
<td>Anti-factor Xa, Prothrombin time, APTT</td>
</tr>
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</table>

Emergency Operations and TSOACs
• Issues to consider
  – Assessing for residual anticoagulant effect
  – Does shortened coagulation time = hemostasis
  – Decreased PT ratio (<1.2) may represent ↓ drug concentration
  – Use and necessity for bridging
  – Resumption of anticoagulants, when?
  – Risks with neuraxial anesthesia/analgesia
• Management Options
  – Hold drug
  – Prothrombin complex concentrates
    • FEIBA for dabigatran
    • Kcentra for rivaroxaban and apixaban

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<tr>
<td>Dabigatran</td>
<td>T½ = 16-18 h, CrCl 30-50 mL/min</td>
<td>Hold 3-4 days</td>
<td>Thrombin time</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>T½ 9-10.5 h, CrCl 30-59 mL/min</td>
<td>Hold 2 days</td>
<td>Anti-factor Xa, Prothrombin time [APTT]</td>
</tr>
<tr>
<td>Apixaban</td>
<td>T½ 17-18 h, CrCl 30-49 mL/min</td>
<td>Hold 3 days</td>
<td>Anti-factor Xa, Prothrombin time, APTT</td>
</tr>
</tbody>
</table>
Kcentra®-4 factor prothrombin complex concentrate

- Not FDA approved for reversal of TSOACs
- FDA approved for reversal of VKAs (warfarin)
- Little clinical trial data available to date
- Anecdotal evidence, some data from healthy subjects (Circulation, Eerenberg ES et al 2012)
- Must consider risk of thrombotic events in susceptible patients and balance risk for hemorrhage

The future

- Drug specific antidotes
  - Andexanet (PRT06445): apixaban, rivaroxaban, edoxaban, phase 2 healthy volunteer study
  - Idarucizumab (BI655075): FAB fragment, dabigatran, phase 3 study of patients on dabigatran
  - Aripazine (PER977): apixaban, rivaroxaban, dabigatran, edoxaban, heparin, rat model only. Small molecule antibody

72 year-old male with need for emergent abdominal exploration. History of atrial fibrillation taking apixaban 5 mg twice daily

1. Proceed with operation immediately
2. Obtain thrombin time and proceed if normal
3. Consider administration of 4 units of FFP
4. Consider administration of FEIBA
5. **Consider administration of Kcentra®**
References

• Choi S and Douketis JD. Management of patients who are receiving warfarin or a new oral anticoagulant and require urgent or emergency surgery. *Polskie Arch Med*. 2012;122 437/
• Connolly G and Spyropoulos. Practical issues, limitations, and periprocedural management of the NOAC’s. *J Thromb Thrombolysis* 2013. published online 27 March