Anticoagulation Reversal in the Hemorrhagic Stroke Patient

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The off-label use of Kcentra, Feiba, Novoseven, tranexamic acid and aminocaproic acid will be discussed and I have no actual or potential conflict of interest in regards to this presentation.

The planners, editors, faculty and reviewers of this activity have no relevant financial relationships to disclose. This presentation was created without any commercial support.
Learning Objectives

At the conclusion of this course participants will be able to

• Recognize available reversal agents used for the management of anticoagulant induced hemorrhage
• Identify novel agents currently in use or in development for target specific oral anticoagulant reversal
• Develop a strategy to manage tPA induced hemorrhage
Hemorrhagic Stroke

• Multi-factorial injury
  – Caused by a weakened blood vessel that ruptures
  – Brain damage due to compression of tissue from expansion of blood from vessel (hematoma)

• Types
  – Intracerebral hemorrhage (ICH)
  – Subarachnoid hemorrhage (SAH, non-traumatic)

Treatment of Hemorrhagic Stroke

• Evaluation by neurosurgery for possible decompression/drainage of hematoma
• Invasive neurologic monitoring
  – Ventriculostomy, if needed
• Supportive therapies when applicable
  – Blood pressure control
  – Reverse coagulopathy
  – Prevention/management of seizures
  – Prevention/management of cerebral vasospasm
Epidemiology

• Anticoagulant induced intracerebral hemorrhage (aICH)
  – Accounts for 12 – 20% of ICH
  – Increasing in frequency
    • Secondary stroke prophylaxis
    • More elderly patients prescribed anticoagulation
  – Combination therapy with antiplatelet agents
    • Cardiac history

“The availability of treatments proven to benefit ICH patients has lagged behind that of ischemic stroke and aneurysmal subarachnoid, and this has resulted in variability in care that ranges from aggressive treatment to a nihilistic approach.”
# Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocritical Care Society</td>
<td>2016</td>
</tr>
<tr>
<td>AHA/ASA sICH</td>
<td>2015</td>
</tr>
<tr>
<td>ACCP</td>
<td>2012</td>
</tr>
</tbody>
</table>

AHA = American Heart Association, ASA = American Stroke Association, sICH = Spontaneous intracerebral hemorrhage, ACCP = American College of Chest Physicians

Anticoagulant Review
Heparin and Derivatives

• Unfractionated Heparin
• Low Molecular Weight Heparin
  – Dalteparin
  – Enoxaparin
  – Tinzaparin
• Factor Xa inhibitor (Pentasaccharide)
  – Fondaparinux

## Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Duration</th>
<th>Elimination</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>IV: Immediate</td>
<td>Dose dependent</td>
<td>Renal, hepatic and RES</td>
<td>aPTT, anti-Xa, ACT</td>
</tr>
<tr>
<td></td>
<td>SQ: 20 – 30 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>SQ: 3 – 5 hours</td>
<td>12 – 24 hours</td>
<td>Renal</td>
<td>Anti- Xa</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>SQ: 2 hours</td>
<td>12 – 24 hours</td>
<td>Renal</td>
<td>Anti- Xa</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>SQ: 2 – 3 hours</td>
<td>12 – 24 hours</td>
<td>Renal</td>
<td>Anti- Xa</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>SQ: 3 hours</td>
<td>16 – 24 hours</td>
<td>Renal</td>
<td>Anti-Xa (Specific)</td>
</tr>
</tbody>
</table>

ACT = Activated clotting time RES = Reticuloendothelial system

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## Half-life of Clotting Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor II</td>
<td>50 hours</td>
</tr>
<tr>
<td>Factor VII</td>
<td>6 hours</td>
</tr>
<tr>
<td>Factor IX</td>
<td>24 hours</td>
</tr>
<tr>
<td>Factor X</td>
<td>36 hours</td>
</tr>
<tr>
<td>Protein C</td>
<td>6 hours</td>
</tr>
<tr>
<td>Protein S</td>
<td>30 hours</td>
</tr>
</tbody>
</table>
Coagulation process and targets of direct oral anticoagulants (DOACs).

Pierre Fontana et al. Eur Heart J 2014;eurheartj.ehu027
## Direct Thrombin Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Half Life</th>
<th>Elimination</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Oral</td>
<td>12 hours</td>
<td>Renal</td>
<td>Not required (aPTT, TT, ECT)</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Parenteral</td>
<td>30 – 60 minutes</td>
<td>Hepatic</td>
<td>aPTT, ACT</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Parenteral</td>
<td>25 minutes</td>
<td>Renal</td>
<td>aPTT, ACT</td>
</tr>
</tbody>
</table>

aPTT = Activated partial thromboplastin time, TT = Thrombin time, ECT = Ecarin clotting time, ACT = Activated clotting time

# Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life</th>
<th>Elimination</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>6 – 13 hours</td>
<td>Fecal/Renal</td>
<td>Not required (aPTT, PT)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>12 – 15 hours</td>
<td>Fecal/Renal</td>
<td>Not required (aPTT, PT)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>10 – 14 hours</td>
<td>Renal</td>
<td>Not required (aPTT, PT)</td>
</tr>
</tbody>
</table>

aPTT = Activated partial thromboplastin time, PT = Prothrombin time


Edoxaban. Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; Version 2.3.2
# Thrombolytics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Plasma half life</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase</td>
<td>5 min</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>20 min</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Reteplase</td>
<td>15 min</td>
<td>Feces, urine</td>
</tr>
</tbody>
</table>

Reversal Agents

• Blood Products
  – Fresh Frozen Plasma
  – Platelets
  – Cryoprecipitate

• Pharmacological
  – Prothrombin Complex Concentrates (PCCs)
    • Activated
    • Non-activated
  – Recombinant Factor VIIa (rFVIIa)
  – Phytonadione (Vitamin K)
  – Antifibrinolytics
    • Aminocaproic Acid
    • Tranexamic Acid
  – Desmopressin (DDAVP)
  – Idarucizumab
Prothrombin Complex Concentrates (PCC)

• **Activated**
  - FEIBA (aPCC)
    • II, VIIa, IX, X, Protein C

• **Non-activated**
  - Three factor
    • II, IX, X
      - Profilnine SD
      - Bebulin VH
  - Four factor
    • II, VII, IX, X
      - Kcentra

• **Advantages**
  - Less volume
  - Rapid administration
  - Quicker reversal

• **Disadvantages**
  - Heparin induced thrombocytopenia
    • Bebulin
    • Kcentra
  - Thrombosis

<table>
<thead>
<tr>
<th>Prothrombin complex concentrate</th>
<th>Factor levels (IU/ml)</th>
<th>Protein levels (IU/ml)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
<td>VII</td>
<td>IX</td>
</tr>
<tr>
<td>3 Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bebulin</td>
<td>24-37</td>
<td>&lt; 5</td>
<td>24-37</td>
</tr>
<tr>
<td>Profilnine</td>
<td>NMT 150/ U/100</td>
<td>NMT 35/ U/100</td>
<td>100 unit</td>
</tr>
<tr>
<td></td>
<td>Factor IX U</td>
<td>Factor IX U</td>
<td>Factor IX U</td>
</tr>
<tr>
<td>4 Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beriplex</td>
<td>20-48</td>
<td>10-25</td>
<td>20-31</td>
</tr>
<tr>
<td>Cofact</td>
<td>30</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Kcentra</td>
<td>19-40</td>
<td>10-25</td>
<td>20-31</td>
</tr>
<tr>
<td>Octaplex</td>
<td>31</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Activated PCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEIBA*</td>
<td>1.3 IU/IU</td>
<td>0.9 IU/IU</td>
<td>1.4 IU/IU</td>
</tr>
</tbody>
</table>

*aAll concentrations are approximate and vary from one lot to another.

NMT = not more than, IU = international units.

*IU/IU = IU/FEIBA unit.
Recombinant Factor VIIa

- Extrinsic pathway activation
- Used with 3 factor PCC to “build” a 4 factor PCC
- Advantages
  - Quick onset
- Disadvantages
  - Thrombosis
  - Short acting
Phytonadione (Vitamin $K_1$)

- Promotes liver synthesis of clotting factors
  - VII, IX, X, II
  - Protein C and S

- Warfarin
  - Inhibits Vitamin K reductase
  - Warfarin insensitive pathway for reduction of phytonadione
    - NADPH dehydrogenases
Role of Phytonadione

• Reversal of vitamin K antagonists
• Administration
  – Subcutaneous
  – Intravenous
  – Oral
• Delayed onset
• Anaphylaxis/Anaphylactoid reactions
  – Low risk
  – Castor oil vehicle in solution

Protamine

- Cationic peptides derived from fish sperm nuclei
  - Inactivates heparin
  - Can be used for LMWH reversal

- Use with caution
  - Too much = more bleeding
  - Too fast = anaphylactoid reaction

Antifibrinolytics

- Aminocaproic acid
- Tranexamic acid
## New Antidotes Approved or in the Pipeline

<table>
<thead>
<tr>
<th>Agents</th>
<th>Target</th>
<th>Structure</th>
<th>Route</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab (Praxbind)</td>
<td>Dabigatran</td>
<td>Fab</td>
<td>IV</td>
<td>Binds to dabigatran with greater affinity than thrombin</td>
</tr>
<tr>
<td>Andexanet alpha (PRT064445)</td>
<td>Direct and indirect Fxa inhibitors</td>
<td>Modified recombinant Fxa</td>
<td>IV</td>
<td>Binds to FXa inhibitors</td>
</tr>
<tr>
<td>Aripazine (PER977)</td>
<td>Universal</td>
<td>Small synthetic molecule</td>
<td>IV</td>
<td>Binds directly to UFH and other anticoagulants</td>
</tr>
</tbody>
</table>

Fab = Human monoclonal antibody, IV = Intravenous, Fxa = Factor Xa, UFH = Unfractionated heparin, MOA = Mechanism of action

Mo Y, Yam FK. Recent advances in the development of specific antidotes for TSOACs. *Pharmacotherapy.* 2015; 35:198-207.
Mo Y, Yam FK. Recent advances in the development of specific antidotes for TSOACs. *Pharmacotherapy*. 2015; 35:198-207.
Idarucizumab

• FDA approved October 2015

• Phase III study (REVERSE-AD)
  
  • Idarucizumab 5 g total dose given to 2 groups
    – Life-threatening bleed defined by treating physician
    – Require surgery or other invasive procedure that cannot be delayed for at least 8 hours

• Supplied as 2 x 2.5 g vials
  
  – Can be give rapid IV push
  
  – Total of 5 g given within 15 minutes

Mo Y, Yam FK. Recent advances in the development of specific antidotes for TSOACs. *Pharmacotherapy.* 2015; 35: 198-207.
Andexanet Alfa

• Breakthrough Therapy Designation by FDA

• 3 Phase III studies
  – Reversal of rivaroxaban and apixaban in older healthy adults 50-75 years old
    • Rivaroxaban (ANNEXA-R)
      – Andexanet alfa 800 mg IV bolus, then 4 mg/min for 2 hours
    • Apixaban (ANNEXA-A)
      – Andexanet alfa 400 mg IV bolus, then 4 mg/min for 2 hours
  – Reversal of factor Xa inhibitors in acute major bleeding

Mo Y, Yam FK. Recent advances in the development of specific antidotes for TSOACs. *Pharmacotherapy*. 2015; 35: 198-207.
Aripazine

• Fast Track Designation granted by FDA
• Phase I and II studies
  – Edoxaban
  – Heparin
  – Enoxaparin
• Greatest potential as a universal reversal agent

KEEP CALM AND STOP THE ANTICOAGULATION
Clinical Considerations for Reversal

• Indication
  – Intensity of anticoagulation and risk of hematoma expansion
  – Surgical intervention
• Choice of reversal agent
  – Past medical history
  – Thromboembolic events
  – Adverse reactions/Allergies
• Outcomes
  – Morbidity
  – Mortality

Warfarin Reversal

• Blood Products
  – FFP 10-15 mL/kg

• Pharmacological
  – Phytonadione
    • 10 mg IVPB x 1
  – 4 factor PCC or aPCC
    • 25 – 50 units/kg
      – Dose based on presenting INR
    • 3 factor PCC
      – FVIIa
  – rFVIIa
    • 1 mg IVP + FFP

• Supportive care
  – Monitoring for adverse reactions
    • Thromboembolism
    • Anaphylaxis and anaphylactoid reactions

  – Efficacy
    • Decrease in PT/INR

Dabigatran Reversal

• Activated Charcoal
  – Acute ingestion (1-2H)
  – 25-50 g dose without sorbitol

• Fluids
  – NS 1 L bolus
  – NS 1 mL/kg/hr

• Idarucizumab
  – 5 gram x 1 dose

• aPCC or 4 factor PCC
  – 50 units/kg x 1 dose

• Hemodialysis
  – 62% removal at 2 hours

• Lab Monitoring
  – Thrombin time
  – aPTT

Intravenous DTIs

• Hirudin analogues and argatroban
  – Shut off drip
  – Fluids

• aPCC or 4 factor PCC
  – 50 units/kg x 1 dose

• Lab Monitoring
  – aPTT

Oral Factor Xa Reversal

• Activated charcoal
  – Not studied, but recommended

• Fluids
  – NS 1 L bolus
  – NS 1 mL/kg/hr

• aPCC or 4 factor PCC
  – 50 units/kg x 1 dose

• Hemodialysis
  – May not be as effective
  – Highly protein bound

• Lab monitoring
  – PT
  – aPTT

Fondaparinux Reversal

• First line agent
  – aPCC 20 units/kg x 1 dose increased thrombin generation time in plasma from healthy volunteers

• If aPCC is contraindicated
  – rFVIIa 90 mcg/kg x 1 dose
    – Immediate normalization of thrombin generation time, aPTT and PT

• Monitoring
  – Anti-factor Xa for fondaparinux

Heparin Product Reversal

**Unfractionated heparin**
- Protamine
  - Immediate reversal
    - 1 mg/100 units heparin
  - Delayed reversal (30-60 min)
    - 0.5 mg/100 units heparin
- DO NOT GIVE FFP
- Monitor
  - aPTT
  - ACT

**Low molecular weight heparin**
- Protamine
  - Enoxaparin
    - Within 8 hours
      - 1 mg/1 mg
    - Within 8-12 hours
      - 0.5 mg/1 mg
  - Dalteparin (within 3-5 half lives)
    - 1 mg/100 units
- Monitor
  - rFVIIA 90 mcg/kg x 1 dose if protamine contraindicated
  - Anti-Xa level

tPA Reversal

• Stop infusion
• Give 10 units cryoprecipitate STAT
  – Goal fibrinogen > 150 mg/dL
• Consider aminocaproic acid or tranexamic acid when cryoprecipitate is contraindicated
  – Aminocaproic acid 5 g IVBP x 1 dose
  – Tranexamic acid 10-15 mg/kg IVPB x 1 dose
• Lab Monitoring
  – Fibrinogen

Nursing Clinical Pearls

• Vitamin K
  – Do not give subcutaneously for life threatening bleeds
  – Monitor for anaphylaxis/anaphylactoid reactions
    • Risk is less than 1%

• Prothrombin Complex Concentrates
  – Flush IV line with normal saline
  – Monitor for infusion related reactions
  – Coags must be drawn 30 minutes after dose complete
  – Monitor for new onset thromboembolism

• Factor VIIa
  – Flush line with NS before and after administration
    • Give over 2 minutes
  – Monitor for new onset thromboembolism
  – Coags must be drawn within 30 minutes of administration

• Protamine
  – Too much = more bleeding
  – Too fast = anaphylactoid reaction
Conclusion

- Early recognition and reversal of anticoagulant or thrombolytic associated hemorrhagic stroke with the appropriate agent is the cornerstone of treatment.
- New antidotes will replace PCCs and rFVIIa for DOAC reversal when they are approved by the FDA.