Pharmacologic Interventions for Reversing the Effects of Oral Anticoagulants

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Learning Objectives

At the conclusion of this presentation, participants will be able to:

• Describe the relative benefits and limitations of emergent anticoagulant reversal strategies

• Discuss the clinical evidence supporting the use of emergent anticoagulant reversal strategies
Points of Consideration

• HOW to reverse
  – Can be standardized
  – Should be standardized
    • Information on reversal not readily available
    • Guidelines – help all healthcare professionals know what is going on

• WHO to reverse
  – Difficult to standardize
  – Risk vs. Benefit
WARFARIN
Clinical Scenarios for Reversal

Oral Anticoagulation

- Supratherapeutic or Bleeding
  - Minimize impact on patient outcomes
- Urgent Procedure Required
  - Reversal of anticoagulation
Vitamin K Dependent Factor Formation

Vitamin K Dependent Factor Precursor → Vitamin K Oxide Reductase → Reduced Vitamin K → Oxidized Vitamin K → Vitamin K Dependent Factor

WARFARIN
Basis for Understanding Reversal

Intrinsic Pathway
- XII
- XI
- Xa
- IXa
- Thrombin (IIa)

Extrinsic Pathway
- Tissue Factor
- VIIa

Platelet Activation
- Fibrinogen
- Fibrin

Clot Stabilization
Reversal with Vitamin K

Exogenous vitamin K allows liver to produce more II, VII, IX, X...

LIVER
IV Vitamin K for Reversal of Warfarin

- **Hold**
- **PO Vitamin K**
- **IV Vitamin K**

IV Vitamin K included in studies of other management strategies
Vitamin K

• Dosing issues
  – Supratherapeutic INR
    • Oral is preferred
  – Urgent situations
    • IV is preferred
    • NO subcutaneous or IM

• Adverse events
  – Anaphylactic reaction to IV
  – May be refractory to warfarin when restarted
    • Use lowest dose possible to avoid
Reversal of Warfarin: Bleeding or Need for Emergent Surgery

Options
• IV vitamin K
  PLUS
• Fresh frozen plasma (FFP)
  OR
• Concentrated Blood Factor Products
  – 3 Factor prothrombin complex concentrate (PCC3)
  – 4 Factor prothrombin complex concentrate (PCC4)
  – Recombinant factor VIIa (rFVIIa)
  – Activated PCC (aPCC)
Fresh Frozen Plasma

• How does it work?
  – Contains all blood factors found in plasma

• Dosing
  – 1 unit ~ 200 – 250 mL
    • Weight based
      – 10 – 20 mL/kg → 20 – 30% increase in any factor level
    • “2 units FFP”

• Disadvantages
  – Volume of fluid administration – 400 mL or more!
  – Thawing may delay therapy
  – Infectious disease concerns
  – Hemolytic transfusion reactions and hypersensitivity

Concentrated Blood Factors

• Available Data
  – Mostly observational
  – Small patient numbers
  – Surrogate endpoint $\rightarrow \downarrow$ INR

• Dosing issues
  – Fixed dosing vs. weight based vs. INR based

• Adverse events
  – Prothrombotic potential
    • Especially with “activated” products
      – rFVIIa, aPCC
    • Anticipated benefit must outweigh prothrombotic risk
## Concentrated Blood Factor Products

<table>
<thead>
<tr>
<th>Brand Names</th>
<th>4-factor PCC</th>
<th>3-factor PCC</th>
<th>rFVIIa</th>
<th>aPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCentra®</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Octaplex®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bebulin VH®</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Profilnine SD®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novo-Seven®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEIBA®</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| U.S. Availability | Yes*               | Yes                | Yes             | Yes           |
| Factors Provided  | II, VII, IX, X     | II, IX, X          | VII             | II, VII, IX, X |
| Activated?        | No                 | No                 | Yes             | Yes           |

*K-Centra is only available US 4-factor product

Options for Reversal of Warfarin

*Generally reflects co-administration of vitamin K ± FFP
Warfarin Reversal: Historical Perspective

2013
First 4-factor PCC approved in the United States

Made due with the agents we had available in the United States

2012
CHEST Guidelines 9th Edition: 4-FACTOR PCC (over FFP) in addition to IV vitamin K recommended for major bleeding

2008
CHEST Guidelines 8th Edition: FFP, PCC or Factor VIIa in addition to IV vitamin K recommended for life threatening bleeding

Options Before 4-Factor PCC

- Fresh Frozen Plasma
- Factor VIIa (rFVIIa)
  - INR reduction data only
- 3-Factor PCC
  - INR reduction data only, some unfavorable data
- Activated PCC (aPCC)
- Build a 4-Factor PCC
  - 3-Factor PCC + rVIIa
  - INR reduction data only
4-Factor PCC

KCentra®
FDA Approved 2013

Octaplex®
Coming Soon?
Warfarin Reversal with a 4-Factor PCC: KCentra®

- Reversal due to bleeding
  - $n = 212$
  - INR > 2
- Randomized, open-label

<table>
<thead>
<tr>
<th></th>
<th>4-Factor PCC</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – less than 4</td>
<td>25 units/kg</td>
<td>10 mL/kg</td>
</tr>
<tr>
<td>4 – 6</td>
<td>35 units/kg</td>
<td>12 mL/kg</td>
</tr>
<tr>
<td>Greater than 6</td>
<td>50 units/kg</td>
<td>15 mL/kg</td>
</tr>
</tbody>
</table>

All patients received IV Vitamin K
4-factor PCC used = KCentra

## Warfarin Reversal with a 4-Factor PCC: KCentra®

<table>
<thead>
<tr>
<th></th>
<th>PCC (n = 98)</th>
<th>FFP (n = 104)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Hemostasis</td>
<td>72.4%</td>
<td>65.4%</td>
<td>7.1% (-5.8% - 19.9%)</td>
</tr>
<tr>
<td>↓ of INR to ≤ 1.3 @ 30 minutes</td>
<td>62.2%</td>
<td>9.6%</td>
<td>52.6% (39.4% - 65.9%)</td>
</tr>
<tr>
<td>Fluid Overload</td>
<td>5.8%</td>
<td>12.8%</td>
<td>-7% (-15.8% - 1.8%)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>8.7%</td>
<td>5.5%</td>
<td>3.2% (-4.7% - 11.5%)</td>
</tr>
</tbody>
</table>

All patients received IV Vitamin K
4-factor PCC used = KCentra

Warfarin Reversal with a 4-Factor PCC

Patients (n=314)
- INR > 1.5
- Bleeding/Procedure Intervention
- O: 1000 IU
- FFP: NR?

1\textsuperscript{o} Outcome
Adverse event composite
- Death, MI, Stroke, VTE, HF, Arterial Thrombosis

Warfarin Reversal with a 4-Factor PCC

**Summary of Evidence**

- 4-Factor PCCs effective for reducing INR compared to FFP
  - Effect on bleeding similar between KCentra® and FFP
  - Less heart failure/fluid overload with 4-factor PCC
- **Dosing approach**
  - INR-specific doses studied mostly with KCentra®
  - Both fixed and INR-specific doses studied with Octaplex®
- **Thromboembolic complications**
  - Infrequent, but have occurred
Decison Making: 4-Factor PCCs?

**KCentra®**
- INR > 2
- INR-specific weight based dosing
- Compared to FFP
  - Similar effect on bleeding
  - Faster INR reduction
  - Less volume overload

**Octaplex®**
- INR > 1.5
- INR-specific weight based dosing
- Compared to FFP
  - Faster INR reduction
  - Less volume overload
## Cost: Pharmacologic Reversal Options

<table>
<thead>
<tr>
<th>Agent</th>
<th>PCC-4 INR 2 - 4</th>
<th>PCC-4 INR 4-6</th>
<th>PCC-4 INR&gt;6</th>
<th>PCC-3 + VIIa</th>
<th>aPCC INR &lt;5</th>
<th>aPCC INR&gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCC-4 (25 mL/kg)</td>
<td>$2540</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCC-4 (35 mL/kg)</td>
<td></td>
<td>$3556</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCC-4 (50 mL/kg)</td>
<td></td>
<td></td>
<td>$5080</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCC-3 (25 units/kg)</td>
<td></td>
<td></td>
<td></td>
<td>$1760</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVIIa (20 mcg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$2960</td>
<td></td>
</tr>
<tr>
<td>aPCC (500 units)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$695</td>
</tr>
<tr>
<td>aPCC (1000 units)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$1390</td>
</tr>
<tr>
<td>Cost/reversal regimen</td>
<td>$2540</td>
<td>$3556</td>
<td>$5080</td>
<td>$4720</td>
<td>$695</td>
<td>$1390</td>
</tr>
</tbody>
</table>

**Strength of Data**

- ++
- +

Assumes 80-kg patient and rounding to nearest vial size. Cost based on Premier Base Prices – PCC-3 = $0.88/unit, PCC-4 = $1.27/unit, Factor VIIa = $2960/2 mg vial, aPCC = $1.39/unit. 

Urgent Warfarin Reversal: Bleeding or Surgery

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Reversal Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>Vitamin K 5 – 10 mg slow IV + 4-factor PCC†</td>
</tr>
<tr>
<td>Surgery in &lt; 24 hours</td>
<td>May have time to use IV vitamin K alone‡</td>
</tr>
<tr>
<td>Surgery in &gt; 24 hours</td>
<td></td>
</tr>
</tbody>
</table>

†Recommendation based on CHEST Guidelines (2C).
‡Recommendation based on published literature and pharmacodynamics of vitamin K.
Target Specific Oral Anticoagulants

- Dabigatran
- Rivaroxaban
- Apixaban
How Do We Reverse Them?

• Not really sure
• Largely theoretical
• Based on very limited data
  – Animal models
  – Healthy volunteer studies
  – Case reports
# Laboratory Monitoring

<table>
<thead>
<tr>
<th>Assay</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT/INR</td>
<td>No</td>
<td>Maybe</td>
<td>Maybe</td>
</tr>
<tr>
<td>aPTT</td>
<td>Yes†</td>
<td>Maybe</td>
<td>Maybe</td>
</tr>
<tr>
<td>Thrombin Time</td>
<td>Yes†</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ecarin Clotting Time</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dilute PT</td>
<td>Maybe</td>
<td>Maybe</td>
<td>Maybe</td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>No</td>
<td>Yes‡</td>
<td>Yes‡</td>
</tr>
<tr>
<td>Heptest</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

†Not useful for quantifying
‡Would need to be calibrated for specific agent

Theoretical Support for Reversal

Intrinsic Pathway

Extrinsic Pathway

Tissue Factor

Dabigatran

Rivaroxaban

Apixaban

Pharmacologic reversal may provide enough blood factors to overwhelm the effects of the drug.
## Human Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>TSOA</th>
<th>Subjects</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Eerenberg    | D, R | Healthy Volunteers (n=12)       | Randomized, Crossover   | D: no effect of PCC  
R: PT and ETP normalized                        |
| Marlu        | D, R | Healthy Volunteers (n = 10)     | Ex – Vivo               | FEIBA > Factor VIIa and  
PCC4 in improving thrombin generation (R > D) |
| Levi         | R    | Healthy Volunteers (n = 34)     | Randomized, Parallel    | PCC3: Greater effect on PT  
PCC4: Greater effect on ETP                                                   |
| Dinkelaar    | R    | Healthy Donors                  | In Vitro, spiked blood samples | Changes in ETP normalized by PCC                                            |

Levi M. *ISTH*. 2013; (abstract ).  
# Dabigatran Reversal: Blood Factors

<table>
<thead>
<tr>
<th></th>
<th>Dumkow</th>
<th>Dager</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td>85 y/o, CrCl = 38.3 mL/min</td>
<td>67 y/o, CrCl = not reported</td>
</tr>
<tr>
<td><strong>Clinical Course</strong></td>
<td>150 mg BID&lt;br&gt;Presented with gastrointestinal bleed</td>
<td>150 mg BID&lt;br&gt;Large bleed after cardiac perforation during ablation</td>
</tr>
<tr>
<td><strong>Reversal Approach</strong></td>
<td>6 units FFP, then 4 units FFP plus PCC3</td>
<td>FEIBA 26 u/kg initially&lt;br&gt;FEIBA 16 u/kg 30 hours later</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Possible initial stabilization, then negative outcome</td>
<td>Visible resolution of bleeding, positive outcome</td>
</tr>
</tbody>
</table>


Dabigatran: Hemodialysis

Pharmacokinetic Study

• 6 patients on hemodialysis
  – Dabigatran 50 mg
  – 4 hour dialysis session

• Amount of drug removed by dialysis
  – 2 hours – 62%
  – 4 hours – 68%

## Dabigatran Removal with Dialysis

<table>
<thead>
<tr>
<th></th>
<th>Warkentin</th>
<th>Harinstein</th>
<th>Esnault</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td>79 yo, CrCl = 36 mL/min</td>
<td>84 yo, CrCl = 54 mL/min</td>
<td>62 y/o, CrCl = 39 mL/min</td>
</tr>
<tr>
<td><strong>Clinical Course</strong></td>
<td>150 mg BID AVR + CABG Massive postop bleed</td>
<td>150 mg BID x 4d CrCl ↓ to 25 mL/min Cecal perforation</td>
<td>110 mg BID Large hematoma after fall trauma</td>
</tr>
<tr>
<td><strong>Reversal Approach</strong></td>
<td>rFVIIa 21.6mg (in 5 doses) HD x 6 hours</td>
<td>rFVIIa 30 mcg/kg preop CVVHD/CVVHDF x 4 days</td>
<td>HD x 2 hours reduced dabigatran levels and aPTT, Needed surgery performed</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Patient improved</td>
<td>Clinical and laboratory improved</td>
<td>Positive</td>
</tr>
</tbody>
</table>


Dabigatran Removal with Dialysis

Patient: 94 yo, CrCl = 79 mL/min

Clinical Course: 150 mg BID – Subdural hematoma

Reversal Approach: FEIBA (8 u/kg) given prior to HD cath placement
HD x 3 hours reduced dabigatran level by < ½.
Dabigatran levels rebounded 2 hours after HD

Outcome: Positive

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban/Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 24 hours</td>
<td>Withhold drug and monitor</td>
<td>Withhold drug and monitor</td>
</tr>
<tr>
<td>1 – 24 hours</td>
<td>Withhold drug, charcoal (if last dose &lt; 2 hrs prior), HD of at least 2 hours</td>
<td>Withhold drug, charcoal (if last dose &lt; 2 hrs prior), charcoal may be repeated 6 hrs later hours</td>
</tr>
<tr>
<td>&lt; 1 hour</td>
<td>Withhold drug, Charcoal (if last dose &lt; 2 hrs prior), prolonged HD, consider:</td>
<td>Withhold drug, charcoal (if last dose &lt; 2 hrs prior), charcoal may be repeated 6 hrs later hours, consider:</td>
</tr>
<tr>
<td></td>
<td>• aPCC (FEIBA)</td>
<td>• PCC4</td>
</tr>
<tr>
<td></td>
<td>• PCC4</td>
<td>• aPCC (FEIBA)</td>
</tr>
<tr>
<td></td>
<td>• PCC3 + rVIIa</td>
<td>• PCC3 + rVIIa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PCC3</td>
</tr>
</tbody>
</table>
Future Directions?

• Specific Antidotes
  – Phase II studies
    • Antibody fragments (DTI)
    • Inactive FXa molecule (Xa antagonists)

• Tranexamic acid
  – Very limited data
    • Less postoperative blood loss – rivaroxaban
    • No safety data

Conclusion

• Reversal of anticoagulation
  – RISK vs. Benefit

• Reversal of warfarin
  – US availability of 4-factor PCC

• Reversal of new oral anticoagulants
  – Limited data
  – Delay invasive procedures when possible
  – Some role for HD and concentrated blood factor products