Anticoagulation Reversal: New Agents and Alternative Strategies

JENNIFER CATLIN, PHARMD, BCPS
SANFORD MEDICAL CENTER- FARGO, ND
Objectives

1. List considerations for urgent anticoagulation reversal
2. Review new therapies for direct oral anticoagulation (DOAC) reversal
3. Describe FDA-labeled warfarin reversal and off-label dosing strategies
Abbreviations

4-PCC – 4 factor prothrombin complex concentrate
3-PCC – 3 factor prothrombin complex concentrate
aPCC – activated 4 factor complex concentrate
rFVIIa – recombinant factor VII
FFP – fresh frozen plasma
DOAC- direct oral anticoagulant
Hbg- hemoglobin
ICH- intracranial hemorrhage
GCS- Glasgow coma scale
PRBC- packed red blood cells
Introduction

• DOAC use increasing

• New reversal agent approved May, 2018

• 4-PCC shortages reported nationwide

2013 4-PCC -US approval

2015 Idarucizumab

2018 Andexanet Alfa

Review

MECHANISMS OF ACTION, DRUG ARMAMENTARIUM
Factor containing products

FFP – Factor V, VII, VII, X, XI, XIII, fibrinogen, plasma proteins, electrolytes

- 200-300 ml

PCC

- 3 factor – inactivated II, IX, X
- 4 factor – inactivated II, VII, IX, X- protein C &S, heparin

aPCC

- FEIBA (factor eight inhibitor bypass activity)
- Activated VII+ inactivated II, IX, X

rFVIIa

- Activated VII
## Factor containing products

<table>
<thead>
<tr>
<th>Vitamin K dependent Coagulation Factors</th>
<th>Recombinant Factor VIIa (rFVIIa)</th>
<th>Fresh Frozen Plasma (FFP)</th>
<th>3-factor prothrombin complex concentrate (3-PCC)</th>
<th>4-factor prothrombin complex concentrate (4-PCC)</th>
<th>aPCC (FEIBA*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>IX</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>VII</td>
<td>✗</td>
<td>✗</td>
<td>—</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>II</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

*Factor eight inhibitor bypassing activity
Case

- MH, 33 y/o M
- CC: HA, increased dizziness s/p fall from roof
- PMH: DVT 3/2018, depression
- Rx rivaroxaban 20mg PO daily
- What are you options for DOAC reversal?
- What other questions/considerations are there?
Assessment of the bleeding patient

- Urgency/Severity
- Labs
- Patient & drug specifics
Patient Characteristics

- Renal function assessment
- Anticoagulant & indication
- Time of last known ingestion
- Co-medications
- Religious preferences
- Allergies
# Pharmacologic Properties

<table>
<thead>
<tr>
<th>Oral Anticoagulant</th>
<th>Time to Peak concentration (hr)</th>
<th>Half-life</th>
<th>Renal Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1-3</td>
<td>7-9, 17</td>
<td>80-85%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2-4</td>
<td>7-17</td>
<td>36%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1-2</td>
<td>8-14</td>
<td>25%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1-2</td>
<td>6-11</td>
<td>26-45%</td>
</tr>
</tbody>
</table>
Urgency of Reversal

- Life threatening bleeding
  - Major often defined as: hemodynamic instability, Hgb decrease by $\geq 2$ g/dL or $\geq 2$ U PRBCs administration

- Urgent/emergent procedure
  - Critical bleeding site
  - High bleeding risk

- Planned vs. unplanned
Labs

- Tests &/or point of care devices readily available?
- Lab turn around time?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Suggested Test</th>
<th>Interpretation</th>
<th>Suggested Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>TT, aPTT</td>
<td>Normal TT excludes clinically relevant* levels</td>
<td>aPTT</td>
<td>Prolonged aPTT suggests that on-therapy or above on-therapy levels are present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolonged TT does not discriminate between clinically important and insignificant levels</td>
<td></td>
<td>Normal aPTT may not exclude on-therapy levels, particularly if a relatively insensitive aPTT reagent is used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal aPTT usually excludes clinically relevant* levels, if a sensitive reagent is used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>None</td>
<td>Normal PT and aPTT do not exclude clinically relevant* levels</td>
<td>PT</td>
<td>Prolonged PT suggests that on-therapy or above on-therapy levels are present</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal PT may not exclude on-therapy or above on-therapy levels, particularly if a relatively insensitive PT reagent is used</td>
</tr>
<tr>
<td>Edoxaban or rivaroxaban</td>
<td>None</td>
<td>Normal PT and aPTT do not exclude clinically relevant* levels</td>
<td>PT</td>
<td>Prolonged PT suggests that on-therapy or above on-therapy levels are present</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal PT may not exclude on-therapy levels, particularly if a relatively insensitive PT reagent is used</td>
</tr>
</tbody>
</table>

*Clinical Objective: Exclude Clinically Relevant Drug Levels

New Agents

ANDEXANET ALFA
Andexanet Alfa

Recombinant modified human factor Xa "decoy" protein

Binds direct and indirect factor Xa inhibitors

**Andexanet alfa dosing**

High dose = 800mg → 8mg/min
Low dose = 400mg → 4 min/min

<table>
<thead>
<tr>
<th>FXa inhibitor</th>
<th>FXa inhibitor last dose</th>
<th>Timing of FXa Inhibitor Last Dose Before Andexanet alfa Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤5 mg</td>
<td>&lt;8 Hours or Unknown</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5 mg/unknown</td>
<td>≥8 Hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>≤10 mg</td>
<td>&lt;8 Hours or Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 mg/unknown</td>
<td>≥8 Hours</td>
</tr>
</tbody>
</table>

100 mg = $3,300 AWP
Ongoing, multicenter, prospective, open-label, single group study

67 patients with acute major bleeding

Primary outcomes:
- % change in anti-Xa activity
- Rate of good or excellent hemostatic efficacy 12 hours after infusion

All patients received bolus → 2 hour infusion

ANNEXA-4

INCLUSION
• Age > 18
• Rivaroxaban, apixaban, enoxaparin within 18 hours
• Acute major bleeding
  ◦ Potentially life threatening overt bleeding with hemodynamic instability
  ◦ Hgb decrease by at least 2g/dL or Hgb < 8 g/dL
  ◦ Critical bleeding site

EXCLUSION
• Scheduled surgery within < 12 hours
• ICH with GCS < 7
• ICH volume > 60 ml
• Survival expected < 1 mo.
• Major thrombotic event in previous 2 weeks

Baseline Characteristics (Efficacy n=47)

• Bleeding site
  ◦ GI = 53%
  ◦ Intracranial bleeding = 43%
  ◦ Baseline GCS 14.1 ± 1.17
  ◦ 67% hematoma < 10 ml

• Age 77.1 years
• 55% male
• Time from presentation until bolus:
  ◦ 4.8 ± 1.8 hr
• Time from last dose to andexanet administration
  ◦ Rivaroxaban: 12 ± 4.1 hr
  ◦ Apixaban: 11 ± 4.7 hr
Good or excellent hemostatic efficacy 12 hours after infusion = 79% overall at 12 hours

ANNEXA -4 Safety Outcomes

NEJM ’16 PUBLICATION

- Thrombotic event rate 12/67 (18%)
- 15% of patients died in 30-day follow-up period

Safety outcomes presented at ACC 2018

- Safety on 227 patients
  - 12% died
  - 11% thrombotic event

- Efficacy on 132 patients
  - Excellent or good hemostasis in 83%
ANDEXANET CRITIQUE

PROS

• First FDA- Approved product for anti-Xa inhibitors

CONS

• No control group
• Quick off-set
• Cost
  • CMS add on payment Oct.1, 2018
• Unavailable to many institutions
  • Gen 2 product expected early 2019
New Agents

IDARUCIZUMAB
Idarucizumab (Praxbind®)

- Humanized monoclonal antibody that binds to dabigatran
- Accelerated FDA approval October 16, 2015
  - RE-VERSE AD
- N = 503
  - Group A n = 301 – uncontrolled bleeding
  - Group B n = 202 in urgent procedure
- Primary endpoint: maximum % reversal of anticoagulant effect at 4 hours (dTT or ECT)
- Secondary endpoints: restoration of hemostasis and safety measures

Idarucizumab – Full Cohort Results

**PRIMARY ENDPOINT**

- Median maximum % reversal: 100%

**SECONDARY ENDPOINTS**

- Time to cessation of bleeding:
  - Group A: 2.5 hours
  - Group B: 1.6 hours
- Periprocedural hemostasis
  - Normal: 93.4%
- Safety - 90 day thrombotic event rate:
  - 6.3% Group A
  - 7.4% Group B
- Mortality: 18.8-18.9%

Warfarin Reversal
4-PCC for Warfarin Reversal

• FDA Indications: VKA reversal in patients with acute major bleeding or need for urgent surgery/invasive procedure

Labeled dosing:

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - &lt; 4</td>
<td>25 units/kg</td>
<td>2,500 units</td>
</tr>
<tr>
<td>4-6</td>
<td>35 units/kg</td>
<td>3,500 units</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50 units/kg</td>
<td>5,000 units</td>
</tr>
</tbody>
</table>
4-PCC

Acute Major Bleeding

- n = 212, 202 in mITT
  - 98 PCC, 104 FFP
- FFP 10, 12, or 15 ml/kg (based on INR)
- Primary endpoints:
  - Hemostatic efficacy 72.4% PCC vs 65.4% - non-inferiority
  - Reduction in INR to 1.3 or less at 30 minutes after end of infusion: 62.2% PCC and 9.6% FFP - superiority

Urgent Invasive or Surgical Intervention

- n = 181, 168 in ITT
  - 87 PCC, 81 FFP
- Primary endpoints
  - Hemostatic efficacy 90% PCC vs. 75% FFP - non-inferiority
  - Reduction in INR to 1.3 or less at 30 minutes after end of infusion: 55% PCC and 10% FFP - superiority

4-PCC Shortage

- Both 1000 & 500 unit vials affected
- Estimated Resupply Dates – CSL Behring is releasing Kcentra® weekly
- ASHP Alternative Agents & Management Strategies:
  - Reserve supplies for patients on warfarin with life threatening bleeding. Consider fixed dosing to conserve supply.
  - Consider aPCC (FEIBA) as alternative
  - FFP

4-PCC – Fixed Dosing Strategies
4-PCC – Fixed Dosing Strategies

• Purpose: Evaluate experience with 1500 IU fixed-dose protocol
• Retrospective review
• Results, n =39
  ◦ 71.8% were ICH
  ◦ Median pre-treatment INR = 3.3, post-treatment INR 1.14 (p < 0.001)
  ◦ 92.3% (36 of 39) achieved INR < 2; 71.8% (28) achieved INR 1.5 or less
  ◦ No thrombotic events
  ◦ Author conclusions: fixed dose 1500 IU 4-PCC leads to high rates of successful INR reversal and no related thrombotic at 7 days.

4-PCC – Fixed Dosing Strategies

• Purpose: Evaluate efficacy of 1500 IU fixed dose 4-PCC to decrease INR to ≤ 1.5 in warfarin treated patients requiring emergent reversal

• Retrospective evaluation

• n=37

• ~ 75% ≤ 1.5 after 1500 & 100% INR ≤ 2

• Median pre-INR: 3.06, post: 1.32
4-PCC – Fixed Dosing Strategies

- 1000 units 4-PCC for ICH vs. weight based (Cofact®)
- Before and after study design
- 1750 IU in weight based n =25 and 1000 IU n=28
- ITT analysis 96% achieved INR ≤ 1.5 – wt based & 68% in fixed dose
- 8% in wt based & 32% in fixed received additional dose
- Median door – to – PCC:
  - 81 vs. 60 min (p = 0.42)
- Author Conclusions: fixed dose needs more PCC infusions more frequently to achieve INR ≤ 1.5; no significant changes in door –to- PCC time, clinical outcome effects remain unknown
4-PCC – Fixed Dosing Strategies

• Purpose: Compare fixed dose of 1000 IU 4-PCC to that of weight-based dosing in ICH

• Primary endpoint: INR < 1.5

• Secondary endpoints: in-hospital mortality, patient disposition, reversal defined by INR < 1.6

• n= 61 (31 weight based, 30 fixed)

• Baseline INR 2.98, 2.84, 71% INR < 1.5 wt based, 53% in fixed (p=0.15), 81% achieved INR < 1.6 wt based & 73% in fixed (p=0.49). No difference in other secondary endpoints

• Author Conclusions: non-statistically significant difference in warfarin reversal to an INR < 1.5 between weight-based and 1000 IU 4-PCC
Alternative Warfarin & DOAC Reversal Strategies
Alternative Reversal Strategies

Warfarin
- 3-PCC: 20 - 50 IU/kg
- aPCC: 50 - 100 IU/kg
- FFP: 10 - 15 ml/kg

DOAC
- aPCC: 50 - 100 IU/kg
- rFVIIa: 90 u/kg
- 3-PCC: 50 IU/kg
Case - Revisited

• MH

• What are your options for DOAC reversal?

• Would your regimen change if patient was taking warfarin instead?
Conclusions

- Reversal of oral anticoagulation requires many considerations, many of which are patient and bleeding site specific.
- Standard lab assays may not represent anticoagulation from oral anticoagulant; gold-standard assays are generally not readily available.
- Andexanet alfa is the only FDA-approved reversal agent for oral factor Xa inhibitors.
- 4-PCC conservations strategies and alternatives should be considered during times of drug shortage.
References


Questions?

CONTACT INFORMATION: JENNIFER.CATLIN@SANFORDHEALTH.ORG