Current and Emerging Therapies for Perioperative Anticoagulation Reversal

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Critical Care Pharmacist-Perioperative Services
Objectives

• Detail the approach to perioperative anticoagulation in a planned surgical patient
• Describe the optimal approach to emergent reversal of anticoagulated patients in the perioperative setting
• Identify new and emerging medications for the emergent reversal of oral anticoagulants
• Apply knowledge to case-based learning
Outline

• Current anticoagulants
• Approaches to planned surgery
• Emergent reversal
  – Past
  – Present
• Future therapies
• Cases
Current Oral Anticoagulants

- Warfarin
- Direct Thrombin Inhibitors
  - Dabigatran
- Anti-Xa inhibitors
  - Rivaroxaban
  - Apixaban
  - Edoxaban
History of Anticoagulants

Warfarin

- Developed in 1930s at the University of Wisconsin
  - Hemorrhagic death in cattle after eating spoiled sweet clover
- First used clinically in 1941
- Most widely used Oral anticoagulant
  - Good bioavailability (>90%)
    - Absorbed in upper GI tract
    - Peak absorption 60-120 min
  - Predictable onset
  - Predictable duration of action
Warfarin Pharmacology

- By suppressing the production of clotting factors, warfarin prevents the initial formation and propagation of thrombus
  - NOTE: Has no direct effect on previously circulating clotting factors or previously formed thrombus
- Antithrombotic effect delayed until circulating vitamin K-dependent factors (II, VII, IX, X) are cleared from the blood
Warfarin Site of Action

Warfarin Inhibits:
- Factor II
- Factor VII
- Factor IX
- Factor X
- Protein C&S
Inhibition of clotting factors

Between day 4 and day 5

Warfarin steady-state concentration achieved
History of Oral Anticoagulant Use

- 1941: Warfarin approved for use
- 2010-2015: Pradaxa (Dabigatran), Xarelto (Rivaroxaban), Eliquis (Apixaban), Savaya (Edoxaban) approved

~70 years
## Novel Oral Anticoagulants (NOACs)

### Approved in the US

<table>
<thead>
<tr>
<th>Direct Factor IIa Inhibitor</th>
<th>Dabigatran (Pradaxa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Factor Xa Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td></td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
<td></td>
</tr>
</tbody>
</table>

### Indications

| Prevention of stroke in patient with non-valvular atrial fibrillation |
| Treatment or secondary prevention of deep-vein thrombosis (DVT) and pulmonary embolism (PE) |
| Prevention of venous thrombosis after orthopedic surgery |
Novel Oral Anticoagulants (NOACs)

Direct Xa Inhibitor

Direct IIa Inhibitor

Factor Xa inhibitors:
- Apixaban
- Edoxaban
- Rivaroxaban

Surface activation (aPTT)

XII → XIIa

XI → Xla

IX → IXa

VIIa → VIIa

VII → VII

IX → IXa

X → Xa

Prothrombin (II)

Thrombin (IIa)

Fibrinogen (I) → Fibrin (Ia)

Fibrin (Ia) → Cross-linked fibrin clot

Direct thrombin inhibitor:
- Dabigatran

Tissue activation (PT)

Stambler BS. IntArch Med 2013;6:46
NOACs compared to warfarin

• Practical advantages over warfarin

1. Safety and efficacy
   • Dabigatran and Apixaban were found to be superior to warfarin for prevention of ischemic stroke and embolism in patients with atrial fibrillation
   • Rivaroxaban was seen to be equivalent to warfarin for prevention of stroke and embolism
   • All had lower incidence of intracranial hemorrhage (ICH) compared to warfarin

2. Laboratory monitoring
   • Do not require routine monitoring

Guideline recommendations

• Use of NOACs has increased:
  – DVT/PE:
    
    *2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).

  – Atrial Fibrillation:
    
    2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), we suggest dabigatran 150 mg twice daily rather than adjusted-dose vitamin K antagonist (VKA) therapy (target INR range, 2.0-3.0) (Grade 2B).

You JJ. CHEST 2012; 141(2)(Suppl):e531S–e575S
## Perioperative Anticoagulation in Planned Surgery

### Warfarin
- **INR: 2.0-3.0**
  - Stop warfarin 5 days before surgery
- **INR: 3.0-4.5:**
  - Stop warfarin 6 days before surgery

### NOACs
- Dependent on renal function

### Apixaban (~25% renal clearance)

<table>
<thead>
<tr>
<th>Estimated Clcr (ml/min)</th>
<th>Estimated t1/2 (hrs)</th>
<th>Time of last dose of apixaban before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>15</td>
<td>Standard Risk of Bleeding: 24 hours</td>
</tr>
<tr>
<td>50-80</td>
<td>15</td>
<td>High Risk of Bleeding: 2 days</td>
</tr>
<tr>
<td>31-49</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

### Dabigatran (80% renal clearance)

<table>
<thead>
<tr>
<th>Estimated Clcr (ml/min)</th>
<th>Estimated t1/2 (hrs)</th>
<th>Time of last dose of dabigatran before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>14</td>
<td>Standard Risk of Bleeding: 24 hours</td>
</tr>
<tr>
<td>50-80</td>
<td>17</td>
<td>High Risk of Bleeding: 2-3 days</td>
</tr>
<tr>
<td>31-49</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>~28 (22-35)</td>
<td></td>
</tr>
</tbody>
</table>

### Edoxaban (50% renal clearance)

<table>
<thead>
<tr>
<th>Estimated Clcr (ml/min)</th>
<th>Estimated t1/2 (hrs)</th>
<th>Time of last dose of rivaroxaban before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>10-14</td>
<td>Standard Risk of Bleeding: 24 hours</td>
</tr>
<tr>
<td>50-79</td>
<td>Not available</td>
<td>High Risk of Bleeding: 2 days</td>
</tr>
<tr>
<td>31-49</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>Not available</td>
<td></td>
</tr>
</tbody>
</table>

### Rivaroxaban (33% renal clearance)

<table>
<thead>
<tr>
<th>Estimated Clcr (ml/min)</th>
<th>Estimated t1/2 (hrs)</th>
<th>Time of last dose of rivaroxaban before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>15</td>
<td>Standard Risk of Bleeding: 24 hours</td>
</tr>
<tr>
<td>50-79</td>
<td>15</td>
<td>High Risk of Bleeding: 2 days</td>
</tr>
<tr>
<td>31-49</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>
Recommendations in Bridging

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation


BRIDGE Trial

– Evaluate incidence of VTE in a. fib patients that were bridged with LMWH vs held

• RESULTS:
  – No difference in incidence of VTE
  – Increased incidence of bleeding (1.3% vs 3.2%)

• CONCLUSIONS:
  – Bridging for patients with A. fib may be unwarranted
## PK/PD

### Pharmacokinetics of NOACs and Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixababan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing frequency</strong></td>
<td>Daily</td>
<td>Twice Daily</td>
<td>Once Daily*</td>
<td>Twice Daily</td>
</tr>
<tr>
<td><strong>Absorption bioavailability</strong></td>
<td>Rapid &gt;90%</td>
<td>Rapid, 4-10%</td>
<td>Rapid, 60-80%</td>
<td>Rapid, 50%</td>
</tr>
<tr>
<td><strong>Time to therapeutic effect</strong></td>
<td>Onset: 24-72hrs</td>
<td>0.5-2hr</td>
<td>1-4 hours</td>
<td>3-4hrs</td>
</tr>
<tr>
<td><strong>Percentage protein bound</strong></td>
<td>99%</td>
<td>35%</td>
<td>~95%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>20-60hrs variable</td>
<td>12-17h (normal)</td>
<td>5-9 normal</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-28h (renal impairment)</td>
<td>11-13 in elderly</td>
<td></td>
</tr>
<tr>
<td><strong>Route of excretion</strong></td>
<td>Liver</td>
<td>80% urine</td>
<td>66% urine</td>
<td>30% urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20% fecal</td>
<td>33% fecal</td>
<td>70% fecal</td>
</tr>
<tr>
<td><strong>Removed by dialysis?</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*initial dosing BID for DVT/PE

Planned surgery conclusions

• Resuming:
  – Atrial fibrillation:
    • Begin anticoagulation without bridge therapy within 24hrs post-operatively or as dictated by surgical hemostasis
  – DVT/PE:
    • Begin therapeutic anticoagulation within 24 hour or as dictated by surgical procedure
      – Warfarin: Therapeutic bridge (UFH or LMWH) until INR within goal range x24hrs
      – NOAC: Resume therapeutic dosing without bridge
        » Dabigatran for DVT/PE requires 7 days then switch
EMERGENT REVERSAL
“Incidence of perioperative bleeding in planned events is 3.3% but increases to 21.6% in emergent procedures”

–Goldstein JN. Lancet 2015
Classifications of reversal

**Target specific**
- Kcentra = Warfarin
- Praxbind = Pradaxa (dabigatran)
- Fresh Frozen Plasma (FFP) = Warfarin

**Non-specific**
- FEIBA
  - Dabigatran
  - Rivaroxaban
  - Apixaban
- Kcentra
  - Rivaroxaban
  - Apixaban
  - Edoxaban
- NovoSeven
  - Warfarin

In the future:
- Adexanant Alpha = Rivaroxaban + Apixaban
REVERSAL OF WARFARIN
Fresh Frozen Plasma and Vitamin K

**Fresh Frozen Plasma (FFP)**
- Contains all coagulation factors in plasma
- Limited thrombosis risk
- Requires ABO typing
- Requires thawing
- May be associated with adverse outcomes
  - TACO
  - TRALI
- Cost: $200-400 per dose
- Recommended dose:
  - 10-15mL/kg

**Vitamin K (Phytonadione)**
- Normalizes INR by providing the substrate to synthesize coagulation factors
- Limited by timing of efficacy
  - INR <1.4 may require 24hr
- Benefit through sustained duration of action
- Route determines onset
  - IV>PO, SQ/IM not used
- Cost: ~ $50.00
- Recommended dose:
  - 10mg IV x1

Another for Vit K
Frontera JA. Neurocrit Care (2016) 24;6-46
Prothrombin Complex Concentrate

Originally developed to treat Hemophilia B

**Profilnine (3F PCC)**
FDA approved 2010

**Kcentra (4F PCC)**
FDA approved 2013

Comparison Data
- No direct studies
- Single study showed ineffective reversal with Profilnine in patients with coagulopathy
- May consider combining 3F-PCC with FFP for more effective

Dosing (based on presenting INR)
- Kcentra: 25-50units/kg
- Profilnine: 20-50units/kg

Product supplied
- Powder + diluent for reconstitution

- Volume difference
  - FFP: 1000-1500mL
  - PCC: 40-100mL

Holland L. Transfusion. 2009; 49:1171-7
Comparison: INR reversal in nonsurgical patients experiencing major bleeding
  – Kcentra + IV vitamin K
  – Fresh frozen plasma + IV vitamin K

Outcomes:
  – Hemostatic efficacy, INR correction (<1.3), and safety

Results:
• Hemostasis: 72.4% in PCC group vs 65.4% with plasma (non-inferior)
• INR: <1.3 in 62.2% in PCC vs 9.6% with plasma (superior)
• Safety:
  – AE: 10 in PCC group, 26 in plasma group
  – Fluid overload: 5 (4.9%) in PCC and 14 (12.8%) in PCC

Results continued

Table 1: Median INR after Start of Infusion

<table>
<thead>
<tr>
<th>Median INR</th>
<th>Kcentra® (N=98)</th>
<th>Plasma (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.90 (1.8-20.0)</td>
<td>3.60 (1.9-38.9)</td>
</tr>
<tr>
<td>30 min</td>
<td>1.20 (0.9-6.7)</td>
<td>2.4 (1.4-11.4)</td>
</tr>
<tr>
<td>1 hr</td>
<td>1.30 (0.9-5.4)</td>
<td>2.1 (1.0-11.4)</td>
</tr>
<tr>
<td>2-3 hr</td>
<td>1.30 (0.9-2.5)</td>
<td>1.7 (1.1-4.1)</td>
</tr>
<tr>
<td>6-8 hr</td>
<td>1.30 (0.9-5.1)</td>
<td>1.5 (1.0-3.0)</td>
</tr>
<tr>
<td>12 hr</td>
<td>1.20 (0.9-2.2)</td>
<td>1.4 (1.0-3.0)</td>
</tr>
<tr>
<td>24 hr</td>
<td>1.20 (0.9-3.8)</td>
<td>1.3 (1.0-2.9)</td>
</tr>
</tbody>
</table>

Figure 1: Mean Factor Levels (Factors II, VII, IX, X, Proteins C & S) over 24 hours.

## Comparison of PCC and FFP

<table>
<thead>
<tr>
<th>Prothrombin Complex Concentrate</th>
<th>Fresh Frozen Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros:</strong></td>
<td><strong>Pros:</strong></td>
</tr>
<tr>
<td>• Low volume</td>
<td>• Widely available</td>
</tr>
<tr>
<td>• Fast reconstitution</td>
<td>• Less expensive</td>
</tr>
<tr>
<td>• Rapid INR correction</td>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>• Lower infection risk</td>
<td>• Need to be thawed/matched</td>
</tr>
<tr>
<td><strong>Cons:</strong></td>
<td>• INR correction can take &gt;30hrs</td>
</tr>
<tr>
<td>• Expensive</td>
<td>• Risk of pulmonary edema</td>
</tr>
<tr>
<td>• Not widely available</td>
<td>• Risk of TACO/TRALI</td>
</tr>
<tr>
<td>• May require redosing?</td>
<td></td>
</tr>
</tbody>
</table>
Warfarin Reversal Conclusion

• For emergent correction of warfarin-related bleeding, Kcentra (4F-PCC) is the drug of choice
• Requires co-administration of Vitamin K (10mg IV) for sustained reversal
• Warfarin-related bleeding that does not require immediate surgical intervention may be addressed with use of FFP + IV Vitamin K
• Caution for potential adverse effects associated with either agent
REVERSAL OF NOVEL ORAL ANTICOAGULANTS
NOAC Anticoagulant Pathway

Surface activation (aPTT)

XII → XIIa

XI → Xla

IX → IXa

Tissue activation (PT)

VIIa → VII

VIIla → VII

Direct thrombin inhibitor: Dabigatran

Factor Xa inhibitors:
Apixaban
Edoxaban
Rivaroxaban

Prothrombin (II)

Thrombin (IIa)

Fibrinogen (I)

Fibrin (Ia)

Cross-linked fibrin clot
Praxbind (Idarucizumab)

• Humanized IgG-1 monoclonial antibody fragment

• Indicated for reversal of dabigatran (PRADAXA) in the setting of life-threatening bleeding

• Binds to dabigatran with affinity 350x that of thrombin, and neutralizes it’s activity
  – Low volume of distribution

• Dosed= 5g
  – Two 2.5g doses not to be given >15 minutes apart

Pollack CV. Idarucizumab for Dabigatran Reversal. NEJM 2015

Idarucizumab for Dabigatran Reversal

Methods:
- 5 grams of intravenous idarucizumab for patients
  - With serious bleed
  - Requiring urgent procedure
- Primary endpoint:
  - Maximum percentage reversal of dabigatran within 4 hrs after administration, based on thrombin time (TT) test
- Secondary:
  - Restoration of hemostasis

Results (based on interim analysis of 90 patients)
- Patients with elevated TT or ECT were normalized in 98% of patients within minutes
- Serious bleed: hemostasis restored in 11.4 hours
- Required procedure: 33/36 had “normal intraoperative hemostasis”
Redistribution of Dabigatran
Lab abnormalities associated with redistribution
Reversal of direct oral Xa-inhibitors: Rivaroxaban, Apixaban, Edoxaban

- Currently no FDA-approved target-specific reversal agent
- Supplemental coagulation factors is widely accepted first line
  - Excess coagulant factors bind up NOACs, facilitate normal clot formation

- Potential agents
  - 4F-PCC
  - 3F-PCC
  - FFP
  - FEIBA
    - 4-Factor PCC with activated factor

*Vitamin K unnecessary
Reversal Protocol for University of Kentucky

### Anticoagulant Reversal Agents

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
<th>Dose</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Known Drug Exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Thrombin Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debitagran (Pradaxa)</td>
<td>Praxbind</td>
<td>5 grams</td>
<td>5 grams</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td>FEIBA (aPCC)</td>
<td>12.5 – 25 units/kg</td>
<td>100 units/kg</td>
</tr>
<tr>
<td>Factor Xa Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
<td>Kcentra (4PCC)</td>
<td>25-50 units/kg</td>
<td>5000 units</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin K Antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Kcentra (4PCC)*</td>
<td>25 units/kg</td>
<td>2500 units</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 units/kg</td>
<td>3500 units</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 units/kg</td>
<td>5000 units</td>
</tr>
<tr>
<td><strong>Specific Agent Unknown</strong></td>
<td>FEIBA (aPCC)</td>
<td>12.5 – 25 units/kg</td>
<td>100 units/kg</td>
</tr>
<tr>
<td><strong>No Anticoagulant Exposure Suspected</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Drug Contribution</td>
<td>rFVIIa</td>
<td>30 mcg/kg</td>
<td>90 mcg/kg</td>
</tr>
</tbody>
</table>

*Assuming vitamin K 10 mg IV has already been administered
KCentra: Administer at 0.12 mL/kg/min (~3 units/kg/min), max rate of 8.4 mL/min (~210 units/min)
FEIBA: Infusion rate must not exceed 2 unit/kg/min (range of 2.5-7.5ml/min)
Obtain INR 30 minutes after administration complete when reversing warfarin
Laboratory assessment of anticoagulants

<table>
<thead>
<tr>
<th>Intensity / Degree of measurement</th>
<th>Dabigatran</th>
<th>Rivaroxaban / Apixaban / Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative</td>
<td>Chromogenic ECT / Dilute TT</td>
<td>Chromogenic Anti-Xa</td>
</tr>
<tr>
<td>Is the drug present (Y/N)</td>
<td>Thrombin time / aPTT &gt; PT</td>
<td>PT &gt; aPTT</td>
</tr>
</tbody>
</table>

Plenty of unanswered questions:
- Timing?
- When aPTT / PT are normal
THE FUTURE
Andexanet Alfa

- Specific reversal agent designed to neutralize the anticoagulant effect of direct and indirect factor Xa inhibitors
  - Apixaban, edoxaban, rivaroxaban
  - LMWH (lovenox)

- Recombinant modified human factor Xa decoy protein
  - Catalytically inactive, but binds active site at 1:1 ratio
  - Sequesters Xa-inhibitors within vascular space

Siegal DM. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity NEJM 2015
Andexanet Alfa

Method:
– Healthy volunteers were given either apixaban 5mg bid or rivaroxaban 20mg daily

Outcome:
– Mean % change in anti-factor Xa activity

Results:
– Apixaban group
  • Anti-Xa activity decreased by 94% vs 21% with placebo
  • Thrombin generation restored to 100% vs 11% within 2-5min
– Rivaroxaban group:
  • Anti-Xa decreased by 92% vs 18%
  • Thrombin generation restored in 96% vs 7% of placebo
– No serious adverse or thrombotic events reported.

Siegal DM. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. NEJM 2015
Phase II study results

• Bolus of both Apixaban and Rivaroxaban
Phase II study results

- Bolus + Continuous infusion
Aripazine (PER977)

- Small synthetic molecule that binds via hydrogen bond to reverse anticoagulant activity
- Targets:
  - Oral Xa inhibitors
  - Direct thrombin inhibitors
    - Dabigatran
  - Unfractionated heparin
  - LMWH

*Figure 1. Effect of PER977 on Whole-Blood Clotting Time.*
Shown are the mean whole-blood clotting times after administration of a single oral 60-mg dose of edoxaban, followed 3 hours later by a single intravenous dose of 25 mg, 100 mg, or 300 mg of PER977 or placebo.

Conclusions for NOAC Reversal

• Idarucizumab is a novel monoclonal antibody that binds and sequesters Dabigatran, removing it from the active site
  – Does not replace coagulation factors
  – May have rebound anticoagulation effect requiring repeat dosing

• Xa inhibitors currently do not have an FDA-approved reversal agent
  – Current guidelines suggest efficacy with 4F-PCC (Kcentra), and activated-4F PCC (FEIBA)

• Andexanet Alfa and Aripazine are potential reversal agents for NOACs, but are currently still in phase III trials and not FDA approved
Cases
Questions?

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