Blood products and pharmaceutical emergencies

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Disclosures

• None
Discover ELIQUIS

ELIQUIS (apixaban) is a prescription medicine used to reduce the risk of stroke and blood clots in people who have atrial fibrillation (AFib), a type of irregular heartbeat, not caused by a heart valve problem.

If you have AFib not caused by a heart valve problem, ELIQUIS may

3 GOOD REASONS TO THINK ELIQUIS

1. In a clinical trial, ELIQUIS was better at reducing the risk of stroke than warfarin.

2. ELIQUIS had less major bleeding than warfarin.

3. In another trial, compared to aspirin, ELIQUIS had a modest increase in major bleeding. ELIQUIS and other blood thinners increase the risk of bleeding problems.
Let’s consult someone

• Surgery
• Neurosurgery
• Orthopedics
• Nephrology
• Infectious disease
• Internal medicine
• Hematology
• Oncology
• Cardiology
• Cardiovascular surgery
• Pediatrics
• Geriatrics
• Pharmacy
Let’s consult someone

- Surgery
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- Pediatrics
- Geriatrics
Objectives

1. Identify pharmaceutical emergencies requiring the use of blood products
2. Identify adverse effects associated with the use of various blood products
3. Recommend reversal strategies for new oral anticoagulants
Medications of concern

• Vitamin K antagonists
  – Warfarin (\textit{Coumadin®})

• Direct thrombin inhibitors
  – Dabigatran (\textit{Pradaxa®})

• Factor Xa inhibitors
  – Rivaroxaban (\textit{Xarelto®})
  – Epixaban (\textit{Eliquis®})

• Antiplatelets
When should we use blood products?
When to use blood products

- Anticoagulated and having life threatening bleeding
- Example key words
  1. Intracranial/subdural/subarachnoid hemorrhage
  2. Aortic dissection or ruptured aortic aneurysm
  3. GI bleed with hypotension and/or requiring transfusion
  4. Requiring emergent surgery
Baseline CT
INR 3.6
Total hematoma volume 15.3 mL

Follow-up CT (19 hours)
INR 1.2
Total hematoma volume 67.6 mL
When **not** to use blood products

- Anticoagulants not present per patient/family report and confirmed with lab testing
- Non-life threatening bleeding
- Key words
  1. “Just in case”
  2. (insert radiologic study here) negative
  3. Prophylaxis
  4. Hemodynamically stable
  5. Discharge or observation status
## Lab studies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Preferred lab</th>
<th>Significant values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>International normalized ratio (INR)</td>
<td>INR &gt; 1.5-2.0</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>aPTT*</td>
<td>aPTT 40-76 sec**</td>
</tr>
<tr>
<td>Rivaroxaban, apixaban</td>
<td>PT* or aPTT*</td>
<td>Varies depending on reagent</td>
</tr>
</tbody>
</table>

*qualitative not quantitative, **observed aPTT range of patients taking dabigatran per package insert*

Blood products

• Fresh Frozen Plasma (FFP)
• Recombinant factor VIIIa- (Novoseven®)
• Prothrombin complex concentrate
  – Three factor (Profilnine®, Bebulin®)
  – Four factor (KCentra®, Octaplex®, Beriplex®, Cofact®)
• Activated prothrombin complex concentrate
  – Factor Eight Inhibitor Bypassing Activity (FEIBA®)
Fresh Frozen Plasma

- Plasma separated from whole blood
- Frozen within 8 hours of donation
- Each unit is 200-250 mL
- Must be ABO matched
- Dose 10-15 mL/kg
- Time to thaw: 20-30 min or 2-3 min
- Onset: 1-4 hours

<table>
<thead>
<tr>
<th>Contains</th>
</tr>
</thead>
<tbody>
<tr>
<td>All clotting factors</td>
</tr>
<tr>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>Physiologic anticoagulants</td>
</tr>
<tr>
<td>(Protein C &amp; S, antithrombin, etc.)</td>
</tr>
<tr>
<td>Added anticoagulants</td>
</tr>
</tbody>
</table>
# Fresh Frozen Plasma

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Widely available</td>
<td>• Slow to obtain and infuse</td>
</tr>
<tr>
<td>• Provides volume</td>
<td>• Provides volume (10-15 ml/kg)</td>
</tr>
<tr>
<td></td>
<td>• Transfusion related acute lung injury (TRALI)</td>
</tr>
<tr>
<td></td>
<td>• Transfusion reaction</td>
</tr>
<tr>
<td></td>
<td>• Risk of blood borne pathogens</td>
</tr>
</tbody>
</table>

## FFP and blood borne pathogens

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 per 7.8 million units</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1 per 2.3 million units</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 per 153,000 units</td>
</tr>
</tbody>
</table>
Prothrombin Complex Concentrate

- Factor concentrates from human plasma
- Most commonly used off label as an alternative to FFP
- Label shows units of factor IX content
- Dose 25-50 units/kg
- 24 hour half life
- Onset: 15 minutes

Contains

<table>
<thead>
<tr>
<th>Factors II, VII, IX, and X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants</td>
</tr>
<tr>
<td>(protein C &amp; S, heparin)</td>
</tr>
</tbody>
</table>

Ann Pharmacother. 2011 Jul;45(7-8):990-9
Prothrombin Complex Concentrate

<table>
<thead>
<tr>
<th>Three factor</th>
<th>Four factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor II</td>
<td>Factor II</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Factor VII</td>
</tr>
<tr>
<td>Factor IX</td>
<td>Factor IX</td>
</tr>
<tr>
<td>Factor X</td>
<td>Factor X</td>
</tr>
<tr>
<td>Profilnine SD®, Bebulin VH®</td>
<td>Kcentra®, Octaplex®, Beriplex®, Cofact®</td>
</tr>
<tr>
<td>Factor composition</td>
<td>Factor II</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Profilnine SD®</td>
<td>≤1.5 IU factor II per 1 IU factor IX</td>
</tr>
<tr>
<td>Bebulin VH®</td>
<td>≤24-38 IU/mL</td>
</tr>
<tr>
<td>Kcentra®</td>
<td>20–48 units/mL</td>
</tr>
</tbody>
</table>
Prothrombin Complex Concentrate

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Easy to administer</td>
<td>• Not widely available</td>
</tr>
<tr>
<td>• No ABO matching</td>
<td>• Specialty product</td>
</tr>
<tr>
<td>• Lower risk of disease transmission than FFP</td>
<td>• Thrombosis risk</td>
</tr>
<tr>
<td>• No risk of fluid overload</td>
<td></td>
</tr>
</tbody>
</table>
PCC Adverse Reactions

• Most common
  – Headache
  – Nausea, vomiting
  – Hypotension

• Thromboembolic events
  – Dose dependent
  – Four factor PCC vs FFP
    • PCC 8.7 % vs FFP 5.5%\textsuperscript{1}
    • PCC 0.6 % vs FFP 2%\textsuperscript{2}

Activated prothrombin complex concentrate factor VIII inhibitor bypassing activity

- Fixed dose 500 – 1000 units
  - Repeated every 30 min
- Thrombosis risk?

<table>
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<tr>
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</tr>
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<tbody>
<tr>
<td>Unactivated factors II, IX, and X</td>
</tr>
<tr>
<td>Activated factor VII</td>
</tr>
</tbody>
</table>
Recombinant Factor VIIa

- Activates factor X
- Duration of action: 4-6 hours
- Administered as a bolus over 2-5 minutes
- Rapid onset: 5-10 min
- Reported dose range: 5 – 160 mcg/kg
- Dose related thrombosis risk
  - Venous and arterial events
# Recombinant Factor VIIa

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Room temperature storage</td>
<td>• Thrombosis risk</td>
</tr>
<tr>
<td>• Ease of administration</td>
<td>• Cost</td>
</tr>
<tr>
<td>• Rapid onset</td>
<td>• Short half life</td>
</tr>
<tr>
<td>• Minimal volume</td>
<td>• Outcomes data?</td>
</tr>
<tr>
<td>• No risk of pathogen transmission</td>
<td></td>
</tr>
</tbody>
</table>
Treatment strategies
Figure 1. Flowchart of the study, a randomized, double-blind, placebo-controlled, crossover trial with healthy male subjects (n=12).

PCC group → Cofact® 50 unit/kg
A

PT

Seconds

Baseline

T = 0

15 min

30 min

1h

2h

4h

6h

24h

Rivaroxaban 20mg BID for two and a half days

PCC or placebo infusion

Time

Placebo

PCC

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A

aPTT

![Graph showing changes in aPTT over time with various interventions.]

- **Baseline to 0**: Dabigatran 150mg BID for two and a half days
- **15 min to 30 min**: PCC or placebo infusion

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Outcomes

• What does this study look at?
• Human vs animal trial
• Lab reversal? (i.e. INR normalizing)
• Radiologic differences (hemorrhage expansion)
• Important ones (rarely examined)
  – Surgical intervention
  – Mortality
Management of Vitamin K antagonists

- CHEST, AHA, ANA: PCC preferred over FFP
- rFVIIa
  - FAST trial showed no mortality or functionality benefit
  - Recommend low dose (20-25 mcg/kg vs 80-100 mcg/kg) if used
- 3 vs 4 factor PCC
  - 4 factor may be superior with super-elevated INR

Chest. 2012 Feb;141(2 Suppl):e531S-75S.
Management of Vitamin K antagonists

• FFP dose: 10-15 ml/kg

• PCC dose
  – Based on INR
    • 2-4: 25 U/kg
    • 4-6: 35 U/kg
    • > 6: 50 U/kg
  – Obese patients, max dose?
  – Round to nearest whole vial

• Always administer vitamin K 5-10 mg IV in addition to PCC, FFP or rFVIIa
Direct Thrombin Inhibitors/Dabigatran

• Animal data
  – In rats 4 factor PCC vs rFVIIa vs FFP
    • Both PCC and FFP reduced hematoma expansion
  – In rats activated PCC vs rFVIIa
    • Both PCC and rFVIIa reduce rat tail bleeding
    • Only rFVIIa lowered aPTT
Direct Thrombin Inhibitors/Dabigatran

• Case Reports
  – Patient with GI bleed and acute renal failure
    • Given several units of FFP and subsequent 3 factor PCC
  – Patient with spinal cord compression following trauma
    • rFVIIa alone was ineffective at restoring hemostasis
Direct Thrombin Inhibitors/Dabigatran

• PCC is preferred for reversal
  – 4 factor PCC may be preferred
  – Activated vs unactivated PCC?
• RFVIIa
  – Consider as second line
  – More data needed
• Consider FFP for volume expansion
• Dialysis
  – 50-60 % removed in a 4 hour hemodialysis session
Factor Xa inhibitors

• Animal studies
  – 4 factor PCC vs rFVIIa vs FFP
    • All reduced hematoma expansion and mortality
    • PT unchanged by PCC and FFP
  – aPCC given to rats
    • Rivaroxaban and edoxaban anticoagulant effects reversed

A  

Rivaroxaban anticoagulation  |  ICH induction  |  Hemostatic therapies  |  Hematoma volumetry
  
-1 h  |  0 h  |  0.5 h  |  24 h

B  

Control  |  Rivaroxaban  |  Rivaroxaban +FVIIa  |  Rivaroxaban +FFP  |  Rivaroxaban +PCC

D  

24h mortality

- 0%  |  10%  |  20%  |  30%  |  40%  |  50%

1 of 14  |  2 of 15  |  0 of 13  |  1 of 14  |  0 of 13

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Factor Xa inhibitors

- PCC is preferred for reversal
  - 3 vs 4 factor PCC
  - Activated vs unactivated
- FFP and rFVIIa are not first line
- Cannot remove via dialysis
Cost
# Cost comparison

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost per unit</th>
<th>Cost to treat a 70 kg individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Frozen Plasma</td>
<td>$47 per unit*</td>
<td>$235</td>
</tr>
<tr>
<td>Profilnine</td>
<td>$0.88 per unit</td>
<td>2000 unit = $1760, using 35 U/kg</td>
</tr>
<tr>
<td>Kcentra</td>
<td>$1.64 per unit</td>
<td>2000 unit = $3280, using 35 U/kg</td>
</tr>
<tr>
<td>NovoSeven (rFVIIa)</td>
<td>$1.44 per mcg</td>
<td>2 mg = $2880, using 25 mcg/kg</td>
</tr>
<tr>
<td>FEIBA</td>
<td>$1.80 per unit</td>
<td>1000 unit = $1800</td>
</tr>
</tbody>
</table>

*current price per MI blood bank
What can you do?

1. Have a plan
   - What do you/does your institution recommend?
     • Agent or agents
     • Dose
     • Restrictions

2. Have an opinion
   - Intervene early
     • Help create the treatment plan
   - High risk, time sensitive therapies
   - Expensive therapies

3. Educate others
Bleeding while using a NOAC

- Mild bleeding
  - Delay or discontinue next dose
  - Reconsider concomitant medication

- Moderate severe bleeding
  - Supportive measures:
    - Mechanical compression
    - Surgical hemostasis
    - Fluid replacement (colloids if needed)
    - RBC substitution if needed
    - Fresh frozen plasma (as plasma expander)
    - Platelet substitution (if platelet count ≤80×10^9/L)
  - For dabigatran:
    - Maintain adequate diuresis
    - Consider hemodialysis
    - ((charcoal haemoperfusion?: await more data))

- Life-threatening bleeding
  - Consider:
    - PCC (e.g. CoFact®) 25 U/kg; repeat 1×/2× if indicated
    - aPCC (Feiba®) 50IE/kg; max 200 IE/kg/day
    - (rFVIIa (NovoSeven®) 90 µg/kg no data about additional benefit)
STOP WARFARIN

Obtain PT / INR

INR ≥ 1.5

- Mild bleed
  - Mechanical compression
  - Consider PO/IV vitamin K administration

- INR < 1.5

- Major/life threatening bleed
  - For reversal: Profilnine (PCC) 30 unit / kg (round to the nearest 500 unit)
  - Administer 10 mg Vitamin K IVPB
  - Re-check INR 15 min post infusion
  - Consider additional 500 to 1,000 unit of Profilnine (PCC) if INR still > 1.5
Assessment Questions

Which of the following situations can be worsened by the administration of blood products?

a. Heparin induced thrombocytopenia in an ICU patient
b. Life threatening GI bleeding in a patient taking warfarin

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Assessment Questions

Which of the following is a disadvantage associated with the use of fresh frozen plasma for anticoagulant reversal?

a. Fluid overload
b. Arterial thrombotic events
c. Takes a long time to infuse
d. A & C
Assessment Questions

You answer the phone. On the other line is a panicking resident. The medical resident wants to know what to administer for his patient who might have an intracranial hemorrhage who is on rivaroxaban.

a. Platelets
b. Vitamin K
c. Recombinant factor Vlla
d. Prothrombin complex concentrate