Available Strategies to Reverse Anticoagulant Medications

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Anticoagulation Reversal

Objectives:
• Describe the pharmacological agents and therapeutic strategies available for use in patients who experience major bleeding
• Discuss the risks and limitations of current agents available for reversal
• Develop treatment plans to manage severe bleeding in a patient on anticoagulation therapy

Chapter 1
The Reversing Agents

- Vitamin K (phytonadione)
- Coagulation factors
  - Fresh frozen plasma (FFP)
  - 4 factor PCC (Kcentra)
  - Activated 4 factor PCC (FEIBA)
  - Recombinant Factor VII (rFVIIa) NovoSeven
- Protamine
- Idarucizumab (Praxbind)
- Tranexamic acid (Cyklokapron)

Universal Caution statement
• Patients taking anticoagulant medications are likely doing so because they are at a higher then normal risk of thrombosis.
• Reversing their anti-thrombotic therapy may lead to development of a life-threatening thrombosis.
• Resume therapy as soon as possible.

No conflicts of interest to disclose
Anticoagulation Reversal

Vitamin K
- Cofactor for liver production of factors II, VII, IX and X
- Onset
  - PO 12-24 hrs
  - IV 4-12 hours
  - SQ/IM not recommended
- Duration dependent on dose

Anticoagulation Reversal

4 factor Prothrombin Complex Concentrate (PCC)-Kcentra
- Indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with: acute major bleeding or need for an urgent surgery/invasive procedure
- 25 X more concentrated than FFP
- Replaces coagulation factors II, VII, IX and X.
- Also contains proteins C and S and *heparin*
- Onset: 5-10 mins; Duration: 12-24hrs

Anticoagulation Reversal

Fresh Frozen Plasma (FFP)
- Blood product that replaces coagulation factors
- Contains all coagulant factors in an inactive form
- Onset: 1-4 hours
- Duration: up to 6 hrs
- Dose: 5-20ml/kg infused at 10ml/min
- Caution: disease transmission, transfusion reaction, volume complications

Anticoagulation Reversal

<table>
<thead>
<tr>
<th>Pre-Treatment INR</th>
<th>Dose of PCC Kcentra units of factor IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3.9</td>
<td>25 units/kg max dose 2500 units</td>
</tr>
<tr>
<td>4-6</td>
<td>35 units/kg max dose 3500 units</td>
</tr>
<tr>
<td>Greater than 6</td>
<td>50 units/kg max dose 5000 units</td>
</tr>
</tbody>
</table>

- Administration rate 3 units/kg/min max 8.4ml/min
- Contraindication: History of heparin induced thrombocytopenia (HIT)

Anticoagulation Reversal

• Kcentra dose
• Available in two vial/kit sizes “500” and “1000” units
• Potency is defined by factor IX content. The range of factor IX units per vial is 400-620 units for the 500 kit and 800-1240 units for the 1000 kit.
• Rounding of dose?
• Vials can be individually administered or pooled together.
### Anticoagulation Reversal

**Activated 4-factor PCC (FEIBA)- Factor Eight inhibitor Bypassing Activity**
- FEIBA is an Anti-Inhibitor Coagulant Complex indicated for use in hemophilia A and B patients with inhibitors for:
  - Control and prevention of bleeding episodes
  - Perioperative management
  - Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Replaces coagulation factors II, VII, IX and X.
- Factor VII is in the 'activated' form- more 'potent' than Kcentra
- Usual hemophilia dose 50-100 units/kg
- Onset: 5-10 mins; Duration: 8-12 hours

### Anticoagulation Reversal

**Protamine**
- Irreversibly combines with heparin to chemically inactivate it.
- Onset: 5 minutes
- 50mg max single dose by slow iv injection or may dilute for infusion. May repeat if needed.
- Caution: hypotension, flash pulmonary edema, allergic reactions (caution- fish allergy, previous exposure)
  - Consider co-administration with diphenhydramine and/or hydrocortisone

### Anticoagulation Reversal

**Idarucizumab (Praxbind)**
- Indication: Reversal of the anticoagulant effect of dabigatran for emergency surgery/urgent procedures or life threatening or uncontrolled bleeding
- A humanized monoclonal antibody fragment with a high affinity to dabigatran and neutralizes the effect of dabigatran.
- Onset: 5 minutes
- Duration: 24 hrs, the complex is renally cleared; no change if patient has severe renal disease

### Anticoagulation Reversal

**Dose: 5 gm**
- Available as 2 x 2.5gm/50ml ready to administer vials
- Thromboembolic Risk: Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Resume anticoagulant therapy as soon as medically appropriate.
- In patients with elevated coagulation parameters and reappearance of clinically relevant bleeding or requiring a second emergency surgery/urgent procedure, an additional 5 g dose may be considered.

### Anticoagulation Reversal

**Recombinant activated factor seven (rFVIIa)-NovoSeven**
- Indication: Treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann’s with refractoriness to platelet transfusions, with or without antibodies to platelets
- Treatment of bleeding episodes and perioperative management in adults with acquired hemophilia
- "Pro-coagulant"- activates the extrinsic clotting cascade to promote thrombin formation
- Usual hemophilia dose 70-90 units/kg Q2-4hrs.
- Onset 5-10 mins; Duration 4-6 hours

### Anticoagulation Reversal

**Warning:** In patients with the condition of hereditary fructose intolerance who have received parenteral administration of sorbitol, serious adverse reactions, including fatal reactions, have been reported. Reactions have included hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure with breakdown of excretory and synthetic function.
- In patients with hereditary fructose intolerance consider the combined daily metabolic load of sorbitol/fructose from all sources
Anticoagulation Reversal

Tranexamic Acid (Cyklokapron)
- Antifibrinolytic agent
- Injection is indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.
- More commonly used to limit blood loss in major trauma and orthopedic surgery
- Very low risk of thrombosis
- Usual doses: 1-1.5gms Q8-12 hrs in 50ml NS infused over 10 mins

Anticoagulation Reversal

Chapter II
The Agents of Harm

Anticoagulation Reversal

Warfarin associated bleeding

<table>
<thead>
<tr>
<th>Situation</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &lt;10 no bleeding</td>
<td>Lower or omit next doses of warfarin, re-evaluate daily</td>
</tr>
<tr>
<td>INR &gt;10 no bleeding</td>
<td>Hold warfarin, administer 2.5-5mg* Vit K</td>
</tr>
<tr>
<td>Non-life threatening bleeding</td>
<td>Hold warfarin, consider 2.5-5mg* Vit K</td>
</tr>
<tr>
<td>Life threatening bleeding</td>
<td>4 factor PCC + 10mg Vit K IV</td>
</tr>
</tbody>
</table>

*R: Patients with a higher daily dose may need a higher dose of Vitamin K. Low doses (1-2.5mg) may be warranted in patients with elevated INR and a high risk of bleeding with a low risk of thrombosis (elderly, CHF, malnourished, recent bleed). Doses greater than 10mg may cause prolonged period of warfarin resistance without further benefit

Dabigatran associated bleeding
- Mild-moderate bleeding: supportive therapy only
- Severe-life threatening: Idarucizumab 5gm IV
- Repeat aPTT in 1 hour... consider 2nd dose if bleeding remains and aPTT elevated at 12 hrs?
- Second line: Consider off-label FEIBA 25-50 units/kg
- Third Line: Consider off-label 4 factor PCC (kcentra) 25-50 units/kg, max dose 5000 units.

Anticoagulation Reversal

Rivaroxaban, Apixaban, Edoxaban associated bleeding
- Mild-moderate: Supportive therapy only
- Severe-life threatening:
  - Tranxamic acid 1gm IV
  - Consider off-label 4 factor PCC (kcentra) 25-50 units/kg, max dose 5000 units.
  - Consider off-label FEIBA 25-50 units/kg
  - Consider Vit K for underlying deficiency

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Fondaparinux associated bleeding
- Consider FFP
- Consider FEIBA at 25-50 units/kg
- Consider rFVIIa 25-100 units/kg, dose dependent on seriousness of bleeding, risk/benefit.
- No benefit with protamine
Anticoagulation Reversal

• Heparin Infusion associated bleeding

<table>
<thead>
<tr>
<th>Time Since Infusion Stopped</th>
<th>Dose of protamine for each 100 units of heparin infused in the preceding 2hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>1 mg/100 units (or fixed 25mg)</td>
</tr>
<tr>
<td>30 mins-2 hrs</td>
<td>0.5mg/100 units (or 10mg)</td>
</tr>
<tr>
<td>Greater than 2 hrs</td>
<td>0.25mg/100 units (or 10mg)</td>
</tr>
</tbody>
</table>

Anticoagulation Reversal

• Partial reversal with protamine

<table>
<thead>
<tr>
<th>Time since last dose</th>
<th>Dose of protamine for each 100 units of dalteparin or 1mg of enoxaparin administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 8 hours</td>
<td>1mg (or 50mg fixed dose)</td>
</tr>
<tr>
<td>8-12 hours</td>
<td>0.5mg (or 25mg)</td>
</tr>
<tr>
<td>Greater than 12 hours</td>
<td>Not likely useful* (or 25mg)</td>
</tr>
</tbody>
</table>

• Consider a repeat dose after 2-4 hours
*consider 0.5mg dosing if severe renal failure.

Anticoagulation Reversal

Chapter III
The Patients

Anticoagulation Reversal

• JM 74 yo
• Male
• Noticed to have slurred speech and difficulty ambulating
• DX: Intracranial hemorrhage
• Drugs: warfarin, metoprolol, lisinopril, furosemide, rosuvastatin

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Low Molecular Weight Heparin associated bleeding

• Partial reversal with protamine

Patient evaluation
• Seriousness of the situation: Minor? Major? Life-Threatening?
  – Where, how much, co-morbidities, etc
• Medication Reconciliation
  – What agent? What dose? Last time taken? What other risky drugs?
• Laboratory: PT/INR, aPTT, SrCr, CBC
• The basics
  – Fluid replacement and hemodynamic support
  – Compression
  – Blood product transfusion
  – Activated charcoal if last oral dose within 2 hours

Bottom line: Life threatening bleeding associated with warfarin

What more do we need to know to adequately treat the patient?
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- INR = 3.3; patient weight = 87 kg

Plan:
- Vitamin K 10mg IV stat
And
- 4 factor PCC (Kcentra) 25 units/kg = 2175 units
- Why both? Why not FFP

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- SB 73 yo Female
- Fall at home with hip fracture requiring surgery
- On warfarin with an INR = 2.9, no acute bleeding
- What's your plan?

Anticoagulation Reversal

- Bottom line: non-life threatening situation requiring normalization of INR within 12-24 hours
- Vitamin K 2.5mg PO X 1
- Perform surgery when INR ≤ 1.5

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- 54 yo M hospitalized for new-onset A-fib and planned cardioversion later today.
- Heparin infusion at 1200 units/hr
- Patient complains of new lower back pain, imaging displays large retroperitoneal hemorrhage.
- MD wants to reverse heparin ASAP
- What's your plan?

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- 68 yo male with hx of stage 3 renal disease receiving dabigatran admitted to the ED with GI bleed. Last dose taken early this morning.
- What's your plan?
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• Life threatening/emergent surgery, yes or no?
  • No
    – Hold further doses of dabigatran
    – Replace blood products as needed per HGB/HCT
    – Monitor closely
  • Yes
    – Idarucizumab 5gm IV X1

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• EK, 35yo 80kg M, brought to ED by ambulance after MVC with multi-trauma with significant active bleeding. Medication history includes apixaban for VTE that occurred 2 months ago.
  • What’s your plan?

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• Tranexamic acid 1gm IV
• 4 factor PCC (Kcentra) 50 units/kg if amount of bleeding considered to be life-threatening and/or significant major surgery is eminent.

• FEIBA or rFVIIa also a valid consideration as secondary options based on risk/benefit

Chapter IV
The Future

Anticoagulation Reversal

• Andexanet alfa (Portola Pharmaceuticals)-modified factor Xa molecule designated as a breakthrough therapy by the U.S. Food and Drug Administration
  • Binds to oral Xa inhibitors and negates their effect
  • Given as a bolus with continuous infusion
  • Phase III trials with apixaban and rivaroxaban already underway.

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• PER977 (Perosphere Inc.) Ciraparantag-designed to bind to heparin and LMWH, also binds to oral Xa inhibitors and dabigatran
  • Phase II trials demonstrate ability to reverse enoxaparin and edoxaban
  • “Broad spectrum” reversal agent?
  • http://perosphere.com/content/research/per977.htm
The Supplement

Anticoagulation Reversal

- What about injectable direct thrombin inhibitors?
- Argatroban and Bivalrudin
- Relatively short half-lives
- No specific treatment other than discontinuation and supportive therapy, consider FFP.
- Serious bleeding, consider rFVIIa or 4 factor PCC

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- What about 3 factor PCC?
- Bebulin VH
- Profilnine SD
- Contain factors II, IX and X (practically no VII)
- Previously considered an option prior to 4 factor availability, very little data, no longer has a role.

Anticoagulation Reversal

- Table of PCC data:

The End