Anticoagulant Therapy

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Disclosures

- No financial disclosures
- Off-label indications discussed
Objectives

• Review pharmacology of anticoagulant agents commonly used in the ICU
• Recommend anticoagulant therapy for patients with organ system dysfunction
• Review pharmacology of new anticoagulant reversal agents
• Recommend reversal agent(s) for patients with major bleeding or urgent procedures
Why Focus on Anticoagulation?

- Narrow therapeutic window
- Risk of bleeding versus clot
- National Patient Safety Goal
JCAHO Anticoagulation NPSG

• Reduce the harm associated with anticoagulation therapy

• Performance elements
  – Anticoagulation management program
  – Unit dose and pre-mixed dosage forms
  – Anticoagulation protocols
  – Baseline labs and appropriate monitoring
  – Education
Which of the following is the worst drug ever?

A. Warfarin
B. Unfractionated heparin
C. Dabigatran
D. Edoxaban
Unfractionated Heparin

• Indirectly inhibits thrombin by binding to antithrombin III
• Large molecule with significant variability
• Pharmacokinetics change based on dose
  – Half-life increases as dose increases
• Where does heparin come from?
Heparin Protocols

• Three main protocols at VUH
  – Lower dose (ACS, atrial fibrillation, etc.)
  – Higher dose (DVT, PE, etc)
  – Custom protocol

• Nurses manage lower and higher dose protocols on implemented floors

• Physicians manage the custom protocol
Concerns with Heparin

• Unpredictable dosing
• Complicated monitoring
  – aPTT every 6 hours
  – Sample error/contamination
• Heparin induced thrombocytopenia
• Heparin resistance
Enoxaparin (Lovenox®)

- Low molecular weight heparin
- Predictable pharmacokinetics
- Simple dosing
- Administered subcutaneously
  - Patient can self-administer at home
- No monitoring required
  - Anti-Xa levels may be used in rare situations
Enoxaparin Dosing

- Use 1 mg/kg SC q12h for therapeutic anticoagulation
- Two doses for DVT prophylaxis
  - 40 mg daily
  - 30 mg q12h
- Dose adjust for renal insufficiency (CrCl <30 ml/min)
  - 1 mg/kg daily for therapeutic anticoagulation
  - 30 mg daily for DVT prophylaxis
- Contraindicated in dialysis patients
Concerns with Enoxaparin

• Adverse events similar to heparin
  – Bleeding
  – Thrombocytopenia
• Lack of monitoring around invasive procedures
• Epidural anesthesia
  – Black box warning
• Dosing in obese patients
Fondaparinux (Arixtra®)

- Inhibits Factor Xa
- Predictable pharmacokinetics
- Simple dosing
- Administered subcutaneously
- No monitoring required
- Long half-life of 17-21 hours
Fondaparinux Dosing

• Weight based dosing for DVT/PE
  – <50 kg: 5 mg once daily
  – 50-100 kg: 7.5 mg once daily
  – >100 kg: 10 mg once daily

• DVT prophylaxis
  – 2.5 mg once daily

• ACS treatment
  – 2.5 mg once daily

• Contraindicated if CrCl < 30 ml/min
Concerns with Fondaparinux

- Bleeding
- Not associated with HIT
  - May be option to treat HIT
- Lack of monitoring around invasive procedures
- Epidural anesthesia
- No reversal agent available
Warfarin (Coumadin)

- Oral anticoagulant drug
- Inhibits vitamin K dependent clotting factors
  - Dietary vitamin K
- Where does warfarin come from?
  - Rat poison
- Indicated for long term anticoagulation
  - Stroke prevention
  - DVT/PE
  - Mechanical heart valves
Determining Warfarin Dose

- Age
- Drug Interactions
- Nutritional status
- Hepatic function
- Thyroid status
- Heart failure
- Alcohol consumption
- Pharmacogenetics
- Weight
- Height
- Smoking status
- Race
- Bleeding/transfusions
- Vitamin K intake
Patient Case

FW is a 78 year old man admitted to the hospital with altered mental status. Head CT in ED reveals large SDH. PMH is significant for CAD, HF and AF treated with warfarin.

Pertinent labs on admission include INR 3.3
Which of the following would be the best option reversal option?

A. 4 units of FFP
B. Idarucizumab 5 grams once
C. Kcentra 500 units once
D. Phytonadione 5 mg IV once
Warfarin Reversal

- **Signs or Symptoms of Bleeding?**
  - yes: Admit to hospital
    - Vitamin K 10 mg IV over 30 minutes
    - Fresh Frozen Plasma (15-30 ml/kg)
    - OR
    - Prothrombin Complex Conc. (25-50 IU/kg)
  - no: INR Value
    - > 10: Interrupt warfarin
      - Oral vitamin K 2.5-5 mg
      - Close outpatient follow-up
    - 4 - 10: Interrupt warfarin
      - Close outpatient follow-up
      - CONSIDER
        - Vitamin K 1-2.5 mg by mouth
        - (Vitamin K may be most helpful for patients at high risk for bleeding)
What are the advantages of PCC vs. FFP?

A. Decreases mortality in ICH
B. Lower risk of thrombosis
C. Lower acquisition cost than FFP
D. Decreased volume and faster administration
PCCs for Warfarin Reversal

• 4 factor Prothrombin Complex Concentrate (4FPCC) now available in US
• Replaces factors deleted by warfarin
  – Factors II, VII, IX, X plus Protein C &S
## Dosing Kcentra

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>Dose</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td>2 to &gt;4</td>
<td>25 units/kg</td>
<td>2500 units</td>
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<tr>
<td>4-6</td>
<td>35 units/kg</td>
<td>3500 units</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50 units/kg</td>
<td>5000 units</td>
</tr>
</tbody>
</table>

Available in 500 and 1000 unit vials

Patient Case

FW is a 78 year old man admitted to the hospital with altered mental status. Head CT in ED reveals large SDH. PMH is significant for CAD, HF and AF treated with apixaban.
Which of the following would be the best option reversal option?

A. 4 units of FFP
B. Idarucizumab 5 grams once
C. Kcentra 2500 units once
D. Phytonadione 5 mg IV once
Dabigatran (Pradaxa)

- Oral, fixed dose direct thrombin inhibitor
  - 150 mg twice a day
  - 75 mg twice a day if CrCl <30 (AF)
- Predictable pharmacokinetics
- Limited drug interactions, no dietary concerns
- No monitoring required
- More effective than warfarin in AF
- Capsule must be swallowed whole
Idarucizumab (Praxbind)

• Monoclonal antibody against dabigatran
  – Specific for dabigatran only

• Indicated for reversal of dabigatran for emergency surgery/urgent procedures or in life-threatening/uncontrolled bleeding

• Administer 5 gram dose (two 2.5 gram vials)

www.praxbind.com
RE-VERSE AD Trial

• Enrolled 90 patients taking dabigatran
  – Group A: uncontrolled/life-threatening bleeding
  – Group B: urgent/emergent procedures
• No placebo group
• Primary outcome maximum percentage reversal of dabigatran
  – Ecarin clotting time and dilute thrombin time

N Engl J Med 2015;373:511-20
Results – Dilute Thrombin Time

N Engl J Med 2015;373:511-20
Results – Ecarin Clotting Time

C  Ecarin Clotting Time in Group A

D  Ecarin Clotting Time in Group B

Time of Blood Sample

N Engl J Med 2015;373:511-20
Rivaroxaban (Xarelto)

• Oral Factor Xa inhibitor
• Substrate of CYP P450 3A4 and pGP
• Take with food (largest meal of the day)
• May give per tube into stomach
• Half life 5-9 hours
Apixaban (Eliquis)

- Oral Factor Xa inhibitor
- Half life approximately 12 hours
- Approximately 25% renal elimination
- Twice a day dosing
- May administer per tube
Edoxaban (Savaysa)

- Factor Xa inhibitor
- Half-life of 10 to 14 hours
- Renal clearance 50%
- Once a day dosing
Andexanet Alfa

• Factor Xa decoy protein
• Reverses all Factor X inhibitors
• No anticoagulant effect
• Half life of 1 hour
• Not FDA approved (yet)

ANNEXA-A and ANNEXA-R

- Double blind, placebo controlled trials
- Healthy volunteers 50-75 years old
- Apixaban 5 mg BID or Rivaroxaban 20 mg daily
- Primary outcome percent change in anti-Xa activity

Results
Conclusions

- Anticoagulants in the ICU are high risk therapies
- Close monitoring is critical to success
- Protocols for appropriate treatment and reversal are a must
- Anticoagulant reversal is evolving, especially around NOACs