A Review of Novel Anticoagulation: Where We Are and Where We Are Going

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Disclosures

• I have no relevant financial or non-financial relationships to disclose in relation to the content of this presentation.
Accreditation

University of Florida is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Experience

- UF Health Anticoagulation Clinic
  - August 2011 – present
  - Expanded clinic to include NOACs

- Have studied Coaguchek XS® in clinic setting
  - Developed a correction calculation for the point of care result to better reflect a venipuncture INR
Overview

- Review of coagulation physiology
- Review of NOACs (aka TSOACs)
  - Novel Oral Anticoagulants and Target Specific Oral Anticoagulants
  - Anticoagulation vs. no anticoagulation
- Appropriate place in therapy for NOACs
- The Future of anticoagulation

The Cascade We are Used To

- Intrinsic
  - XI
  - XII
  - XIIa
  - XIa
  - IXa
  - IX
  - Xa
  - X
  - V
  - Va
  - VIII-VW
  - VIIIa
  - TF
  - VII
  - VIIa
  - II
  - IIa
  - V
  - Va
The Cascade We are Used To

• AT III
  • Inhibits factor X and Thrombin

• Protein C and S
  • S activates C
  • C inhibits factors V and VIII

A Better Understanding

• Where extrinsic meets intrinsic
• Not just floating around in plasma
• Body’s checks and balances for clot formation
Hypercoagulable Conditions

- Factor V Leiden
- Antiphospholipid Antibody Syndrome
- Protein C/S deficiency
- Antithrombin III deficiency

Novel Anticoagulants

![Diagram of clotting factors and anticoagulants]
Novel Anticoagulants

• Dabigatran
  • Half-life: 14-17 hours
    • 3-7% bioavailable
  • Almost completely excreted as unchanged drug
    • P-gp efflux transporter NOT CYP3A4 metabolite
    • Of the drug absorbed: 80% renal and 20% in feces
  • NO reversal agent

Novel Anticoagulants

• Dabigatran
  • Non-valvular atrial fibrillation, CVA prophylaxis
    • 150 mg BID
    • CrCl 15-30 mL/min: dose reduce to 75 mg BID
    • CrCl less than 15 mL/min: do not use
    • CrCl 30-50 mL/min WITH 3A4 inhibitor: 75 mg BID
    • CrCl less than 30 mL/min WITH 3A4 inhibitor: do not use
Novel Anticoagulants

• Dabigatran
  • VTE/PE Treatment
    • 150 mg BID starting after 5-10 days of parenteral anticoagulant therapy
  • VTE/PE prophylaxis
    • 150 mg BID

Novel Anticoagulants

• Apixaban
  • Half-life: 8-15 hours
    • 66% bioavailable
  • 70% excreted unchanged (CYP3A4)
    • 25% renal, “70% in feces
  • REVERSAL: Prothrombin Complex Concentrates
Novel Anticoagulants

• Apixaban
  • Non-valvular atrial fibrillation, CVA prophylaxis
    • 5 mg BID
    • 2.5 mg BID (any 2 of these contraindications)
      • Age greater than 80 OR
      • SeCr greater than 1.5 mg/dL OR
      • Weight less than 60 kg
    • Can use in renal failure
  • DVT/PE
    • 10 mg BID x 7 days, then 5 mg BID

Novel Anticoagulants

• Rivaroxaban
  • Half-life: 5-9 hours
    • 80% bioavailable
  • 50% excreted as unchanged drug (CYP3A4, 2J2)
    • 70% renal and 30% in feces
  • REVERSAL: Prothrombin Complex Concentrates
Novel Anticoagulants

- Rivaroxaban
  - Non-valvular Atrial Fibrillation
    - 20 mg once daily
    - CrCL 15-50 mL/min: 15 mg daily
    - CrCL less than 50 mL/min WITH 3A4 inhibitor: do not use

- VTE prophylaxis while having orthopedic surgery or acutely ill
  - 10 mg once daily
  - CrCL less than 30 mL/min: do not use

Novel Anticoagulants

- Rivaroxaban
  - VTE/PE treatment
    - 15 mg BID for 3 weeks post event, then 20 mg once daily
    - CrCL less than 30 mL/min: do not use
Novel Anticoagulants

- Edoxaban
  - Half-life: 10-14 hours
    - 62 % bioavailable
  - 50% renal elimination
  - REVERSAL: Prothrombin Complex Concentrates

Novel Anticoagulants

- Edoxaban
  - Atrial Fibrillation
    - 60 mg once daily
    - CrCl 15-50 mL/min: 30 mg once daily
Novel Anticoagulants

• **Edoxaban**
  - **VTE/PE**
    - Body weight greater than 60 kg: 60 mg once daily starting after 5-10 days of parenteral anticoagulation therapy
    - Body weight less than 60 kg: 30 mg once daily starting after 5-10 days of parenteral anticoagulation therapy

Reversal of Novel Agents

• **Direct Anti-Xa Agents**
  - **Kcentra®**
    - Possibly an accepted reversal agent
    - Not FDA approved
Kcentra®

- 4 factor PCCs discussed as best current option
  - Kinetic models show complete reversal of direct anti-Xa agents

- Kcentra®
  - 50 units/kg IV infusion
  - Study performed in Europe using Cofact®
    - Showed complete reversal based on prothrombin time

Andexanet alfa

- Binds to direct anti-Xa agents AND LMWH/fondaparinux activated ATIII
  - a decoy

- Phase 2 trial
  - 420 mg IV bolus of andexanet alfa plus 2 hour infusion
    - 2 minute post bolus 92% apixaban effect reversed
    - After 2 hour infusion 91% apixaban effect reversed

- Currently in Phase 3 trials
  - ANNEXA-A–R–E
Idarucizumab

- RE-VERSE AD trial (Phase 3)
  - 4-5 g IV Bolus
  - Expected completion 2017

- Dabigatran
  - Antibody against Dabigatran
    - Affinity 350 times greater than thrombin

Aripazine

- Dosing
  - 100-400 mg IV bolus

- Rivaroxaban, apixaban, edoxaban, dabigatran, UFH, LMWH and fondaparinux
  - Non-covalently binds to these agents and prevents activity

- Currently in Phase 2 trials
Scoring for Treatment

- CHADS2
- CHADS2-VASc
- HASBLED

CHA2DS2-VASc

- When is this more useful than CHADS2?
  - CHADS2 less than 2
    - Better management of low risk patients
CHA2DS2-VASc

- C - CHF 1
- H - HTN 1
- A - Age ≥ 75 2
- D - DM 1
- S - Hx Stroke 2
- V - Vascular Disease 1
- A - Age 64-74 1
- Sc - M or F 1 if F

HASBLED

Bleeds per 100 pt years

HOW DO WE USE THIS?

- HASBLED should be higher than CHADS2 or CHA2DS2-VASc

SHOULD WE EVEN BE TREATING THESE PATIENTS?

HAS-BLED

- H – HTN - 1
- Abnormal Hep/Ren Fxn - 1 or 2
- Hx of Stroke - 1
- Bleeding - 1
- Labile INR - 1
- Elderly > 65 - 1
- Drugs or EtOH - 1 or 2

HAS-BLED

- Hypertension
  - Systolic greater than 160 mm Hg

- Hepatic Dysfunction
  - Chronic Hepatic disease, documented abnormalities (bilirubin 2x upper normal limit, AST/ALT 3x upper normal limit)

- Renal Dysfunction
  - Chronic dialysis, transplant, SeCr of 200 mmol/L (2.3 mg/dL)

- Hemorrhagic Stroke
  - Sudden onset neurologic deficiency lasting greater than 24 hours caused by bleeding

- Bleeding
  - Any bleeding not from stroke requiring hospitalization and/or causing Hgb decrease greater than 0.2 g/dL and/or blood transfusion
Patient Case 1

• 70 year old female patient in anticoagulation clinic wishes to try a NOAC for therapy. Patient has been on warfarin (most recently 5 mg daily) for 5 years for a diagnosis of atrial fibrillation. Patient has no history of heart valve disorder. Patient has only significant other medical history for HTN (controlled at 130/85) and hypothyroidism. Patient is 50 kg with a serum creatinine of 1.0. Patient has historically been out of therapeutic INR range:

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<th>Dose</th>
<th>Notes</th>
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<tr>
<td>1</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>5 mg daily</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>4</td>
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</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>5 mg daily</td>
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Patient Case 1

• What options are there for her anticoagulation?

• Patient is also taking Amiodarone. Is this significant?

Estimated GFR is 41 mL/min. Rivaroxaban would require a renal dose adjustment. Dabigatran and apixaban would presumably not require any adjustment from normal dosing.

Rivaroxaban is contraindicated and apixaban will require dose adjustment. Dabigatran would require dose adjustment due to interaction and renal function.

• Does the patient even need anticoagulation?

CHADS2-VASc of 2. HASBLED of 2-3. Should probably not even be anticoagulating this patient at this point.
Patient Case 2

• 65 year old male patient discharged the hospital after an acute DVT 2 weeks ago. Patient had a long road trip from Roanoke, VA to Gainesville, FL that is attributed to provoking the DVT. Warfarin therapy was started at discharge, and the patient would like to try a NOAC to decrease clinic visits. Past medical history is significant only for HTN and takes lisinopril 10 mg daily. He is 65 kg with a serum creatinine of 1.0. His INR today in anticoagulation clinic is 1.5.

Patient Case 2

• What options are there for his anticoagulation?
Are Novel Agents For Everyone?

- Indigent/Non-Compliant
  - NOACs are often cost prohibitive

- Factor V Leiden
  - Should we investigate this mutation more intensely and use of NOACs with this condition?
  - Anecdotal reports are present with patients on Anti-Xa agents having worsening DVT.

Questions for the Future

- Better for ATIII Deficiency?
  - Should we turn to NOACs in patients with ATIII Deficiency?
  - NOACs bypass ATIII mechanism of action utilized by injectable agents.
Questions for the Future

• Why not in heart valve patients?
  • It is one thing to know we should not use these agents in these patients, but what is the mechanism?

• Development of renally cleared Anti-Xa?
  • Easier dosing than current drugs with enzymatic interactions

• Should we develop application of HAS-BLED for DVT/PE Prophylaxis?

Thank You

• Any Questions?