New Anticoagulants and Critical Care

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Difficult Task

- New anticoagulants
- 30 minutes
- Emphasis on 2 new oral anticoagulants
  - Dabigatran
  - Rivaroxaban/Apixaban
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Coagulation Cascade

Injury → Clot

Waterfall/ Cascade Model: 1960’s

Anticoagulants Historically

- Narrow therapeutic window
- Variable dose response among pts
- Interactions with drugs and diet
- Laboratory control needs to be standardized
- Maintenance is difficult
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Waterfall/Cascade Model

Intrinsic Pathway (aPTT)
- Kallikrein
  - fXII
    - fXI
      - fX
        - fVIII
        - fVII
        - Antithrombin
          - Heparin
          - Fibrin

Extrinsic Pathway (PT)
- Tissue Factor
  - fX
    - fVIII
    - fII
    - fXII
    - fXI
    - fVII
    - Warfarin

Direct Thrombin Inhibitors

Intravenous
- Hirudin
- Lepirudin
- Desirudin
- Argatroban
- Bivalirudin

DTI - advantages
- Inhibit thrombin bound to fibrin (clot)
- Lack of required co-factor (AT)
- Predictable response
  - Not bound to plasma proteins
  - Not neutralized by PF4
- No induction of immune-mediated thrombocytopenia
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Intravenous DTI

- Monitor with aPTT or ACT
- FDA approval in HIT or PCI
- Fairly short acting
- Shown to work as well as heparin in large cardiology trials for PCI
- Also lots of off-label uses

Argatroban: other uses

- Ischemic stroke
  LaMonte et al, Stroke 2004;35:1677-82
- Hemodialysis and CVVH
  Koster et al, J Thorac Cardiovasc Surg 2007;133:1376-7
- Peripheral vascular surgery

Bivalirudin: other uses

- CPB
  Dyke et al, J Thorac Cardiovasc Surg 2006;131:533-9
- Vascular surgery
  Hallak et al, Cardiovasc Intervent Radiol 2007;30:906-11
- Neuroendovascular procedures
  Hassan et al, Neurocrit Care 2010
Direct Thrombin Inhibitors

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<td>40-50 min</td>
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Direct Thrombin Inhibitors

Intravenous
- Hirudin
- Lepirudin
- Desirudin
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- Bivalirudin

Oral
- Ximelagatran/melagatran
- Dabigatran

New DTI-Dabigatran etexilate

- Pradaxa®
- Approved by FDA 10/2010
- In Europe and Canada since 2008
- New oral anticoagulant in > 50 yrs!
- Half life: 12-17 hours
- Esterase metabolism to dabigatran
Studies – Alphabet soup

- RE-NOVATE
- RE-MOBILIZE
- RE-MODEL
- RECOVER
- RE-LY
- ROCKET
- EINSTEIN
- EINSTEIN-Extension
- MAGELLAN
- ARISTOTLE

Dabigatran Indications

- VTE prevention after hip and knee surgery
- Treat acute DVT/PE
- Cardiac events in ACS
- Prevent stroke and emboli in nonvalvular AF

Pharmacokinetics

- Low drug-drug or drug-food interactions
- No effect on cytochrome P450 enzymes
- 80% of drug is eliminated by kidneys
- Fixed 150 mg BID dose

Dabigatran Monitoring Recs

- No monitoring is recommended except elderly or renal failure patients
  - Emergency surgeries
  - Liver failure
  - Concern about interaction with another drug
  - Bridging

Douxfils et al, J Thromb Haemost 107.5, 2012
Dabigatran and PT

- Thrombin time is too sensitive
- Linear with lower concentrations
- Greatly prolonged at higher levels
- NI TT excludes the presence of significant drug levels

Dabigatran and PTT

Dabigatran and ECT

Dabigatran and Thrombin Time

- Thrombin time is too sensitive
- Linear with lower concentrations
- Greatly prolonged at higher levels
- NI TT excludes the presence of significant drug levels
Case Report

- Participant in RE-LY undergoes CABG
- Drug stopped 2 days prior to OR, but pt had CRI (CrCl 36 mL/min)
- Therapeutic on dabigatran
- Massive postoperative bleeding


Bleeding Events

- 5 fatal cases reported in Japan
- 260 fatal bleeding events worldwide between March 2008 and October 2011

Problems

Pradaxa (dabigatran etexilate mesylate): Drug Safety Communication - Safety Review of Post-Market Reports of Serious Bleeding Events

AUDIENCE: Cardiology, Pharmacy, Hematology

ISSUE: (FDA) is evaluating post-marketing reports of serious bleeding events in patients taking Pradaxa (dabigatran etexilate mesylate). Bleeding that may lead to serious or even fatal outcomes is a well-recognized complication of all anticoagulant therapies. The Pradaxa drug label contains a warning about significant and sometimes fatal bleeds. In a large clinical trial (18,000 patients) comparing Pradaxa and warfarin, major bleeding events occurred at similar rates with the two drugs.
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Side Note on PCC

- Contain: prothrombin (II), VII, IX, X, protein C and S
- 4 factor PCC contain VII
  - Cofact®
- 3 factor PCC do not contain VII
  - Bebulin®
  - First 4 factor nonactivated PCC, just approved by FDA (Kcentra® or Beriplex® in Europe)

Dabigatran Reversal

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate
A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects
Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meetje K. Sijpkes, BSc; Joost C. Mielke, PhD; Harry R. Buller, MD; Marcel Levi, MD

Background—Rivaroxaban and dabigatran are new oral anticoagulants that specifically inhibit factor Xa and thrombin, respectively. Clinical studies on the prevention and treatment of venous and arterial thrombosis show promising results. A major disadvantage of these anticoagulants is the absence of an antidote in case of overt bleeding or when an emergency intervention needs immediate correction of coagulation. This study evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of these drugs.

Methods and Results—In a randomized, double-blind, placebo-controlled study, 42 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 20 days, followed by either a single bolus of 20 U/kg PCC concentrate or a saline solution of glucose. After a washout period, this procedure was repeated with the other anticoagulant treatment. Rivaroxaban induced a significant prolongation of the prothrombin time (15.2±1.3 versus 12.9±1.2 seconds at baseline; P=0.001) that was immediately and completely reversed by PCC (12.5±1.0; P=0.001). The endogenous thrombin potential was inhibited by rivaroxaban (V1=22%; baseline, V1=12%; P=0.002) and normalized with PCC (V1=34±26%; P=0.001), whereas saline had no effect. Dabigatran increased the activated partial thromboplastin time, elastic clotting time (ECT), and thrombin time. Administration of PCC did not restore these coagulation tests.

Conclusions—Prothrombin complex concentrate immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the anticoagulant action of dabigatran at the PCC dose used in this study.

Circulation 2011;124:1573-1579
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Dabigatran Reversal

What does this mean?
- Unclear what relationship laboratory tests have to clinical bleeding
- Are they surrogate markers for bleeding tendency?
- Manufacturer recommends:
  - PCC - may be helpful in rats with tail incision
  - rFVIIa - corrected rat tail bleeding time
  - FFP - may be helpful in mice

Dabigatran Reversals
- Dialysis: ~60% removed over 2-3 hours
- Oral activated charcoal may effectively absorb drug after recent ingestion

FXa Inhibitors

Intrinsic Pathway (aPTT)
- Kallikrein
- fXII
- fXI
- fIX
- fVIII
- Antithrombin
- Heparin
- Fondaparinux

Extrinsic Pathway (PT)
- Tissue Factor
- fVII
- fX
- fII
- Fibrin
Chromogenic Factor Xa assay

FXa Inhibitors

Oral Xa inhibitors-Rivaroxaban

Rivaroxaban

• FDA approval July 2011 for DVT prophylaxis after hip/knee replacement surgery

• FDA approval Sept 2011 for stroke prophylaxis in Afib
**Rivaroxaban Testing**

- Chromogenic anti-factor Xa assay
- Not yet available as rivaroxaban assay
- Not yet STAT lab

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**Rivaroxaban Reversals**

- No data on activated charcoal
- Is highly protein bound so unlikely that it can be removed by hemodialysis
- No data on FFP in animal or human studies

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**Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate**

A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eisenberg, MD, Pieter W. Kamphuisen, MD, Meertien K. Sigikinks, BSc; Joost C. Meijers, PhD, Harry R. Buller, MD, Marcel Levi, MD

**Background**—Rivaroxaban and dabigatran are new oral anticoagulants that specifically inhibit factor Xa and thrombin, respectively. Clinical studies on the prevention and treatment of venous and arterial thromboembolism show promising results. A major disadvantage of these anticoagulants is the absence of an antidote in case of serious bleeding or when an emergency intervention needs immediate correction of coagulation. This study evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of these drugs.

**Methods and Results**—In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (×6) or dabigatran 150 mg twice daily (×6) for 3 days, followed by either a single dose of 200 U/kg PCC (A1) (×1) or a similar volume of saline. After a washout period, the procedure was repeated with the other anticoagulant treatment. Rivaroxaban induced a significant prolongation of the prothrombin time (15.4 ± 1.5 versus 12.4 ± 0.7 seconds at baseline; P = 0.001). The prothrombin time was significantly reduced by the PCC (12.4 ± 1.0 versus 9.2 ± 2.7 seconds; P < 0.001) and normalized with PCC (11.4 ± 0.6; P < 0.001), whereas saline had no effect. Dabigatran increased the activated partial thromboplastin time, prothrombin time, and thrombin time. Administration of PCC did not reverse these coagulation tests.

**Conclusions**—Prothrombin complex concentrate immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the anticoagulant action of dabigatran at the PCC dose used in this study.

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**Rivaroxaban Reversal**

- rivaroxaban drug level
- rivaroxaban length of stay
- rivaroxaban treatment
- rivaroxaban severity
- rivaroxaban test results
- rivaroxaban treatment details
- rivaroxaban adverse effects
- rivaroxaban complications
- rivaroxaban medication
- rivaroxaban disease
Rivaroxaban reversals

- **PCC**
  - Reduced PT in human volunteers
  - Reversed prolonged BT in rats on high dose rivaroxaban
- **rFVIIa**
  - Reduced rat mesenteric bleeding time
  - Modest decrease in bleeding time in baboon


Apixaban

- **Eliquis®**
- Approved for nonvalvular Afib – Dec 2012
- Half-life 8-15 hours
- Twice a day dosing

Summary

- Exciting: clinical anticoagulant therapy
- Dissatisfying:
  - Only INR standardized for warfarin
  - Any other coagulation test used to monitor any other anticoagulant lacks standardization

Pt bleeding on dabigatran or rivaroxaban therapy

- **Mild Bleeding**
  - Delay dose or temporarily discontinue
- **Moderate Bleeding**
  - Local control measures
  - Supportive Rx
    - Fluids
    - FFP
    - Monitoring
- **Severe Bleeding**
  - HD – dabigatran
  - PCC-rivaroxaban
  - rFVIIa

Supportive Rx

- Fluids
- FFP
- Monitoring

HD – dabigatran

PCC-rivaroxaban

rFVIIa
Withholding dabigatran

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<th>High Bleeding Risk</th>
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<tr>
<td>CrCl &gt; 50 mL/min</td>
<td>Hold 24 hours</td>
<td>Hold 2-4 days</td>
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<tr>
<td>CrCl 30-50 mL/min</td>
<td>Hold 2 days</td>
<td>Hold 4 days</td>
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<tr>
<td>CrCl &lt; 30 mL/min</td>
<td>Hold 2-5 days</td>
<td>Hold &gt; 5 days</td>
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Withholding rivaroxaban

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<td>CrCl &gt; 50 mL/min</td>
<td>Hold 1-2 days</td>
<td>Hold 3-4 days</td>
</tr>
<tr>
<td>CrCl 30-50 mL/min</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min</td>
<td>Do not use</td>
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Summary - dabigatran

- TT is sensitive test to ensure there is no presence of dabigatran
- Back-up is normal aPTT – suggests levels are low therapeutic or subtherapeutic

Summary - rivaroxaban

- Normal PT suggests low or no levels of rivaroxaban
- Wait for anti-factor Xa activity assay for rivaroxaban
Summary – Massive Bleeding

- Supportive Care – fluid resuscitation, compression, transfusion
- Discontinue Drug
- Activated charcoal for overdoses
- HD for dabigatran
- FFP not helpful – but fluid resuscitation
- rFVIIa/PCC - ? Unknown effect on clinical bleeding  

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Coagulation Cascade

**Intrinsic Pathway (aPTT)**
- Kallikrein → fXII
- fXI
- fIX

**Extrinsic Pathway (PT)**
- Tissue Factor → fVII

**fXa inhibitors**
- Fondaparinux
- Antithrombin
- Heparin

**fII**
- Warfarin
- DTI

**fVIII**
- fIX
- fX

Questions?