Novel Anti-coagulant Agents

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Objectives

- Provide an overview of the normal coagulation, including perioperative testing
- Discuss pharmacology of novel anti-coagulant agents (NOACs) and their potential impact on patient care
- Consider strategies for peri-operative management of NOACs
Models of coagulation

- Cell based

- Takes into account the interaction between factors found freely in plasma and those bound to cells
Models of coagulation

• Initiation
• Amplification
• Propagation

• Note the importance of negative feedback
• Positive only feedback loops require an end-point ie labor
Cell based model
Common Pathway

X
(prothrombinase)

Xa

Prothrombin

Thrombin

↑ Fibrinogen (I)

Fibrin (Ia)

XIIIa

XIII

Cross linked fibrin clot

KEY
- Activates
- Catalyses
- Inactivated form
- Activated form

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Coagulation tests

- Rarer tests needed
- Thrombin Time
- Dilute Thrombin Time
- Ecarin test
- Chromogenic anti-Factor Xa activity
Testing

• Important to consider the question that is being asked

• Is the coagulation normal?
Climate vs Weather

• Why are coagulation tests so limited in their applicability?

Or

• If Plavix works, then why doesn’t it affect the PT/INR?
PT and INR

• PT developed by Quick in 1935

• ‘…accepted with some hesitation and trepidation as I knew nothing about coagulation…’

• The Development and Use of the Prothrombin Tests – Armand J Quick 1959 - Circulation
Intrinsic and Extrinsic Pathways

• “The division of the clotting cascade into the intrinsic, extrinsic and common pathways is medieval”

• “Has no in vivo validity”

• “Useful concept for interpreting results of laboratory tests”
Common Pathway

- **X (prothrombinase)**
- **Prothrombin** → **Thrombin**
- **↑ Fibrinogen (I)** → **Fibrin (Ia)**

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**Cross linked fibrin clot**
Thrombin time

- Add bovine or human thrombin to plasma
- Thrombin will convert fibrinogen to fibrin
- Essentially a test of fibrinogen
- But is also sensitive to inhibitors present in plasma
- Can be modified by diluting plasma sample
Common Pathway

Xa (prothrombinase) → Thrombin → Fibrin (Ia)

X → Prothrombin

↑ Fibrinogen (I) → Fibrin (Ia)

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Cross linked fibrin clot
Ecarin testing

• Ecarin clotting time

• Test of direct thrombin inhibitors, including lepirudin

• Ecarin cleaves prothrombin to a metabolically active metabolite
Ecarin test

- The metabolite is inhibited directly by lepirudin and other direct thrombin inhibitors
- Linear response to DTI concentrations
Chromogenic testing

Anti Factor Xa assay

- Plasma sample with Xa inhibitor present
- Add known amount of excess Xa
- Add marker activated by Xa and measure
Chromogenic testing

• Needs calibration to correct substance

• Will give a plasma concentration of the substance measured

• Need to know significance of the concentration
Common pathway - NOACs

- Two classes
  - Direct thrombin inhibitor – dabigatran
  - Anti Xa – Rivaroxaban, Apixaban, Edoxaban and Betrixaban
- Given away by the XA in the name
Common Pathway

- X (prothrombinase)
- Prothrombin
- Thrombin
- Fibrinogen (I)
- Fibrin (Ia)
- XIIIa
- Cross linked fibrin clot

**KEY**
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Dabigatran (Pradaxa)

- Direct thrombin antagonist
- Licensed to reduce risk of thromboembolic stroke in presence of non-valvular atrial fibrillation

- Bioavailability 3-7%
- Half-life 12-17 hours
Dabigatran (Pradaxa)

- APTT and especially INR may be normal in presence of clinically significant levels of drug
- Thrombin time will show presence of dabigatran, but too sensitive to quantify effect
- May be mitigated by dilute thrombin test
Dabigatran (Pradaxa)

• Ecarin chromogenic assay will accurately assess plasma levels
• Also Ecarin clotting time will also do this
• No cut-off has been established

• These tests may not be available at your hospital
Dabigatran (Pradaxa)

- ASRA coags app guideline

- Wait 5 days
- Or, if <65 years old, not hypertensive or on anti-platelets
- Then 3 days if CrCl >80ml/min
- Or 4 days if CrCl 50-79ml/min
- Or check dTT or ECT
Rivaroxaban (Xarelto)

- Factor Xa inhibitor
- Atrial Fibrillation and embolic event
- Prophylaxis of DVT in patients undergoing THR or TKR

- Black box warning for patients undergoing spinal or epidural anesthesia
Rivaroxaban (Xarelto)

- 80-100% bioavailability

- Half-life 5-9 hours, 11-13 hours in elderly
Rivaroxababan (Xarelto)

- APTT and INR may all be normal
- TT and dTT test at the wrong part of the pathway
- The PT is prolonged, but massive variability between agents
- Possibility exists to construct a Rivaroxoaban-INR
- Can not use at present
Rivaroxaban (Xarelto)

• Chromogenic anti-Xa testing is gold standard, but not widely available

• ASRA – Wait 3 days, or check Mass Spect or anti-Xa level
Apixaban (Eliquis)

- Factor Xa inhibitor
- Reduce embolic events in A Fib
- DVT prophylaxis for TKR and THR
- Treatment of DVT and PE, and reduction of risk of recurrence
- Also black box warning for neuraxial block
Apixaban (Eliquis)

- Bioavailability 50%
- Half-life 12 hours
- FDA recommends stopping 24-48 hours prior to surgery
Apixaban (Eliquis)

- None of the standard laboratory tests can be used to assess the effect of apixaban.

- Chromogenic anti-Factor Xa test will indicate presence of apixaban.
Apixaban (Eliquis)

- FDA vs ASRA

- ASRA coags suggest 72 hours needed to proceed prior to placement of neuraxial, and to check anti-factor Xa activity if <72 hours

- Increasingly patients on apixaban present with only 48 hour hold
Edoxaban (Savaysa)

- Factor Xa inhibitor
- Licensed only for A Fib
- And only if CrCl <95ml/min
- Otherwise it doesn’t work
Edoxaban (Savaysa)

- Bioavailability 62%
- Half-life 10-14 hours
Edoxaban (Savaysa)

- Unreliable effects on both APTT and PT/INR
- May be significant clinical effect with PT and APTT in normal range
- Chromogenic assay will give a yes/no result
Edoxaban (Savaysa)

- ASRA suggest holding for 72 hours prior to neuraxial blockade

- Behaves in a similar way to apixaban
Betrixaban (Bevyxxa)

- Factor Xa inhibitor – approved June 2017

- *Prophylaxis of VTE in adults hospitalized for an acute medical illness who are at risk for thromboembolic complications*

- Essentially an alternative to enoxaparin
Betrixaban (Bevyxxa)

- Bioavailability 34%
- Half-life 19-27 hours
Betrixaban (Bevyxxa)

- Only recommended test is chromogenic assay
- Both FDA and ASRA agree that 72 hours is the time to wait prior to neuraxial block
- Although up to 135 hours with CrCl <30ml/min
Perioperative management

• Elective vs Emergent or Urgent surgery

• Elective – ASRA coags app

• Full guidelines sometime vary from the app

• May differ from pre-op assessment recommendations
Perioperative management

- Emergent surgery
- History – timing
- Compare to half-life
- Testing
Reversal

- Specific reversal agents for both classes
- Expensive

- Non-specific agents
- Relatively less expensive, more widely available
Reversal - dagibatran

- Idarucizumab - Praxbind
- Mono-clonal antibody that binds dagibatran
- Dose – 5g, or two vials
- Costs around $4000
- Half-life 12-17 hours
Cautions - Idarucizumab

- Thrombembolic event
- Re-elevation of coagulation parameters
Idarucizumab - trials

• REVERSE-AD Trial – NEJM 2017
• 503 patients on dabigatran
• Life-threatening bleeding (n=301) or required emergent surgery (n=202)

• Peri-procedural hemostasis normal in 93.4%
REVERSE-AD trial

• Median reversal by ECT or dTT was 100% within 4 hours

• 30 day thrombosis rate 4.8%

• Re-elevation of clotting times in 114 patients

• Significant bleeding in 10 patients
Reversal Xa inhibitors

- Adexanet alpha - Andexxa
- Accelerated license only for apixaban and rivaroxaban
- Should work for edoxaban and betrixaban
Andexanet alpha

- Recombinant modified Factor Xa
- Acts as a false target for anti Xa drugs, but due to its modification does not activate downstream cascade

- Allows endogenous Xa to act normally
- Limited duration of action – still need to wait for Xa inhibitor to be eliminated
Andexanet alpha

- Should also reverse enoxaparin and fondaparinux also

- Cost $50,000

- Studied in ANEXXA-4 trial

- Bolus plus 2 hour infusion
ANEXXA-4 – interim results

- 67 patients, major bleeding within 18 hours of administration of FXa antagonist
- Median decrease of 89% after initial bolus
- Remained similar through infusion
- Four hours after infusion – activity 39% of baseline for rivaroxaban and 30% for apixaban
ANEXXA-4 interim results

- Clinical analysis of hemostasis at 12 hours

- 79% good or excellent, despite anti-FXa levels rising again

- ’Prolonged reversal may not be necessary to gain a good hemostatic response’
ANEXXA-4

- Thrombosis rate 18% at 30 days
- Mainly patients with GI or intra-cranial bleed
PCC

- 3 factor (II, IX and X)

- 4 factor (II, VII, IX and X + Protein C and S)

- Activated 4 factor – II, VII, IX and X plus activated factor VII
Levi et al 2014

- Compared 3 and 4 factor PCC in rivaroxaban reversal
- Healthy volunteers
- 50 IU/kg dose
- Measured PT – 4 factor reduced by 2.5-3.5 s, vs 0.6-1.0 s

- This from an average high of 21 s
- Mean normal 12 s
Other PCC studies

• Small studies

• Suggest aPCC more effective than PCC in reversal of dabigatran
PCC

• Limited data for use in reversal
• Four factor has most evidence
• Did not reverse coagulation tests for patients on dagibatran, but did for edoxaban and rivaroxaban

• Activated PCC had better results with dagibatran
Reversal

• However - cheaper and more widely available option
• One of dose of 50IU/kg, or follow your local guidelines for its use

• Still expensive but less so
• In absence of specific agents are likely to be best or only way for rapid NOAC reversal
ACS guidelines - 2018

• Recommend Idarucizumab for dabigatran
• 4 factor PCC in reversal for ‘partial’ reversal of other NOACs
• Andexxa – no specific recommendation given
In development

• Under fast-track review at FDA

• Ciraparantag (Aripazine)
  • In phase 2 trials – clinically shown reversal of edoxaban and rivaroxaban

• Non clinical studies show reversal of all NOACs (inc dagibatran) and enoxaparin
Summary

• Be aware of widening indications for NOAC use
• Assessment prior to urgent surgery depends on timing of last dose
• Routine lab testing unhelpful, specific tests dependent on local lab availability
• Expensive antidotes exist
Discussion

Thank you!