Emergent Reversal of Anticoagulation in the ED and ICU Settings

Shirley Chen, DO
Baptist Medical Center, Jacksonville, FL
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Disclosures

• None
Objectives

• Review coagulation cascade, common parenteral and oral anticoagulants

• Discuss reversal agents and strategies for emergent reversal of anticoagulation

• Consider laboratory monitoring and potential reversal agents of new oral anticoagulants

• Discuss anticoagulant and reversal drugs in development
Warfarin (coagulopathy)-related ICH

- 30-day mortality up to 67% (without coagulopathy, 35-52%)
- tend to be larger than non-warfarin-related ICH
- increased risk of expansion: 50% (vs. 30%)
- mean ICH expansion in warfarin-associated 21hrs (up to 7 days) vs. 8-24 hrs

Coagulopathy-related ICH
Contact activation (intrinsic) pathway

(VII, XI, IX, VIII)

Tissue factor (extrinsic) pathway

(VII, TF[III])

Common pathway

(X, V, II, I, XIII)
Common Parenteral Anticoagulants

- Indirect FXa inhibitors
- Unfractionated heparin
- LMWH
  - enoxaparin (Lovenox)
  - dalteparin (Fragmin)
  - tinzaparin (Innohep)
- Pentasaccharides
  - Fundaparinux (Arixtra)
Oral Anticoagulants

- Warfarin (Coumadin, Jantoven)
- Direct Thrombin Inhibitors
  - Dabigatran (Pradaxa)
- Direct FXa Inhibitors
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
  - Edoxaban (Savaysa)
- In development: Betrixaban, Letaxaban, Darexaban, Erixaban

*Discov med* 2012;13(73):445-450.
Warfarin
Vitamin K Dependent
(II, VII, IX, X, Protein C and S)
**Vitamin K Dependent**

(II, VII, IX, X, Protein C and S)

**Direct FXa Inhibitors**

**Direct Thrombin Inhibitors**

(X, V, II, I, XIII)
Potential Reversal Agents

- Protamine sulfate
- Vitamin K
- FFP
- rFVIIa
- PCC (Prothrombin (FIX) Complex Concentrate)
- FEIBA (“activated” PCC)
- Idarucizumab (Praxbind)
- In development: Andexanet alfa, Aripazine, modified thrombin molecules
Heparin Reversal

• Protamine sulfate
• Adjust for time elapsed since last dose:
  • < 30 min → 1 mg/100 U
  • 30-120 min → 0.5 mg/100 U
  • > 120 min → 0.25 mg/100 U
• continuous infusion: 1mg/100U heparin given in previous 2-3 hours
• max rate 5mg/min, max dose 50mg (hypotension, bradycardia)

LMWH (Enoxaparin) Reversal

- Protamine sulfate (30-60% reversal)
- 1mg/100 U, adjust for time elapsed since last dose:
  - < 8 hr → 1 mg/100 U
  - > 8 hr → 0.5 mg/100 U
- max rate 5mg/min, max dose 50mg (hypotension, bradycardia)

Fondaparinux Reversal

- Fondaparinux
  - no reversal agent
  - protamine ineffective
  - may consider FEIBA/aPCC (20 U/kg)

_Neurocrit Care_ 2016;24:6.
Warfarin Reversal

- Vitamin K
  - 10 mg IV (4-24hrs for reversal)
    - PO/SC (~24 hrs)
  - slow, but important for sustained correction of coagulopathy
  - risk of anaphylactoid reaction (slow IV, 1mg/min)
  - do not give alone
Warfarin Reversal

- FFP
- 15-20 mL/kg (30 mL/kg)
- 1 unit ~250mL
- large volume, long infusion time (3-6 hrs), transfusion reactions, variability of clotting factors
- normalization of INR takes ~30 hrs
Calculating FFP or PCC Dose to Target INR

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[Target level (%) - Current level (%)] x Weight (kg) = mL FFP or IU of PCC

*NEJM* 2003;349:675.
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Ex: Target level 1.4, Current level 3.0, weight 75 kg

NEJM 2003;349:675.
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\text{[Target level (\%) - Current level (\%)]} \times \text{Weight (kg)} = \text{mL FFP or IU of PCC}
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**Ex:** Target level 1.4, Current level 3.0, weight 75 kg

\[
(40-15) \times 75 = 1875 \text{ mL FFP or 1875 IU PCC (~150mL)}
\]

*NEJM 2003;349:675.*
4 Factor PCC

- Kcentra (Beriplex in Europe)
  - FII 380-800 U
  - FVII 200-500 U
  - FIX 400-620 U
  - FX 500-1020 U
  - Protein C 420-820 U
  - Protein S 240-680 U
  - small amount of heparin, human albumin, antithrombin III
4 Factor PCC

• Kcentra
  • currently the only 4 PCC available in US
  • approved for urgent reversal of Vit K antagonist (warfarin) in acute major bleeding
  • thromboembolic events ~5-9% (vs. ~4-6% for FFP)
  • reversal can be achieved in 10-30 min

Kcentra (Prothrombin Complex Concentrate) [prescribing information]. 2013 Dec.
4 Factor PCC

• Kcentra Dosing:
  • INR 2-4, 25 IU/kg (max 2500 IU)
  • INR 4-6, 35 IU/kg (max 3500 IU)
  • INR > 6, 50 IU/kg (max 5000 IU)
“activated” PCC

- FEIBA (Factor Eight (VIII) Inhibitor Bypassing Activity)
  - FVII (mainly activated) + FII, IX, X (non-activated)
  - 500 U, 1000 U, 2500 U (50-100 U/kg)
  - approved for use in hemophilia A or B patients with inhibitors (control of bleeding, perioperative, routine prophylaxis)

FEIBA [prescribing information]. 2013 Nov.
“activated” PCC

- FEIBA (Factor Eight (VIII) Inhibitor Bypassing Activity)
  - limited off-label experience for Warfarin reversal
  - compared w FFP, faster INR correction, goal INR 50% vs. 33%
  - thromboembolic events 7%
  - animal models - lower dose probably just as effective as higher dose

Warfarin-Reversal

• rFVIIa
  • onset in minutes
  • half-life only 2.6 hrs
  • thromboembolism, expensive
  • improves INR reversal and decreases FFP requirements (as ADJUNCT to Vit K + FFP)
    • alone, not adequate for warfarin reversal
  • ? dose

Warfarin Reversal

• rFVIIa
  • INR reversal w/o adequate hemostasis?
  • animal studies suggest despite INR normalization, bleeding time and thrombin generation not as good as with PCC (four factor repletion)
  • alone, NOT recommended for Warfarin reversal

Potential Thrombotic Events

(rFVIIa and PCC)

• Arterial thromboembolic events:
  • MI, stroke, retinal artery thrombosis, limb/bowel infarct

• Caution: DIC, advanced atherosclerotic disease, crush injury, septicemia, concomitant use of rFVIIa and PCC (circulating TF or predisposing coagulopathy)
Potential Thrombotic Events (rFVIIa and PCC)

- Possible RF:
  - multiple dosing
  - high dose
  - immobility s/p orthopedic procedures
  - hepatic disease
  - severe vascular disease

*Blood Reviews* 1998;12:35-44.
Proposed Protocol: Warfarin Reversal

- Vitamin K 10mg IV>PO>SC daily x 3 days
  +
- 4-Factor PCC (Kcentra) based on INR:
  - 2-4 → 25 IU/kg (max 2500)
  - 4-6 → 35 IU/kg (max 3500)
  - > 6 → 50 IU/kg (max 5000)
- Alternative to PCC: FEIBA
  - INR < 5 → 500 Units
  - INR > 5 → 1000 Units
  - (alternatively 50 U/kg)
- Recheck INR in 10-30-min, give additional FFP if adequate reversal not achieved
Dabigatran Reversal

- Idarucizumab (Praxbind)
  - monoclonal antibody fragment
  - binds to thrombin binding site of dabigatran (free and thrombin-bound)
  - 5g IV (two 50mL bolus infusions)
  - mild adverse affects (headache, erythema)
  - reversal (dTT, ECT, aPTT, TT) within minutes, sustained at least 24hrs
  - ? hemostatsis - 11h

*NEJM* 2015;373:511-520.
Emergent Reversal

- Direct Thrombin Inhibitors (Dabigatran)
  - Idarucizumab (Praxbind)
  - maintain diuresis (80% renal elimination)
  - lipophilic - if ingestion within 1-2 h, give activated charcoal PO
- consider hemodialysis (4hrs, removal of 48% at 200mL/min, 60% at 400mL/min)
- consider FEIBA (50 U/kg), PCC

Thromb Haemost 2010;103: 1116-27.
Emergent Reversal

• Direct FXa Inhibitors
  • Rivaroxaban
    • if within 8h ingestion, give activated charcoal
    • maintain adequate diuresis (66% renal elimination)
  • Apixaban
    • if within 4h ingestion, give activated charcoal
Emergent Reversal

• NOACs
  • overall, limited to animal studies, healthy volunteers
  • FFP, FVIIa don’t appear to be effective
  • PCC, aPCC show possible promise, probably reasonable to consider in emergent situations
Monitoring Adequate Reversal

- PT, INR for Warfarin
- aPTT for Heparin
- anti-FXa level for LMWH (renal failure, obese, long-term anticoagulation)
- But what about the new oral anticoagulants?
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban
Coagulation Studies

• Novel Oral Anticoagulants (NOACs)
  • Assays demonstrate high variability in sensitivity to the new oral anticoagulants, depending on what reagent is used
  • Thus no standardization from lab to lab
Coagulation Studies

• Direct Thrombin Inhibitors (Dabigatran)
  • PT/INR - little effect
  • aPTT
    • relatively insensitive but still may provide qualitative indication of anticoagulant activity
    • prolonged aPTTT = presence of activity (does not quantify how much)
    • normal aPTT = no pharmacologically relevant anticoagulant activity
Coagulation Studies

• Direct Thrombin Inhibitors (Dabigatran)
  • ECT (ecarin clotting time)
    • specific assay for thrombin generation
    • direct measure of direct thrombin inhibitor activity
    • not readily available everywhere, reagents in different labs not standardized
  • Others: dilute thrombin time (dTT), ecarin chromogenic assay

Thromb Haemost 2010;103:1116-27.
Coagulation Studies

• Direct Thrombin Inhibitors (Dabigatran)
  • TT, TCT (thrombin clotting time)
  • extremely sensitive
  • prolonged TT = presence of drug
  • normal TT = no pharmacologically relevant anticoagulant activity
• Hemoclot Thrombin Inhibitor assay (Hyphen BioMed) - research only in US
Coagulation Studies

- Direct Thrombin Inhibitors (Dabigatran)
  - By decreasing sensitivity:
    - TT > ECT > aPTT
  - in animal models, even when clinical bleeding reduced, no changes in above lab values noted

**Thromb Haemost** 2010;103:1116-27.
**Circulation** 2011;123:1436-50
Coagulation Studies

• Direct FXa Inhibitors (Rivaroxaban, Apixaban)

• prolong PT > aPTT

• varying response depending on reagent

• INR cannot be applied

• no effect on TT

• modified chromogenic anti-Xa assays can be used, but must use reagents standardized to specific drug
Reversal Agents in Development

• Andexanet alfa
  • modified, recombinant FXa
  • binds to and inactivates FXa inhibitors and antithrombin activated by heparin/LMWH/fondaparinux, oral direct FXa inh
  • 400mg IV bolus, 4mg/min continuous infusion
Reversal Agents in Development

- Aripazine
  - small molecule
  - binds to and inhibits heparin, LMWH, fondaparinux, direct FXa inhibitors, direct thrombin inhibitor
  - may require different doses for reversal of Apixaban and Rivaroxaban
  - unclear mechanism of action

Summary

• Warfarin-related ICH is associated with high morbidity and mortality rates

• Rapid reversal of coagulopathy is crucial in preventing hematoma expansion

• High quality trials lacking in comparing various modalities, and demonstrating improvement in outcome
Summary

• Vitamin K should be given with one of the following, for emergent Warfarin reversal:
  • FFP (widely available but slow, unpredictable, large volume)
  • 4-Factor PCC (rapid, physiologic correction, thrombotic events)
  • FEIBA/aPCC (off-label, rapid, limited experience)
Summary

• NOACs - even less evidence for effective reversal strategy, but more to come..
  • Dabigatran - Idarucizumab, support diuresis, consider HD, activated charcoal within 1-2h ingestion
  • Rivaroxaban - support diuresis, activated charcoal within 8h ingestion
  • Apixaban - activated charcoal within 4h ingestion
  • in all, consider PCC, FEIBA/aPCC - FFP and rFVIIa probably not as effective
Summary

• NOACs - but more to come..
  • Future directions:
    • Andexanet alpha (direct FXa inh, LMWH, Fondaparinux)
    • Aripazine (heparin, LMWH, Dabigatran, direct FXa inh)
Wake Up!

Break Time

COFFEE

TEA