Reversal of Anticoagulants

30th David Miller Trauma Symposium
Bill Beck, MD
Assistant Professor of Surgery
Trauma, Emergency General Surgery, Critical Care
Disclosures

• None

• I will be discussing off label uses of medications (will be noted)

• I use a Mac and everyone else should too
Why does this matter?

• Preventable deaths-hemorrhage

• No precise estimate of incidence
  • At least 25 million (could be 2-5x this number)
  • Prevalence only increasing

• Doesn’t include OTC meds
  • Aspirin
  • Supplements
Initial Evaluation

• Medical history most important

• Physical Exam
  • Scars on legs, neck, groins, chest
  • AV grafts/fistulas

• Coagulation testing
  • PT/INR/Rotational thromboelastography
  • P2Y12/PFA’s
  • Factor Xa
Decision Tree

Yes

Reverse Anticoagulation

No

Planned Procedure?

Yes

Reverse

No

Observe

BLEEDING???
ASPIRIN

• Most commonly used oral anticoagulant (globally)
  • >100 billion tablets taken yearly

• Cyclooxygenase inhibitor
  • Blocks thromboxane A2 formation-platelets

• Not-reversible
Aspirin-Measurement

• Aspirin Response Test (VerifyNow)

• Platelet Function Assay

• Light Transmission Aggrometry

• TEG Platelet Mapping Assay
Aspirin-Is Reversal Needed?

- Not in the vast majority of trauma patients
  - 25-50% aren’t therapeutic by platelet assay

- Platelets (1 multi donor pack) reverse dysfunction in ~50%, usually more than one req.

- “no clear benefit of platelets to prevent expansion”

Efficacy of platelet transfusion in the management of acute subdural hematoma

John Ogunlade\textsuperscript{a,b,*}, James G. Wiginton IV\textsuperscript{a,b}, Hammad Ghanchi\textsuperscript{a,b}, Zein Al-Atrache\textsuperscript{c}, Margaret Wacker\textsuperscript{a,b}, Rosalinda Menoni\textsuperscript{a,b}, Dan Miuuli\textsuperscript{a,b}
Thienopyridines

- Includes clopidogrel, prasugrel, ticagrelor
  - Plavix, Effient, Brillinta

- Work by inhibiting P2Y12 receptors on platelets
  - Irreversibly prevents platelet inhibition

- Measure with P2Y12 assay
Thienopyridines

- Reverse with platelets
  - P2Y12 LESS THAN 194
  - Dose responsive effect

- Desmopressin (DDAVP)
  - 0.3 mcg/kg per dose

- Monitor P2Y12 to assess for treatment effect
Low Mol. Weight Heparin

- Enoxaparin (Lovenox), Dalteparin (Fragmin)
  - Half-life = ~4.5 hours

- Fondaparinux (Arixtra)
  - Half-life = ~20 hours

- Can measure with anti-Xa level
Antithrombin 3
Low Mol. Weight Heparin

- Protamine (60% effective as compared to UFH)

- Dependent on time of last dose
  - LESS THAN 8 HOURS: 1mg per 1mg enoxaparin/100u dalteparin
  - 8-12 HOURS: 0.5
  - >12 HOURS: Waste of money

- Can consider 4 factor PCC (50% efficacy/expensive)
4 Factor Prothrombin Complex Concentrate

- II, VII, IX, X, C, S
- Do not give if hx of HIT
- Doses range from 25-50u/kg
4 Factor Prothrombin Complex Concentrate

• FDA: “Kcentra, Prothrombin Complex Concentrate (Human), is indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding”

• Trauma surgeons:

• P&T Committee: $1.34/unit
Warfarin

- Vitamin K antagonist
- Inhibits production of II, VI, IX, X, C, S
  - (Same contents as 4F PCC)
- 20 million Americans on Warfarin (2008)
Warfarin

- Fresh Frozen Plasma
  - Median-4 units to reverse for INR>2

- Vitamin K-10mg IV once

- 4F PCC

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2 – &lt; 4</th>
<th>4 – 6</th>
<th>&gt; 6</th>
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</thead>
<tbody>
<tr>
<td>Dose* of Kcentra (units† of Factor IX) / kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose‡ (units of Factor IX)</td>
<td>Not to exceed 2500</td>
<td>Not to exceed 3500</td>
<td>Not to exceed 5000</td>
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</tbody>
</table>
Novel Oral Anticoagulants (NOAC)

• First introduced in 2010
  • Dabigatran (Pradaxa)
  • No reversal agent

• Two different classes
  • Factor Xa inhibitors
  • Direct thrombin inhibitors

• ORBIT-AF Study
  • New onset Afib-50%
  • Chronic Afib-25%
Direct Thrombin Inhibitors

- Dabigatran (Pradaxa)-only FDA approved

- No monitoring (and no readily available monitoring method)
  PTT/Thrombin clotting time

- Half-life = ~15 hours (normal CrCl)
Dabigatran

- 2014

>150 units
Platelets, cryo, FVII

A Promising Drug With a Flaw

By KATIE THOMAS  NOV. 2, 2012

Dr. Bryan A. Cotton, a trauma surgeon in Houston, had not heard much about the new anticlotting drug Pradaxa other than the commercials he had seen during Sunday football games.
Idarucizumab (Praxbind)

- Hey guys! We found an antidote! (2015)
- Dose 5mg once IV
  - Of course comes in 2.5mg vials-so need 2.
- Works really well-near complete reversal at 1 hour
  - Costs $3500/dose
Factor Xa inhibitors

• “-Xaban’s”
  • rivaroxaban (Xarelto), apixaban (Eliquis), betrixaban (Bevyxxa), edoxaban (Savaysa)

• ROCKET-AF Trial

• “Don’t need to monitor”
Factor Xa inhibitors

• “-Xaban’s”
  • rivaroxaban (Xarelto), apixaban (Eliquis), betrixaban (Bevyxxa), edoxaban (Savaysa)

• First introduced in US in 2012

• Again-no reversal agent available
Factor Xa inhibitors

• All NOAC’s are not created equal!
  • Not cleared with dialysis
  • No reliable method for monitoring

• Rivaroxaban most common

• But, again, no antidote…..so PCC?
PCC for Xa inhibitor reversal

- Off label use-not FDA approved
- Typical dose-35u/kg empirically
  - 84% with hemostasis
  - Expensive
- Use 4F PCC as opposed to 3F PCC
Factor Xa inhibitors

- Not without risk

**Tolerability and effectiveness of 4-factor prothrombin complex concentrate (4F-PCC) for warfarin and non-warfarin reversals.**

Santibanez M, Lesch CA, Lin L, Berger K.

**RESULTS:** The final analysis included 212 patients. Primary reversal indication was major bleed in 165 patients (77.8%) and emergent surgery in 47 patients (22.2%). Thromboembolism occurred in 22 patients (10.4%), more in emergent surgery than major bleed reversals (17% and 8.5%, respectively). MTP and heart transplant patients had the highest thromboembolic event rates (44.4% and 28.6%, respectively). Hemostatic effectiveness was 65.8% (68% in major bleed and 58.1% in emergent surgery). DOAC patients achieved hemostasis most often (78.9%). Administration of any reversal agent, major surgery within 14 days, and MTP activation were significant predictors of thromboembolism.

44.4% DVT risk in patients who received MTP
Rivaroxaban/apixaban
andexanet alfa (Andexxa)

- Recombinant Factor Xa

- Has higher affinity for the Xa inhibitor drug, so keeps the native Xa receptors available to make clot

Greater than 90% return of Xa function

- Placebo bolus + 2hr infusion (n=8)
- ANDEXXA 400 mg bolus + 480 mg x 2hr infusion (n=23)
Andexanet alfa (Andexxa)

- Low dose
  - 400mg load followed by 4mg/min x 120 min

- High dose
  - 800mg load followed by 8mg/min x 120 min
Take-home points

• Aspirin—most doesn’t need reversal, platelets
• Plavix/etc—platelets, +/- desmopressin. P2Y12
• Heparins—protamine, follow Xa levels. +/- PCC
• Warfarin---FFP, Vit K, PCC if volume an issue.
• Pradaxa--- Praxbind, Praxbind, Praxbind.
• Xa inhibitor--Andexxa if you can, PCC #2 (35/kg)
Final Thoughts

• Counsel your patients on anticoagulants

• Ask your pharmacy if they carry reversal agents
  • Talk with your PCP providers

• A word about TXA
  • PATCH-Trauma
Thank you!

• Questions?

Bill Beck
wcbeck@uams.edu
@bill_bec