Reversal of Oral Anticoagulation in Critical Care

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Conflicts of Interest

- No conflicts to report
Objectives

- Understand impact of oral anticoagulants on “typical” coagulation assays
- Discuss anticoagulant antidotes, including prothrombin complex concentrate, idarucizumab, and andexanet alfa
- Implement bleeding management and reversal protocols in your hospital
Patient Case Examples

- **Case 1**
  - 72 y/o F fell down 6 stairs and hit her head at 1100. GCS 5 and intubated at the scene
  - Home meds include warfarin for Afib
  - INR 3.2 on arrival to ED
  - CT scan with large SDH

- **Case 2**
  - Same hypothetical patient, but now on rivaroxaban 20mg with dinner for Afib. Last dose likely take evening PTA, but unknown
  - INR 1.8 on arrival to ED - is this therapeutic? Is there enough in system to even worry about “reversing?”
Case 3

78 y/o M patient seen in ED at 1330 for a two day history of black, tarry stools and general feeling of malaise. Otherwise, patient AAO x 4.

Vitals include HR 95 NSR, BP 100/70, Tmax 37, and RR 22 on 2LNC (O2 sat 95%)

Labs include H/H 6.5/19.3 and a Scr of 0.78 mg/dL (eCrCL > 70 ml/min)

Home meds include dabigatran 150mg twice daily for a PE diagnosed 2 weeks PTA. Patient thinks last dose taken yesterday morning, but hasn’t felt well so didn’t take all meds.

Should he receive idarucizumab? Is there any dabigatran in patient’s system? What are the pros and cons of reversing this patient’s anticoagulation?
A couple disclaimers...

- I have no experience with ROTEM or TEG interpretation
  - Protocols I’ve helped develop do not use thromboelastograms, but theoretically this data may help make decisions

- I have no experience (or access) with more exotic coagulation assays
  - Example: Ecarin clotting time, dilute thrombin time, modified protime, drug specific assays

- In general, oral anticoagulant use IN critically ill patients isn’t a great idea
  - Typically, we convert to an IV or SC regimen (heparin or enoxaparin) until patient stable enough for transfer
Warfarin

- Patients are still on warfarin
  - DOAC use is on the rise
  - In Afib, DOAC use ~= warfarin use

- Now, probably the easiest bleeding complication to manage / reverse

- Monitored via INR
  - Goal of most reversal protocols is cessation of bleeding with an INR < ~ 1.5

Warfarin Bleeding Management

- INR value alone should not dictate reversal
  - INR < 6 and not bleeding - no reason to give vitamin K (any route) unless maybe going for procedure
  - INR > 6 and not bleeding - consider vitamin K, but keep it a LOW DOSE (5mg or less ORALLY x 1 dose)

- For emergency / life-threatening bleeding regardless of INR
  - Vitamin K INTRAVENOUSLY
  - 4fPCC (Kcentra®) alone or 3fPCC (Profilnine® / Bebulin®) + 2 - 4 units FFP

- Must always weigh risk of giving a procoagulant
  - Example: Femur fracture in a patient on warfarin with mechanical heart valve(s)

Vitamin K: The route matters!

- **SC**
  - The most ineffective, yet relatively common, route of administration
- **IV**
  - Most rapid
- **PO**
  - Equivalent to IV if rapid reversal not needed

Dzik W. Transfusion 2012; 52:45S
BUT!!!! IV Vitamin K = Anaphylaxis!

- Common misconception
- AnaphylactOID rxns related to Cremophor EL (solubilizing agent)
  - Incidence est 3 per 10,000 doses
  - Rate of administration or not diluting drug
- Rxns reported with SC and PO administration
- Recommendation: Don’t be afraid of IV vit K!
  - Dilute in IVF and run over 30 minutes

Dzik W. Transfusion 2012; 52: 455
Fiore LD. J Thromb Thrombolysis 2001; 11: 175
Rigert-Johnson DL, Volcheck GW. Ann Asthma Allergy Imm 2002; 89: 400
Prothrombin Complex Concentrate

- By now, every hospital is probably obligated to carry SOME form of PCC

- Four-factor PCC (4fPCC)
  - Contains measurable amounts of non-activated factor VII
  - Commercially available as Kcentra®
    - Kcentra® does contain small amounts of heparin, so theoretical concern with HIT
  - Only FDA approved medication for warfarin reversal

- Three-factor PCC (3fPCC)
  - Contains small / negligible amounts of non-activated factor VII
  - Typically given with small amounts of FFP (2 units or so) to make a complete product

- Activated PCC (aPCC)
  - 4fPCC with activated factors VII and X
3fPCC vs. 4fPCC

- No head-to-head comparisons
  - 2015 poster by group out of Wake Forest indicates similar outcomes

- 3fPCC does lack some FVII
  - INR highly dependent on FVII
  - Theoretically, 3fPCC is an “incomplete” product so must supplement with plasma

- 4fPCC compared to plasma and study excluded most severe bleeds (ICH w/ GCS < 7, etc.)
  - Did show better reversal of INR vs. plasma, but achievement of effective hemostasis non-inferior

- No matter what intervention chosen, MUST follow clinical exam and INR

Zane L, Reichert M. ACCP Annual Meeting - Poster #14
Other Considerations

- Correct hypocalcemia
  - Especially important for trauma patients / massive transfusion
  - Keep ionized calcium > ~ 1.0 mmol/L

- Correct acidosis and hypothermia
  - Clotting factors are proteins and need a near-physiologic level to work well
  - Hypothermic and acidic patients unlikely to benefit from factor replacement

- Consider TXA for trauma

- NovoSeven® (rFVIIa)?
  - Avoid except in refractory cases - most guidelines recommend AGAINST use
  - Increases risk of thrombotic events (especially in older patients)
  - Much more expensive with little benefit over other methods

Rosovsky RP, Crowther MA.  Hematology Am Soc Hem Educ Program 2008; 36
Morgenstern LB, et al.  Stroke 2010; 41: 2108
Dabigatran (Pradaxa®)

- First of the DOACs on US market
  - Oral direct thrombin inhibitor
- Initially for stroke prevention in Afib, now indicated for variety of thromboembolic issues
  - VTE prevention and treatment
- Highly dependent on renal clearance
  - Half-life out to 24+ hours in eCrCL < 30 ml/min
- First DOAC with an antidote
  - Idarucizumab
    - ~ $3500 a dose

Determining Dabigatran “Levels”

- Should have some objective tool to determine if dabigatran is playing a role in patient’s bleeding disorder
  - Patient may be on concomitant antiplatelets, etc.

- The “optimal” coagulation studies are often unavailable for most of us
  - Ecarin clotting time (ECT)
  - Dabigatran serum concentrations

- Conventional assays may help guide therapy
Coagulation Assays - aPTT

- Linear over therapeutic range, but plateau
- Low elevation at low end of therapeutic range
- aPTT ~ 1.5x or more than normal may indicate therapeutic dabigatran levels

Coagulation Assays - Thrombin Time

- Clot-based assay to directly measure thrombin activity
- MOST labs can run this test
  - If not done routinely, may take up to an hour
- Looking for a TT ratio (patient’s:normal) of > ~ 4 as low end of therapeutic
  - At THD, normal is ~ 18 seconds
  - Use 75 seconds as cutpoint for considering reversal

Managing Bleeding

- Charcoal, if overdose
  - Must be used within ~1 hour of overdose
- Stop/hold dabigatran and any other antiplatelet agents
  - Including fish oils and OTCs (like vitamin E)
- Local measures, if applicable
  - Mechanical compression
- Start IV fluids STAT
  - NS/LR
  - Maintain good UOP as drug is 80% renally excreted
- Basic resuscitation
- Check coagulation labs
- Consider idarucizumab
Idarucizumab (PraxBind®)

- Specific dabigatran mab
  - Binds dabigatran with affinity 350x that of thrombin
  - Binds free and thrombin bound dabigatran

- Approved in late 2015 for emergency dabigatran reversal
  - 5 gm dose for all patients - 2.5 gm x 2 IV pushes
  - ~ $3500 per dose
REVERSE-AD (NEJM 2015)

- N = 90 patients
  - Interim analysis
  - Group A = emergency bleeding issue -> 51 patients
    - Overt, uncontrollable, or life-threatening bleeding that would otherwise require reversal
  - Group B = emergency surgical issue -> 39 patients
    - Surgery that could not be delayed > 8 hours
- All patients received 5 grams of idarucizumab
  - 2.5 gm bolus infusions given no more than 15 minutes apart
- Primary endpoint
  - % reversal of anticoagulant effect

Pollack Jr CV, et al. NEJM 2015
Baseline characteristics
- > 90% dabigatran used for Afib
- ~ 15 hours since last dose to enrollment
- Median age ~ 77 years
- Median weight = 71.9kg (highest weight in study = 127.5 kg)

Types of bleeds
- ICH - 35%
- GI - 39%
- Trauma - 18%
- “Other” - 22% (not stated in text or supplement)
REVERSE-AD

- Primary outcome
  - Via dTT (68 of 90 patients)
    - Median maximal reversal = 100% (95% CI, 100 - 100)
    - Normalized in 98% (group A) and 93% (group B)
  - Via ECT (81 of 90 patients)
    - Median maximal reversal = 100%
    - Normalized in 89% (group A) and 88% (group B)
- Patients with “normal” results (N = 22)
  - Better renal function, longer time from last dose (30 hours vs. 13 hours)
  - Higher rates of ICH in these patients
REVERSE-AD

- Clinical outcomes
  - COMPLETELY subjective and not standardized
  - Group A (N = 51)
    - 3 had no bleeding assessment at baseline
    - 13 could did not have documented cessation of bleeding
    - Of remaining patients, investigator reported bleeding cessation at 11.4 hours
  - Group B (N = 39)
    - 36 evaluated for bleeding
    - 33/36 had “normal” hemostasis intra op

- Thrombotic events
  - 5 of 90 patients (5.6%)
    - Earliest was 2 days after idarucizumab, latest was 26 days after treatment
Idarucizumab

- **Does it “work?”**
  - It will neutralize dabigatran to an almost 90-100% degree
  - No signs of infusion reactions in Phase III studies (low immunogenicity)
  - Assessment of bleeding and effect on outcomes remains to be proven
    - Is it any better or worse than giving procoagulant products?

- **Concerns**
  - Still no way to monitor this drug as has been done in clinical trials
    - ECT and dTT aren’t done at 95%+ of institutions
    - Using aPTT and undilute TT at THD
  - Will the availability of an antidote drive providers to choose the wrong patient upfront?
    - Just prior to PraxBind® approval, saw at least 2 serious bleeding events at THD
  - What if patient continues to bleed despite idarucizumab??
Emergent Reversal of Pradaxa® (Dabigatran)

Background/Disclaimer: Despite potential INR elevations, there is NO role for vitamin K, unless patient was accidently on both dabigatran and warfarin. For overdose within last 1-2 hours, oral activated charcoal is highly effective. The both dabigatran and idarucizumab-bound dabigatran are renally excreted, so maintenance of urine output is important.

Initial Laboratory Testing (STAT)
1. Activated Partial Thromboplastin Time (aPTT)
2. Thrombin Time (TT)
3. CBC
4. CMP (specifically for serum creatinine)
5. Fibrinogen
6. Ionized calcium (point of care)

1. Indications for Initiating This Order Set (All Criteria Must be Met)
   1. Patient currently taking dabigatran (attempt to obtain last time dose was taken/ administered)
   2. Either criterion a or b
      a. Life-threatening or critical-site bleeding event requiring immediate hemostasis, such as:
         i. Intracranial hemorrhage
         ii. Retroperitoneal hemorrhage
         iii. Intraocular hemorrhage
         iv. Hemopericardium
         v. Massive GI bleed
      b. Emergent surgery (within next 8 hours) with high potential for substantial blood loss, such as:
         i. Hip fracture
         ii. Neurosurgical intervention
         iii. Coronary artery bypass grafting
   3. Either aPTT > 40 seconds or TT > 75 seconds (TT ratio >4) (especially important if unknown when last dose taken/administered)

General Supportive Measures
1. Packed red blood cells as needed
2. Cryoprecipitate if fibrinogen < 150 mg/dL
3. Keep patient normothermic and non-acidotic – administer sodium bicarbonate 50-100 meq if needed
4. Calcium gluconate 2gm IVPB over 15 minutes if ionized calcium < 1.0
5. Consider - Platelet transfusion if platelets < 75,000/ml or on concomitant antiplatelet agents

Therapy for Life-Threatening Bleeding / Emergency Surgery with High Bleeding Potential

*** IMMEDIATELY CALL PHARMACY ***

Normal saline 20-30 ml/kg IV bolus x 1
PraxBind® (Idarucizumab) 2.5 gram slow IVP x 2 (total dose = 5 gram)

Monitoring Response
PraxBind® promptly reverses coagulation assay abnormalities, but the clinical effects on bleeding are not well studied. Continue to monitor patient for uncontrolled bleeding.

1. If continued uncontrolled bleeding > 30 minutes after PraxBind® administration:
   a. Correct acidosis, hypothermia, and hypocalcemia
   b. Replace other blood components (fibrinogen, platelets, etc)
   c. Consider FEIBA® 15 units/kg (max 1500 units) x 1 dose ** FEIBA MAY CAUSE THROMBOSIS – ONLY GIVE AS LAST LINE IF UNCONTROLLED, LIFE-THREATENING BLEEDING **
2. Continued bleeding despite procoagulants, consider emergency nephrology for hemodialysis
Oral Xa Inhibitors

- Rivaroxaban, apixaban, edoxaban, and betrixaban

- All have different dosing, frequencies, indications, and pharmacokinetics
  - In general, mostly metabolized by liver with some renal involvement
  - Most have moderate to high protein binding (so non-dialyzable)
  - Half-lives and duration of action HIGHLY variable
    - Betrixaban - duration > 72 hours w/ up to 27 hour half-life
    - Rivaroxaban - duration ~ 24-36 hours w/ up to 13 hour half-life

- This makes a one-size fits all antidote very difficult!!
Oral Xa Inhibitor Coagulation Assays

- Most institutions don’t have drug specific assays
- Some oral Xa’s prolong protime with little to no effect on aPTT
- ALL of the agents will prolong anti-Xa level
  - Even without a drug specific calibration, WILL see prolongation of anti-Xa level

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anti-Xa</th>
<th>aPTT</th>
<th>PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Strong effect</td>
<td>Minor effect</td>
<td>Moderate effect</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Strong effect</td>
<td>Little to no effect</td>
<td>Minor to little or no effect</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Strong effect</td>
<td>Minor to little or no effect</td>
<td>Minor effect</td>
</tr>
</tbody>
</table>

*aPTT = activated partial thromboplastin time, PT = prothrombin time.

Faust AC, et al. AJHP 2016
Andexanet Alfa

- Not currently FDA approved
  - Owned by Portola Pharmaceuticals
  - Pursuing accelerated approval through FDA as an orphan drug
    - Initially was rejected
    - Resubmission for Feb 2018 pending
- Acts as a dummy Factor Xa protein
  - Xa inhibitors have higher affinity for this dummy protein than native Xa
  - Binds ALL Xa inhibitors, including enoxaparin
- Dosing is complicated, as all Xa inhibitors have different pharmacokinetic properties
  - Protein binding, volume of distribution, half-life, etc.
Older, healthy patients given either rivaroxaban 20mg/day or apixaban 5mg BID x 3.5 days

- Age 50 - 75 years old
- Essentially NO concomitant medical conditions (especially no reasons for anticoagulants)

3 hours after the last dose of apix or riva, given study drug

- Regimen 1: Bolus only
  - 400mg for apixaban
  - 800 mg for rivaroxaban
- Regimen 2: Bolus + infusion
  - 400mg then 4mg/min x 120 minutes for apixaban
  - 800 mg then 8 mg/min x 120 minutes for rivaroxaban
**ANNEXA Studies**

- **N = 101 healthy volunteers**
- **Results (in summary)**
  - Andexanet reduces anti-Xa activity, thus reversing anticoagulant effect
  - Bolus + infusion suppresses anti-Xa activity longer
  - Anti-Xa activity increases back to placebo level once infusion stopped
    - May actually OVERSHOOT with rivaroxaban
  - No assessment on bleeding
  - No assessment on thrombotic events
- **Essentially, this was a glorified phase II study published in NEJM**
  - No one got hurt, but we don’t know how the drug works in real life scenarios

Siegal, et al. NEJM 2015
67 patients who presented with major bleeding within 18 hours of taking a Xa inhibitor (including enoxaparin)

- Only 47 patients clinically evaluable
- Majority on rivaroxaban (median daily dose 20mg/day) or apixaban (median daily dose 5mg), with a few on enoxaparin

Andexanet dosing

- If on apixaban or rivaroxaban (taken > 7 hours ago): 400 mg x1, then 4mg/min x 2 hours
- If on enoxaparin, edoxaban, or rivaroxaban (taken < 7 hours ago): 800 mg x 1, then 8 mg/min x 2 hours

Outcomes

- Reversal of anticoagulant effect
- Cessation of bleeding (independent review)

Connolly SJ, et al. NEJM 2016
Effect of andexanet on anti-Xa levels

Rivaroxaban
- Anti-Xa activity reduced by 89% (277 ng/mL to 16.8 ng/mL)
- Increased back to 177.7 ng/mL at 4 hours post-infusion

Apixaban
- Anti-Xa activity reduced by 93% (149.7 ng/mL to 10.3 ng/mL)
- Increased back to 103 ng/mL at 4 hours post-infusion

Clinical outcomes
- 37 of 47 patients judged to have excellent or good hemostasis by independent review committee
  - 20 patients with ICH = 80% excellent or good hemostasis (95% CI, 56 - 94%)
  - 25 patients with GIB = 84% excellent or good hemostasis (95% CI, 64-96%)

Safety
- No infusion reactions
- 12 patients developed thrombotic complications
  - 4 within 3 days of treatment
Andexanet alfa

- Reduces anti-Xa level
- Appears to have good effect on hemostasis
- High rates of thrombotic events
- Complicated dosing regimens
  - Do we always know time of last dose?
- Not yet FDA approved
PCC

- Eerenberg, et al. (Circ 2011)
  - Riva 20mg BID (higher than any studied dose)
  - Young, healthy volunteers
  - PT normalized w/ PCC (50 units/kg 4-factor product)
**PCC**

- **Rat Model (2009)**
  - Rats given 2 mg/kg riva IV
    - BT and PT prolonged
  - Cut, then given 25 u/kg, 50 u/kg PCC or placebo
    - 25 u/kg: Little change in BT (data on PT and thrombin generation not shown)
    - 50 u/kg: Normalization of BT, little change on PT, increase in thrombin generation

- Not sure if rat dose = human dose??
- PT does NOT = BT

*Perzborn E, et al. ISTH 2009 abstract*
PCC for Oral Xa Inhibitors

- Check anti-Xa level and attempt to ascertain last dose
  - If anti-Xa level < ~ 0.3, nothing left to reverse
  - If 0.3 - 0.8 or so, similar to a “subtherapeutic” INR
  - Typical goal range with oral Xa’s is 2.0 - 3.0

- Case series of 3 SDH’s at THD
  - Received 25 - 35 units/kg of 3fPCC + 1-3 units of plasma

- Given lack of currently available antidote, PCC is about the best we have to offer

Emergent Reversal of Oral Xa Inhibitors (Apixaban, Rivaroxaban, etc.)

Background/Disclaimer: Apixaban and rivaroxaban are oral direct factor Xa inhibitors currently indicated for stroke/embolism prevention and treatment. There are no current direct antidotes for these drugs, and, due to high protein binding, dialysis is not effective in removal. Despite elevations in INR, Vitamin K is NOT effective in reversal and should not be used. There are no data on oral charcoal for overdose situations, but may be reasonable if overdose within 2 hours.

I. Initial Laboratory Testing
   1. Prothrombin Time (PT)
   2. Anti-Xa level
   3. CBC
   4. CMP (specifically for serum creatinine)
   5. Fibrinogen

II. Indications for Initiating This Order Set (All Criteria Must be Met)
   1. Patient currently taking apixaban (last dose should have been within last 24 hours. If elderly, may extend to 48 hours)
   2. Either criterion a or b
      a. Life-threatening or critical-site bleeding event requiring immediate hemostasis, such as:
         i. Intracranial hemorrhage
         ii. Retroperitoneal hemorrhage
         iii. Intracocular hemorrhage
         iv. Hemopericardium
         v. Massive GI bleed
      b. Emergent surgery with need for immediate hemostasis, such as:
         i. Hip fracture
         ii. Neurosurgical intervention
         iii. Coronary artery bypass grafting
   3. If unsure of last dose: Order PT and anti-Xa level. If either is abnormally elevated, indicates some drug activity remaining in system

III. Therapeutics
   1. Stop all anticoagulants and antiplatelets
   2. Normal saline or LR infusion to maintain adequate urine output
   3. Packed red blood cells as needed
   4. Cryoprecipitate for fibrinogen < 150 mg/dL
   5. Consider platelet transfusions for concomitant antiplatelet agents
   6. Profinine® (PCC) 35 units/kg (max 2500 units) + 2-4 units of FFP

IV. Monitoring Response
   PCC reversal of bleeding may not be reflected in a reduction in coagulation assays. Coagulation assays confirm presence of anticoagulant, but are not as helpful to guide therapy
   1. Consider hematology consult to assist in repeat dosing of pro-coagulants
      a. If continued bleeding, give another 15 units/kg PCC + 2 units FFP pending consult
      b. If low risk for thrombotic complications, use FEIBA® (activated PCC) 25 units/kg in place of PCC + FFP
   2. Repeat PT 30 minutes after end of PCC + FFP infusion
   3. CBC for monitoring continued bleeding
   4. Frequent neuro checks if ICH

Summary

Always weigh pros and cons of giving procoagulant products
  - They are not without risk!!

Check coagulation assays
  - You don’t need fancy assays - most hospitals can check protime, aPTT, TT, and probably anti-Xa

Use available antidotes and pharmacological bleeding management strategies
  - But don’t forget to correct things like hypocalcemia, acidosis, and hypothermia

Use clinical exam to guide bleeding cessation and redosing issues
THANKS!!!  Questions?