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Session Title: Reversing Life-Threatening Anticoagulant Hemorrhage

Objectives

- Interpret practical laboratory values helpful for evaluating degree of anticoagulation in the acute care setting
- Describe the clinical pharmacology of available anticoagulants and reversal agents
- Evaluate potential agents and strategies for reversal of anticoagulants including warfarin, direct thrombin inhibitors, and direct factor Xa inhibitors

General Strategy: Step 1 - D/C the drug; Step 2 - Antidote; Step 3 - Factor Replacement; Step 4 - Adjunctive therapy

Recommended Readings

1. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage (Frontera 2016)
2. Laboratory testing in patients treated with DOACs: a practical guide for clinicians (Douxfils 2018)
3. An update on laboratory assessment for DOACs (Gosselin 2019)
4. ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants (Tomaselli 2020)
    a. ACC Consensus on Management of Anticoagulant-Related Bleeding: Key Points (Barnes 2020)

Direct Thrombin Inhibitors

1. Step 1 - D/C the drug
2. Step 2 - Antidote: Idarucizumab 5 gm
    a. Idarucizumab first studied in 110 healthy male volunteers 18-45 yrs (Glund 2015)
        i. No effect on coagulation/endogenous thrombin potential (ETP) in absence of dabigatran
    b. Randomized, placebo-controlled, double-blind phase I study to assess safety, tolerability, and efficacy of idarucizumab on reversal of dabigatran-induced anticoagulation (Glund 2015)
    c. REVERSal Effects of Idarucizumab in Patients on Active Dabigatran (RE-VERSE AD™)
        i. Methodology for prospective, phase 3 trial (Pollack 2015)
        ii. Full trial published in 2017 (Pollack 2017)
            1. 503 patients (301 in Group A and 202 in Group B)
            2. Primary outcome: maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after administration of idarucizumab
            3. No control group
            4. Authors reported almost universal and complete binding of dabigatran as evidence by minimal unbound dabigatran concentrations after idarucizumab
            5. 9 patients required more than the 5 gm dose of idarucizumab
            6. 10% of patients in the full cohort had no laboratory evidence of dabigatran's presence prior to administration of idarucizumab (normal ECT and/or dTT).
            7. Large discrepancy between clinically relevant bleeding cessation times in the interim (11.4 hrs) versus full analyses (2.5 hrs).
                a. It seems in the full analysis, >55% of Group A were excluded from time-to-bleeding assessment. Reasons for exclusion included no cessation of bleeding within 24 hours or the bleeding location could not be identified. This change in reporting favors idarucizumab.
    d. Though idarucizumab reverses lab markers of dabigatran, it does not repair the damaged vessel. Cases of sustained bleeding after idarucizumab have been reported (Alhashem 2017; Steele 2018)

   e. Approved 5 gm dose may not be sufficient in all cases, particularly in patients with renal failure who are unable to clear dabigatran. (Simon 2017)
   f. Impaired renal function associated with increased exposure/decreased clearance of idarucizumab; dabigatran also cleared more slowly with decreased renal function (Glund 2017, Eikelboom 2019)
3. Step 3 - Factor Replacement
   a. If idarucizumab is unavailable activated prothrombin complex concentrate (aPCC) or four factor prothrombin complex concentrate (4F-PCC) (Tomaselli 2020)
4. Step 4 - Adjunctive therapy
   a. Charcoal
      i. Consider for known recent ingestion within 2-4 hours (Tomaselli 2020)
   b. HD/CVVH
      i. Intermittent HD removes dabigatran effectively but is not always feasible in a hemodynamically unstable patient (Liesenfeld 2016).
         1. Rebound in dabigatran concentration may occur upon cessation of HD. (Chai-Adisaksopha 2015)
      ii. CVVHD does not reach comparable elimination rates and is not fast enough to prepare for urgent interventions in patients with high bleeding risks.
      iii. Rebound dabigatran concentrations are reported after idarucizumab administration in the setting of severe renal failure. (Stecher 2017, Eikelboom 2019)

Factor Xa Inhibitors

1. Step 1 - D/C the drug
2. Step 2 - Antidote
   a. Andexanet alfa is a modified recombinant human factor Xa decoy protein that sequesters factor Xa inhibitors to restore endogenous FXa activity.
   b. In two randomized, double-blind, placebo-controlled parallel trials of healthy volunteers, ANNEXA-A and ANNEXA-R evaluated adults aged 50-75 years assigned apixaban or rivaroxaban, respectively. (Siegal 2015)
      i. Subjects were given andexanet as either bolus only (400 mg for apixaban/800 mg for rivaroxaban) or bolus plus a 120-minute infusion (4 mg/min for apixaban or 8 mg/min for rivaroxaban).
      ii. Andexanet decreased anti-FXa activity in both apixaban and rivaroxaban compared with placebo regardless of bolus and/or infusion regimen ($p < 0.001$) for up to 2 hours
      iii. No serious adverse events reported, though andexanet recipients did have non-neutralizing antibody development (17% compared with 2% placebo).
      iv. Funded by Portola Pharmaceuticals (maker of andexanet)
   c. ANNEXA-4 was multicenter, prospective, open-label, single-group study of patients with acute major bleeding (Connolly 2019)
      i. REBEL EM has a full summary and analysis of the trial
      ii. 352 patients with acute major bleeding who had received apixaban, rivaroxaban, edoxaban, or enoxaparin within 18 hours of enrollment
      iii. Bleeding locations were GI (64%), intracranial (26%), and other (10%)
      iv. Anti-FXa activity decreased in pts on rivaroxaban after andexanet bolus (92%, 95% CI 88-94%) and returned to 70% of baseline by 4 hours
      v. Anti-FXa activity decreased in pts on apixaban after andexanet bolus (93%, 95% CI 87-94%) and infusion (92%, 95% CI 91-93%) and returned to 60% of baseline by 4 hours
      vi. Efficacy Outcomes (254 patients):

1. 204 (82%) “excellent” or “good” hemostatic efficacy at 12 hours (95% CI 77 – 87)
    a. GIB – 85% (95% CI 76 – 94)
    b. ICH – 80% (95% CI 74 – 86)
2. Safety Outcomes:
    a. Death within 30 days occurred in 49 patients (14%)
    b. Thrombotic events occurred in 34 patients (10%)

vii. No control group
viii. Funded by Portola Pharmaceuticals

3. Step 3 - Factor Replacement
    a. Many hospitals use 4F-PCC in place of Andexxa
    b. SR and MA found no difference between the two treatments, though the quality of trials is low (Nederpelt 2021, Jaspers 2021)
    c. After 4F-PCC, thrombin generation was 76% higher than placebo at 30 min and 24% higher at 24 hrs (Nagella 2016)
    d. ACC recommends andexanet alfa as first-line, but if not available can administer 4F-PCC or aPCC (Tomaselli 2020)
4. Step 4 - Adjunctive therapy
    a. Charcoal
        i. Effective at reducing rivaroxaban absorption at least 8 hours post-dose (Ollier 2017)
        ii. Probably not helpful in GI bleeding, patient already has life-threatening bleeding
        iii. May consider if patient overdoses and presents to hospital within the following 8+ hours

Warfarin

1. Step 1 - D/C the drug
2. Step 2 - Antidote
    a. Vitamin K (phytonadione) remains a mainstay of treatment for reversing warfarin.
    b. Vitamin K effects delayed (even IV); initial INR reduction with IV takes 6 to 8 hours (Kalus 2013)
    c. Vit K alone is not sufficient for rapid reversal; ICH pts at risk of experiencing hematoma expansion early on after the initial bleed. (Brott 1997; Kazui 1996; Huttner 2006)
    d. Recommended dose/route: 5-10 mg IV (Hemphill 2015; Holbrook 2012)
    e. Infusion rate should not exceed 1 mg/minute to minimize the risk of anaphylactoid reactions; many institutions dilute a 10 mg IV vitamin K dose in 50 or 100 mL of 0.9% sodium chloride.
    f. Oral onset time is too long in emergent cases, subcutaneous associated with erratic and unpredictable absorption, and IM may cause bleeding and hematoma formation at the injection site. (Lubetsky 2003; Crowther 2002; Watson 2001)
3. Step 3 - Factor Replacement
    a. Four-Factor Prothrombin Complex Concentrate (4F-PCC)
        i. Recommended by ACC (Tomaselli 2020) - INR 2-4: 25 units/kg, INR 4-6: 35 units/kg, INR >6: 50 units/kg
        ii. Available in Europe since 1996; approved in U.S. in 2013; contains concentrated source of inactivated coagulation factors II, VII, IX, and X
            1. Faster INR reversal compared to FFP (Goldstein 2015; Sarode 2013)
            2. Package insert dosing of 4F-PCC for urgent VKA reversal recommends 25-50 units/kg of factor IX (maximum weight of 100 kg) based on the patient’s body weight and INR
            3. Concomitant IV vitamin K 5-10 mg to maintain coagulation factor levels to prevent a rebound INR elevation (Sin 2016)
            4. Currently no robust safety/effectiveness evidence of repeat 4F-PCC dosing

5. If INR ≥1.4 after 4F-PCC, consider further correction with FFP (Frontera 2016)

iii. 4F-PCC vs. FFP (Sarode 2013)
1. 202 patients randomized to receive 25-50 units/kg of 4F-PCC (n=98) or 10-15 mL/kg of FFP (n=104) for urgent VKA reversal in acute major bleeding
2. At 30 minutes after infusion, 4F-PCC was deemed superior to FFP in achieving an INR ≤1.3 (62.2% versus 9.6%; difference, 52.6%; 95% CI, 39.4 to 65.9)

iv. 4F-PCC vs. FFP (Steiner 2016) - INCH trial
1. Randomized trial comparing 30 units/kg of 4F-PCC (n=27) with 20 mL/kg of FFP (n=23) for VKA reversal specifically in patients with ICH
2. At 3 hours after start of treatment, more patients in 4F-PCC group achieved INR ≤1.2 when compared to the FFP group (66.7% versus 8.7%; OR, 30.6; 95% CI, 4.7 to 197.9).
3. At 3 hours, mean hematoma expansion was lower in the 4F-PCC group (9.7 mL versus 23.7 mL; difference, 16.9 mL; 95% CI, 2.5 to 31.3).
4. 5 deaths due to hematoma expansion within 48 hours of treatment (all FFP)

v. Pooled data from an international registry found equivalent adjusted risk of mortality in ICH patients who received either a 3- or 4-factor PCC (n=585) versus FFP (n=377) alone (Parry-Jones 2015)

vi. Multicenter retrospective cohort study of spontaneous ICH patients associated with VKA use (n=1176) found achievement of INR <1.3 within 4 hours was associated with lower rates of hematoma expansion (OR, 0.27; 95% CI, 0.15 to 0.43) (Kuramatsu 2015)

vii. Fixed dosing (not validated in large clinical trials)
1. Recommended by ACC (1000 units for non-ICH, 1500 units for ICH) (Tomaselli 2020)
2. Proposed benefits include cost-savings and minimizing delays. (Gorlin 2017)
3. Doses of 1000, 1500, or 2000 units effective at INR correction. (Klein 2015; Hirri 2014; Khorsand 2012; Khorsand 2011; Varga 2013; Fuh 2020)
4. One study in patients with intracranial bleeding demonstrated a fixed dosing strategy of 1000 units was not as effective in achieving an INR ≤1.5. (Abdoellakhan 2017)
5. Fixed weight-based doses of 25 units/kg and 30 units/kg may be effective. (Appleby 2017; Steiner 2016)

b. Fresh Frozen Plasma (FFP)
i. FFP recommended if 4F-PCC not available at 10-15 mL/kg (Frontera 2016; Tomaselli 2020)
ii. FFP provides exogenous source of all clotting factors and proteins found in blood
iii. FFP risks: transfusion-related acute lung injury, infusion reactions, hypocalcemia, infectious complications, and transfusion-associated circulatory overload. (Pandey 2012)
iv. INR of FFP estimated at 1.6; difficult for FFP alone to decrease patient's INR to ≤1.5
v. Administration takes up to several hours in standard clinical practice
vi. Concomitant vitamin K administration critical to correct INR
vii. FFP's utility further limited due to potential procurement delays (e.g., checking for blood compatibility, thawing) (Lee 2006; Goldstein 2006)

c. Other Concentrated Coagulation Factor Products
i. 3F-PCC, activated prothrombin complex concentrate (aPCC), and recombinant activated factor VII (rFVIIa) not currently FDA approved for this indication.
ii. rFVIIa not recommended; aPCC and 3F-PCC have limited data and should only be considered in absence of 4F-PCC availability

4. Step 4 - Adjunctive therapy
a. Not many adjunctive options for warfarin reversal