Reversing Medications That Cause Bleeding

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The Agony and The Ecstasy of Platelets and Clotting

- The Ecstasy
  - We can change how people clot
  - We can prevent strokes
  - We can prevent DVT and PE
  - We can improve cardiac outcomes in ACS

- The Agony
  - Variable efficacy
  - Narrow therapeutic index
  - Potential drug / food interactions
  - Need for monitoring
  - Bleed risk
  - Antidotes and reversibility

Newer is Better... Right?

- Depends on what color glasses you are looking through...
  - As a cardiologist?
  - As a neurologist?
  - As an emergency physician?
  - Or... as a patient?

Issues with the New Agents

- For emergency practitioners
  - Can we measure their activity if we need to?
  - Can we reverse their effects in cases of bleeding requiring emergency care?
Will NOT cover
- Dalteparin (Fragmin)
- Fondaparinux (Arixtra)

Antiplatelet Agents
Aspirin
- Tried and true
- Poisons platelet for life of the platelet
  - 5-10 days
- Can reverse with (and/or)
  - Platelet concentrate
  - DDAVP (0.3-0.4 µg/kg)
  - Reversal in 15-30 minutes

Antiplatelet Agents
Clopidigrel and Prasugrel
- Thienopyridine derivatives
- Block ADP receptor on platelet
- Can be effectively combined with aspirin in some cases
- Increases bleeding risk significantly
  - Therefore, in some cases the combination overall is not worth the risk

Antiplatelet Agents
Clopidigrel and Prasugrel
- Clopidigrel (Plavix®) vs. Prasugrel (Effient®)
  - Prasugrel has stronger antiplatelet effect
  - In general
    - More effective than clopidigrel
    - More major bleeding events than clopidigrel

Antiplatelet Agents
Clopidigrel and Prasugrel
- Can reverse with (and/or)
  - Platelet concentrate (15-30 minutes)
  - Maybe add DDAVP (0.3-0.4 µg/kg)
  - Reversal in 15-30 minutes

Anticoagulants
Heparin
Anticoagulants

Heparin

- Binds to antithrombin
- Potentiates inhibition of thrombin and factor Xa (by 1000-fold)
- Half-life of 60-90 minutes

Anticoagulants

Heparin

- If stopped, hemostasis restored in 3-4 hr
- Reversed with protamine sulfate
  - Dosing is 1 mg protamine per 100 units heparin given in last 2-3 hours
    - Usually 25-30 mg effective
    - Maximum dose 50 mg
    - Half-life 10 minutes
  - Reversal is immediate
  - May cause allergic reaction

Anticoagulants

Low Molecular Weight Heparin

- Low dose vs. high dose have differing half-lives
- Both, however, last longer than regular unfractionated IV heparin

Anticoagulants

Low Molecular Weight Heparin

- If stopped, hemostasis restored in 12-24 hours
- Partially reversed by protamine sulfate
  - 1 mg protamine per 100 units LMWH given in the last 8 hours
    - Maximum dose 50 mg
    - Half-life 10 minutes; infusion may be needed
  - Reversal, when effective, is immediate

Anticoagulants

Vitamin K Antagonists
Anticoagulants
Vit K Antagonists: Warfarin
- Long experience with its use
- Blocks production of vitamin K dependent coagulation factors (II, VII, IX, X)
  - Induces a factor deficiency state
  - Means we may be able to replace these factors to reverse it
- Risk of major bleeding 0.5% per year
- Risk of ICH is 0.2% per year

Anticoagulants
Vit K Antagonists: Warfarin
- Risk of bleeding directly related to height of INR
  - Over 3.0, incidence doubles when compared to INR of 2.0-3.0
- Risk of bleeding increases with co-administration of antiplatelet agents
- Elderly have two-fold increased risk of ICH

What is a PCC?
- Prothrombin Complex Concentrate
  - Briplex, Octaplex – 4 factors
  - Profilnine, Bebulin – 3 factors
  - Contain multiple factors, including prothrombin
  - Have more prothrombin than FFP

Anticoagulants
Factor Xa Inhibitors
The “xabans”
Anticoagulants
Factor Xa Inhibitors
- The “xabans”
  - Rivaroxaban – Xarelto® (approved 7/11/11)
  - Apixaban – Eliquis® (approved 12/30/12)
  - Dabigatran

Anticoagulants
Factor Xa Inhibitors
- Rivaroxaban – Xarelto® (approved 7/11/11)
  - Surgical DVT prophylaxis
  - Stroke prevention in nonvalvular AF
  - DVT/PE treatment
  - ACS coming down the pike?
- Apixaban – Eliquis® (approved 12/30/12)
  - Stroke prevention in nonvalvular AF
- Edoxaban - Lixiana®

Anticoagulants
Factor Xa Inhibitors
- The “xabans”
  - Rivaroxaban – Xarelto®
    - Half-life 5-13 hours
  - Apixaban – Eliquis®
    - Half-life 9-14 hours
  - Edoxaban - Lixiana®
    - Half-life 9-10 hours

Anticoagulants
Factor Xa Inhibitors
- Reversal in bleeding
  - Cessation of medication will reverse anticoagulant effect
    - How long it takes depends on half-life
  - Immediate reversal
    - No antidotes found to date
    - Factor Xa inhibitor antidotes would be useful, being investigated but not available to date

Anticoagulants
Factor Xa Inhibitors
- General efficacy / safety data (so far)
  - Compared with LMWH (DVT prophylaxis)
    - Lower bleeding risk
    - Similar efficacy
  - Compared with warfarin (stroke in AF)
    - Noninferior to warfarin
    - Lower rate of bleeding (2.1 % vs 3%)
Anticoagulants
Direct Thrombin Inhibitors

- Hirudin was prototype (leech spit)
- Dabigatran - Pradaxa ® (appr. Oct 2010)
- Competitive, direct thrombin inhibitor
- Approved for
  - Stroke prevention in A Fib (2010)
  - DVT prophylaxis after surgery
  - (ACS coming soon?)
- Half-life 12-17 hours

Anticoagulants
Direct Thrombin (IIa) Inhibitors

- Dabigatran - Pradaxa ®
- Benefits over warfarin
  - Anticoagulation immediate
  - No transient hypercoagulable state
  - Does not require blood testing to monitor
  - Minimal interactions with food/drugs
- Not recommended in renal failure or in patients with impaired hepatic function

Anticoagulants
Direct Thrombin (IIa) Inhibitors

- Issues for emergencies
  - Cannot follow blood testing for anticoagulation effect (non-linear effect)
  - Coagulation studies are elevated, but do not correlate with bleeding risk

(Note: These rates were in trials; we'll see what happens in the "real world")
Anticoagulants

**Direct Thrombin (IIa) Inhibitors**

- **Issues for emergencies**
  - Treatment of bleeding
  - Activating thrombin
- **Supportive care**
  - pRBCs, IV fluids, stopping bleeding by direct means
- **Removing dabigatran**
  - Not highly protein bound
  - 4 hours of dialysis removes 68% of dabigatran

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**Time to hemostasis after stopping taking medication**

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Time to reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>3-4 hr Prothrombin</td>
</tr>
<tr>
<td>LMW Heparin</td>
<td>12-24 hr Prothrombin (partial)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>24-30 hr Recomb Vila</td>
</tr>
<tr>
<td>Fondaparinux (intravenous)</td>
<td>5-15k Recomb Vila</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>60-80 hr Vit K IV</td>
</tr>
<tr>
<td>Aminoglycosides (oral)</td>
<td>12-16 hr Vit K oral PCCs</td>
</tr>
<tr>
<td>Oral thrombin and factor Xa inhibitors</td>
<td>Usually within 12 hr Recomb fact Xa Thrombin???</td>
</tr>
<tr>
<td>Aspirin</td>
<td>5-10 days DDAVP, platelets</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1-2 days Platelets, maybe DDAVP</td>
</tr>
</tbody>
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**Thank You For Your Attention!**

Any Questions?