Effects of New Oral Anticoagulants on Measures of Anticoagulation

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Objectives
1. Describe the mechanisms of action of the new anticoagulants and their effects on the clotting cascade.
2. Discuss the parts of the clotting cascade that are measured in standard laboratory tests used to assess anticoagulation.
3. Interpret effects of the new anticoagulants on laboratory test and used to assess anticoagulation.

New Oral Anticoagulants
- Dabigatran, and Rivaroxaban both recently on the market
- Apixaban NDA application (FDA review June 2012)
- Rates of major hemorrhage and intracranial hemorrhage are similar to or superior to warfarin
- Lack of specific reversal agents and monitoring parameters is a concern in the milieu of hemorrhagic emergency

Factor Xa and IIa Inhibitors
- Two classes of Factor IIa and Xa inhibitors
  - Indirect, Anti-thrombin-III (ATIII) dependent
    - Catalytic
    - Irreversible ATIII-mediated inhibition of factors IIa and Xa
    - Inhibits only free factor
  - Direct (Non-ATIII-dependent)
    - Stoichiometric
    - Specific and reversible inhibition of a single factor
    - Inhibit both free factor and bound factor

Factor Xa Inhibitors
- Indirect ATIII-dependent inhibitors
  - Unfractionated Heparin
  - LMWHs
    - Enoxaparin
    - Dalteparin
    - Tinzaparin
    - Pentasaccharides
      - Fondaparinux

- Direct Xa Inhibitors
  - Apixaban (Eliquis®)
  - Rivaroxaban (Xarelto®)
  - DU176b Edoxaban

Vitamin K Antagonists (VKAs)
- Warfarin

Factor IIa Inhibitors
- Direct IIa Inhibitors
  - Lepirudin
  - Bivalirudin
  - Argatroban
  - Dabigatran (Pradaxa®)
  - Ximelagatran

Vitamin K Antagonists (VKAs)
- Warfarin
Secondary hemostasis. Ca²⁺ = calcium; fibrinogen is Factor I; PL = phospholipid surface; prothrombin is Factor II.

Warfarin

LMWH's

Fondaparinux

Heparin

Tests Used to Measure Anticoagulant

<table>
<thead>
<tr>
<th>PT/INR</th>
<th>aPTT</th>
<th>TT</th>
<th>ECT</th>
<th>aPTT</th>
<th>HepTest</th>
<th>PICT</th>
<th>Chromogenic Assay*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors</td>
<td>II, VII, X</td>
<td>II, VII, X</td>
<td>II</td>
<td>II</td>
<td>II, V, VIII, X, X, X, XI</td>
<td>X</td>
<td>X, V</td>
</tr>
<tr>
<td>Units</td>
<td>Seconds</td>
<td>Seconds</td>
<td>Seconds</td>
<td>Seconds</td>
<td>Seconds</td>
<td>Seconds</td>
<td>Specific Activity</td>
</tr>
<tr>
<td>Uses</td>
<td>Warfarin</td>
<td>Input = antithrombin</td>
<td>LMH</td>
<td>LMH</td>
<td>LMH, LMWAF</td>
<td>LMH, LMWAF, LMH, LMWAF</td>
<td>LMH, LMWAF, LMH, LMWAF</td>
</tr>
</tbody>
</table>

*Anti-Xa assay is commonly available, anti-IIa is not widely available.

PT = prothrombin time; aPTT = dilute prothrombin time; TT = thrombin time; ECT = ecarin clotting time; aPTT = activated partial thromboplastin time; PICT = Prothrombinase induced clotting time

Decreased levels of VIIa, IXa, Xa, and IIa

Warfarin

LMWH's

Fondaparinux

Heparin

Rivaroxaban, Apixaban

Decreased Xa activity

Dabigatran

Decreased Thrombin activity

Prothrombin Time [PT], International Normalized Ratio [INR]
Effects on PT/INR

- Dabigatran
  - Causes PT/INR elevations
  - False elevations of INR have been reported
  - Relatively insensitive and variable
  - We do not yet know what INR elevations mean in relation to levels of anticoagulation with Dabigatran
  - Has not proven useful in hemorrhagic emergencies
- Rivaroxaban
  - Prolongs PT in a concentration dependent fashion
  - Only has a weak effect at therapeutic concentrations, more profound at higher concentrations
  - Converting to INR appears to increase variability of results
  - May be useful in hemorrhagic emergencies
- Apixaban
  - Prolongs PT in a concentration dependent fashion
  - Converting to INR appears to increase variability of results
  - May be useful in hemorrhagic emergencies

Effects on aPTT

- Dabigatran
  - aPTT more sensitive and less variable than PT
  - Supratherapeutic doses prolong aPTT in (curvi)linear fashion
    - Response curve may flatten at very high concentrations
  - No relationship established yet with outcomes
  - Could be useful in hemorrhagic emergency
- Rivaroxaban
  - Concentration dependent prolongation
  - Minimal variability between reagents
  - PT appears to be more sensitive compared to aPTT
  - Less useful than aPTT in hemorrhagic emergency
- Apixaban
  - Prolongs aPTT in dose dependent manner
  - High degree of variability between reagents
  - PT is much more sensitive than aPTT
  - Less useful than aPTT in hemorrhagic emergency

Other Tests

<table>
<thead>
<tr>
<th>PT</th>
<th>dPT</th>
<th>TT</th>
<th>ECT</th>
<th>aPTT</th>
<th>HepTest</th>
<th>PICT</th>
<th>Chromagenic Assay</th>
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</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Rivaroxaban</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Apixaban</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Summary

- Dabigatran
  - aPTT
    - Appears to be a useful measure in hemorrhagic emergency
    - Therapeutic ranges have not yet been established
  - Ecarin clotting time
    - Also useful in hemorrhagic emergency, but not widely available.
- Rivaroxaban and Apixaban
  - Prothrombin time, but not INR
    - Appears to be useful in hemorrhagic emergency
    - HepTest, PICT, and chromagenic assay all appear to be useful, but not commonly available

References