Laboratory Testing in Patients on Novel Oral Anticoagulants (NOACs)

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NOACs

• Direct Thrombin Inhibitors (DTI):
  – Ximelagatran (liver toxicity – failed approval process)
  – Dabigatran (Pradaxa®)
• Direct Factor Xa Inhibitors (DXI):
  – Rivaroxaban (Xarelto®)
  – Apixaban (Eliquis®)

“Direct” in that no plasma cofactor is needed
Heparin is “Indirect” requiring Antithrombin III
Current Indications

- Venous Thromboembolism prophylaxis post-Orthopedic surgery.
- Non-Valvular Atrial Fibrillation.
- Treatment of DVT and Pulmonary Embolism.

ie. largely as an alternative to Warfarin.

All characterized by Peak and Trough Pharmacokinetics

- Peak @ 2-4 hours
- Trough just before next dose
- Unlike warfarin which produces a “steady” level of anticoagulation
Routine Monitoring

• No routine coagulation monitoring:
  – Specific testing not widely available.
  – Therapeutic ranges NOT known.
• Do NOT use NOACs in patients at extremes of weight:
  – <50 kg
  – >100 kg
• Must monitor RENAL FUNCTION (CREATININE):
  – Clearance depends mostly on Renal Function:
    • Renal Dependence: Dabigatran > Rivaroxaban > Apixaban
  – Product monographs recommend monitoring q1 year.
  – Anti-Coagulant Management Service at UAH recommends:
    • q3 months if stable creatinine
    • q1 month if unstable creatinine
  – Discontinue NOAC therapy if CrCl<30 ml/min.

Non-Routine Testing

• Peri-operatively.
  – Especially Urgent/Emergent Surgery.
• Compliance.
  – Is the patient taking the drug?
  – Has the patient stopped taking the drug?
• Bleeding complications.
  – When has the drug been cleared?
• Thrombosis/Thrombolysis.
  – Especially in Ischemic Stroke.
• Unavailable History.
  – Eg. Obtunded patient with abnormal coags.
• Overdose.
• Renal Failure.
What is needed of testing?

1. The result is needed urgently/emergently.
2. Must be sensitive to drug in high Acuity Patients.
3. Needs to be relatively specific.
4. Quantifying the exact amount of drug present is unnecessary.
5. Simple, low cost = widely available.
PTT vs TT

J van Ryn et al. Thromb.Haemost., 2010; 103: 1116–1127

aPTT (Intrinsic)
Ca\(^{2+}\)
Phospholipid
Neg Charge

PT (Extrinsic)
Ca\(^{2+}\)
Phospholipid
Tissue Factor

= Rivaroxaban or Apixaban

Fibrinogen  Fibrin

IIa (Thrombin)  IIa

V  Va

X  X

IX  IXa

XI  Xla

XII  XIIa

neg charge

Multiple dose
y = 0.86 + 0.06873x\(^{10}\)
\(r^2 = 0.8514\)

Multiple dose
y = 2.4040 + 0.05851x
\(r^2 = 0.8568\)
Sensitivity of Coagulation tests to Rivaroxaban


- European Proficiency Testing using Rivaroxaban *in vitro* spiked samples.
- n=number of participating labs

<table>
<thead>
<tr>
<th>Riva, µg/L</th>
<th>INR n=22</th>
<th>Mean (range)</th>
<th>CV(%)</th>
<th>APTT n=22</th>
<th>Mean (range), s</th>
<th>CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>1.07 (0.99–1.20)</td>
<td>6.7</td>
<td></td>
<td>34.7 (28.7–42.1)</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>146</td>
<td>1.13 (1.02–1.40)</td>
<td>10.7</td>
<td></td>
<td>40.2 (31.9–48.5)</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>305</td>
<td>1.33 (1.12–1.75)</td>
<td>14.6</td>
<td></td>
<td>43.3 (34.0–52.6)</td>
<td>15.5</td>
<td></td>
</tr>
</tbody>
</table>

Heparin Level (aka Anti-Xa Assay)

Exogenous FXa

Plasma Rivaroxaban/ Apixaban

CBS 52.44 → OD/min @ 405 nm → pNA

OD/min → LMWH (U/ml) → Report LMWH Level (U/ml)
Heparin Level (aka Anti-Xa Assay)


Specificity

- Thrombin Time detects DTIs (not DXIs) but also affected by:
  - Hypo-/Dysfibrinogenemia → fibrinogen level
  - Heparin → neutralizable
- Heparin Level (Anti-Xa Assay) only detects DXIs (not usually DTIs).
  - Heparin → neutralizable
  - Cannot distinguish Rivaroxaban from Apixaban
- Warfarin does not affect Thrombin Time or Heparin Level.
- Other PARENTERAL drugs can also affect TT (lepirudin, bivalirudin, argatroban) or Heparin Level (fondaparinux, danaparoid).
Are our needs met?

<table>
<thead>
<tr>
<th></th>
<th>TT for Dabigatran</th>
<th>Anti-Xa for Rivaroxaban/Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short TAT</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensitive in Acute Patients</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Specific</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Quantitative</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Widely available</td>
<td>Expanding</td>
<td>No – future?</td>
</tr>
</tbody>
</table>

Conclusions

- INR and PTT are poor tests for NOACs.
- A normal Thrombin Time excludes the presence of Dabigatran.
- A normal/negative Heparin Level (aka Anti-Xa assay) excludes the presence of Rivaroxaban/Apixaban.
- It is very unlikely for an outpatient to have another reason for an abnormal TT/Heparin Level.