New Anticoagulants: Laboratory Monitoring??

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Ideal Anticoagulant
(Hirsh et al 2004)

- High efficacy to safety ratio
- Predictable dose response (no monitoring)
- Oral and parenteral
- Rapid onset of action
- Available safe antidote
- No side effects
- Minimal drug interaction
# New Oral anticoagulants

## Rivaroxaban and Dabigatran

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-drug</td>
<td>No</td>
<td>Yes (D. etexilate)</td>
</tr>
<tr>
<td>Target</td>
<td>Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Half life</td>
<td>7 - 11 hours</td>
<td>14-17 hours</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>65%</td>
<td>80%</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Protease inhibitor (Ritonavir), Antifungal (Ketoconazole)</td>
<td>Anti-arrhythmics (Quinidine, Amiodarone)</td>
</tr>
</tbody>
</table>
Rivaroxaban and Dabigatran

- Safety/efficacy data show non-inferior or superior to warfarin or LMWH

- Predictable pharmacodynamics

- Fixed doses

- No monitoring in clinical trials - so no routine monitoring for dose adjustment
JTH April 2010.

Debate
New Oral Anticoagulants: A need for laboratory monitoring?
Against: Bounameaux and Reber

• While monitoring may be needless, measuring the drug or its activity might be useful in a few situations
  – Poor renal function
  – Extreme body weights
  – Pregnancy
  – Children
  – Urgent surgery
  – Overdose
For: Mismetti and Laporte

- Variability in drug response is low in highly selected (Trial) patients - no routine need to monitor

- Some inter and intra individual variability
  - Renal function
  - Hepatic function
  - Advanced age
  - Drug-drug interactions

Laboratory monitoring should be assessed for these patients
New anticoagulants
Information on Drug Concentration?

• Compliance?

• Bleeding patients (up to 2%)
  – What effects on clotting tests?
  - How to measure concentration?
Specific tests to measure concentrations

- Specific calibrators are required
- Xa inhibitors
- Anti Xa assays
- Thrombin inhibitors
- Chromogenic anti IIa assay (Hyphen, Siemens etc)
- Clotting assays (semi specific) – eg Hemoclot (Hyphen), Ecarin
What concentrations will occur in patients?
Rivaroxaban

• Dose escalation study (selected cases)
• Prophylactic doses of 5-20mg /day
• Up to 0.2 µg/ml in plasma
• 10 mg /day now in use
• Plasma levels in routine use?
Effect of Rivaroxaban on PT Ratio

Samama et al Thromb Haem 2010
Effect of Rivaroxaban on PT/INR with CUC XS POC device

Samama et al Thromb Haem 2010
Effect of Rivaroxaban on APTT

Samama et al. Thromb Haem 2010
Prothrombinase Induced Clotting Time- PiCT RVV/Xa/PL to generate IIa then calcium

Samama et al Thromb Haem 2010
Rivaroxaban prolongs DRVVT

Samama et al Thromb Haem 2010
What concentrations will occur? Dabigatran

- Mean peak plasma level of 0.3 µg/ml after 300 mg bd (Eriksson et al 2004)
- After Renovate/Remodel post orthopaedic trials - 220 mg day
# Peak and Trough Dabigatran (van Ryn 2010)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Indication</th>
<th>Peak</th>
<th>Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>220 mg od</td>
<td>Ortho surgery</td>
<td>0.183 µg/ml (95% CI 0.06 to 0.45)</td>
<td>0.04 µg/ml (24 hr)</td>
</tr>
<tr>
<td>150 mg bd</td>
<td>AF</td>
<td>0.184 µg/ml (95% CI 0.06 to 0.44)</td>
<td>0.09 µg/ml (12 hour)</td>
</tr>
</tbody>
</table>
Effect of Dabigatran on INR

Method not stated (van Ryn 2010)

0.2µg/ml
Dabigatran

- Similar prolongation PT with all reagents
- 0.5 µg/ml – PT ratio approximately 1.7 -1.9
- Innovin, Thromborel S, Simplastin, Recoimbiplastin Neoplastin, Neoplastin +

Samama personal communication
Effect of Dabigatran on APTT

Method not stated (van Ryn 2010)

![Graph showing the effect of dabigatran on APTT ratio with a concentration of 0.2 µg/ml.](image.png)
Dabigatran effect on APTT
Method not stated (Eriksson et al 2004)
Dabigatran effect on APTT

• Prolongs APTT

• 150 mg bd Median peak levels 2x control

• 12 hours later (trough) Median is 1.5x control

• Method not stated

van Ryn et al 2010
STH – case report  (june 2011)

- Patient on 110 mg bd
- Sample collected 11.5 hr post ingestion
- PT 11.3 sec (n range 9.5-11.3)

- APTT (AFS) – 39.3 sec, ratio 1.52 (N range 20.3-31.2)

- TT >150 sec (nr 11-17)
Effect of Dabigatran on APTT
58 participant labs and core facility different methods
Dabigatran at 0.6 µg/ml (van Ryn 2010)
Effect of Dabigatran on Hemoclot Thrombin time (van Ryn 2010)

0.2µg/ml
Hirudin calibrations

Calibration Curves for Hemoclot

- CS2100i: $r^2 = 0.9971$
- ACL Top: $r^2 = 0.9995$
Dabigatran and Rivaroxaban
Specific Factors/Thrombophilia investigations

- APTT based assays - Factor VIII, IX, XI assays (under estimation at low dilution)

- AT assays – Xa or IIa inhibition (overestimation)

- Interference in clot based tests – APC resistance, DRVVT (LAC)
Rivaroxaban and Dabigatran

- Clotting based tests affected – some reagent dependent effects
- Specific assays needed for drug concentration in specific patients
How fast will VKA be replaced?

- Resistance to change – clinicians, patients
- Not all indications studied
- Regulatory clearances - (Ximelagatran!)
- Costs
## Costs

<table>
<thead>
<tr>
<th></th>
<th>Daily dose</th>
<th>BNF “list” price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>5 mg</td>
<td>£0.04</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10 mg</td>
<td>£4.50</td>
</tr>
<tr>
<td></td>
<td>(STH pharmacy £1.86)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>2 x 110 mg tablets</td>
<td>£2.10</td>
</tr>
</tbody>
</table>
Where will the money come from?

- NHS lab - Reagents/instruments/staff/lab overheads - INR = £3.50
- Private laboratory INR – US - $25 UK - £15
- Phlebotomy, Anticoagulant clinics, laboratories??
- Savings from Primary care?
- Savings from Secondary care?
- WORRIED ABOUT JOB PROSPECTS?