What to do in case of hemorragia with NOAC?

L Camoin – Jau
Service d’Hématologie
APHM
Marseille
Disclosure

- Boehringer
- Bayer
- Daishi
- Sanofi
- BMS
Pharmacodynamic and kinetic properties of new oral anticoagulants.

<table>
<thead>
<tr>
<th></th>
<th>Time to peak concentration (hours)</th>
<th>Half-life (hours)</th>
<th>Extent of renal excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1-3</td>
<td>12-14</td>
<td>80-85 %</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2-4</td>
<td>7-17</td>
<td>36 %</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1-3</td>
<td>8-14</td>
<td>25 %</td>
</tr>
</tbody>
</table>

*Acta Anaesthesiol Scand 2014; 58: 651–659*
Management of the bleeding patient on NOAC

How much drug is on board?

- Timing of last dose
- Drug half-life
- Renal function
- Concomitant medications (anti-platelet drugs, P-glycoprotein and CYP 3A4 enzyme inhibitors)
- Blood levels
# Measurement of anticoagulant activity of NOACs

<table>
<thead>
<tr>
<th>Test</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific</td>
<td>Anti-IIa</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
</tr>
<tr>
<td>Non specific</td>
<td>aPTT</td>
<td>↑↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>PT</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>↑↑↑↑</td>
<td>No effect</td>
</tr>
</tbody>
</table>

- Measurement of anticoagulant activity of NOACs
When should I consider reversing anticoagulation in a bleeding patient?

- **Dabigatran**
  - aPTT ratio >1.2
  - Drug level >30-50 ng/ml

- **Rivaroxaban**
  - PT < 70 %
  - Drug level >30-50 ng/ml

- **Apixaban**
  - Drug level >30-50 ng/ml

**Drug level > 400 ng/ml**
**Major hemorrhagic risk**

Can Journal of Cardiol 2014; 30 : 381
Reversal of NOACs

- Activate coagulation to overcome the effect of the drug
- Neutralize drug
Activate coagulation to overcome the effect of the drug

**EHRA algorithm**

**Bleeding while using a NOAC**

- **Mild bleeding**
  - Local hemostatic measures
  - Delay or discontinue next dose
  - Reconsider concomitant medication

- **Moderate/severe bleeding**
  - Supportive measures
    - Mechanical compression
    - Surgical haemostasis
    - Fluid replacement (colloids if needed)
    - RBC substitution if needed
    - FFP (as plasma expander)
    - Platelet substitution (if platelet count ≤60×10⁹/L)

- **Life-threatening bleeding**
  - Intensive care setting
  - Hemodynamic support
  - Consider
    - 4-factor PCC 25 U/kg; repeat 1×/2× if indicated
    - aPCC 50 IU/kg; max 200 IU/kg/day
    - rFVIIa 90 µg/kg

Adjunctive therapies for severe/life-threatening bleeding

Remove drug by hemofiltration or hemodialysis
- Restricted to non-protein bound drug (dabigatran are partly unbound)
- Limited availability, expensive, burdensome
- Slow drug clearance (hours)
- Only partially effective

Oral charcoal for dabigatran ingestion within 2 hours

Desmopressin

Antifibrinolytic agents

Siegal D et al, Blood 2014; 123: 1152
Can Journal of Cardiol 2014; 30 : 381
Neutralize the effects of the drug
Specific antidotes

<table>
<thead>
<tr>
<th></th>
<th>Idarucizumab: PraxBind®</th>
<th>Andexanet alpha</th>
<th>Aripazine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Humanized Fab fragment</td>
<td>Human rXa</td>
<td>Synthetic small molecule</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Dabigatran</td>
<td>FXa inhibitors</td>
<td>Universal</td>
</tr>
<tr>
<td><strong>Binding</strong></td>
<td>Non competitive</td>
<td>Competitive</td>
<td>Synthetic small molecule:</td>
</tr>
<tr>
<td></td>
<td>High affinity (350 times greater affinity than thrombin)</td>
<td></td>
<td>charge–charge interactions (heparin); hydrogen bonds (NOACs)</td>
</tr>
<tr>
<td><strong>Investigation status</strong></td>
<td>Phase III&lt;br&gt;Patients requiring urgent surgery/major bleeding; May 2014&lt;br&gt;Submitted for approval Mar 2015</td>
<td>Phase III&lt;br&gt;Patients with bleeding; Jan 2015</td>
<td>Phase II&lt;br&gt;Ongoing</td>
</tr>
</tbody>
</table>
Idarucizumab: an antidote specific to dabigatran

• Restoration of coagulation
  – Potent binding affinity ~350 times higher than the binding of dabigatran to thrombin
  – No procoagulant or anticoagulant effects
  – Short half-life

• Easy and rapid administration
  – IV administration, immediate onset of action

• Low risk of adverse reactions
  – No Fc receptor binding
  – No endogenous targets

Glund et al. Thromb Haemost. 2015;
Schiele et al. Blood 2013
Idarucizumab demonstrated immediate, complete, and sustained reversal of dabigatran in healthy subjects

End of idarucizumab injection (5-min infusion)

Dabigatran + placebo

Dabigatran plus:
- Placebo (n=9)
- 2 g idarucizumab (day 4) (n=9)
- 4 g idarucizumab (day 4) (n=8)

Normal upper reference limit (n=86)
Mean baseline (n=86)

‘Normal upper reference limit’ refers to (mean+2SD) of 86 pre-dose measurements from a total of 51 subjects
Glund S et al. AHA 2013; abstr 17765
Andexanet: Designed to Reverse Activity of FXa inhibitors

Recombinant engineered version of human factor Xa produced in CHO cells

- Acts as a fXa decoy and retains high affinity for all direct fXa inhibitors
- Change of serine to alanine to eliminate catalytic activity and prevent prothrombin cleavage
- GLA domain removed to prevent anticoagulant effect

Factor Xa

- No known interaction with other coagulation factors except Tissue Factor Pathway Inhibitor (TFPI)
- Retains high affinity for Antithrombin III-inhibitor complex and can reverse ATIII-dependent anticoagulant effects of enoxaparin and fondaparinux in vitro and in vivo

Andexanet Alfa

Andexanet alfa administration was well tolerated in subjects aged 50-65.

Andexanet significantly, rapidly and reversibly reduced anti-fXa activity and free rivaroxaban, and restored thrombin generation to baseline (pre-rivaroxaban) levels. Andexanet produced normalization of coagulation parameters within 2 minutes of completion of infusion.
In summary

- Bleeding in patients receiving NOACs occurs with a frequency less to VKAS
- Most bleedings are minors or moderates
- Major or life-threatening bleeding require proceduralist-led interventions, life sustaining therapies and non specific procoagulant medications
- Specific antidotes will be soon available