WCN 2019 Teaching Course
ICH RELATED TO ORAL ANTICOAGULANTS

Prof Selma Kesraoui
Department Of Neurology : Prof M.Arezki
Blida Hospital University (Algeria)
Kes_selma@yahoo.fr
Disclosures

I declare that I have no conflicts of interest
Objectives

To determine and understand
1/The mode of action and pharmacokinetic of Anticoagulant therapy
   Vitamine K Antagonists
   Direct oral anticoagulants

2/ Causes of cerebral hemorrhage

3/ Association ICH and OAC and its complication

4/ Reversal of anticoagulation related to ICH
Introduction

- Intracerebral hemorrhage (ICH) is a non-traumatic brain parenchymal hemorrhage, that may extend into the ventricular system or into the subarachnoid space (1).
- Intracerebral hemorrhage (ICH) is responsible for most deaths caused by bleeding complications during long-term anticoagulation (2).
- These bleedings are due to hypertension and cerebral amyloid angiopathy.
- However anticoagulant therapy concerns also a part of these causes, generally in patients taking oral anticoagulant the annual rate of intracranial hemorrhage is 0,3% to 0,6% of these 46% to 86% are intracerebral (3,4).
1/ Anticoagulant therapy

1) Vitamin K antagonists (VKAs)
   Oral anticoagulants are a main component of cardiovascular therapy, and for over 60 years vitamin K antagonists (VKAs) were the only available agents for long-term use.

• Overall effect: dose-dependent anticoagulant effect
• Avantages: self-monitoring and self-management programmes.
• Inconvenients: Slow onset of action
  Variable dose requirement
  Multiple drug-drug interactions
  Dietary vitamin K intake
2) Direct oral anticoagulants (DOACs)
4 (DOACs)
- Dabigatran,
- Rivaroxaban,
- Apixaban,
- and Edoxaban are as efficacious and safe as warfarin for stroke prevention in patients with atrial fibrillation (AF).(5)

• Theses molecules have been developed to limit pharmacodynamic and pharmacocynetic variability
Pharmacocynetetic parametters

<table>
<thead>
<tr>
<th></th>
<th>Mechanism of action</th>
<th>Tmax (h)</th>
<th>Voie d’élimination</th>
<th>T ½ (h)</th>
<th>dialyse</th>
<th>Pro-drug</th>
<th>Food effect</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Direct F IIa inhibitor</td>
<td>2</td>
<td>Rénale 80%</td>
<td>14-17</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>1x/day (DVT, prevention) 2x/day (DVT,AF)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct F Xa inhibitor</td>
<td>2-4</td>
<td>Fécale 65%</td>
<td>7-13</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1x/day (DVT,AF,PE)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Direct F Xa inhibitor</td>
<td>3-4</td>
<td>Fécale 75%</td>
<td>8-15</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2x/day all indications</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Direct F Xa inhibitor</td>
<td>1-2</td>
<td>Renal 40%</td>
<td>9-11</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1 x/ day (DVT,AF,PE)</td>
</tr>
<tr>
<td></td>
<td>Advantages</td>
<td>Inconvenients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
<td>---------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA</td>
<td>The INR is widely available with rapid turn-around, can be determined at the bedside</td>
<td>Food and drug interactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOACs</td>
<td>No food interactions do not generally require regular international normalisation ratio blood test monitoring. They have faster onset and offset of action</td>
<td>Routine coagulation tests are less useful for measuring the anticoagulant effects an absence of or a limited choice of antidotes, some of which are also expensive.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2/Causes of ICH

- Intracerebral hemorrhage is provoked by diseases of large (15%) or small (85%) cerebral vessels.
  - Large vessel diseases includes:
    - arterial aneurysm
    - AVM
    - and less frequently dural fistules and venous malformations
  - Small vessel disease: deposition of extracellular lipid « lipohyalinose » and β amyloid in « amyloid angiopathy ».

(9)
3/ Association ICH and OAC

• Current data suggests that intracerebral hemorrhage in patients taking OAC reflects spontaneous bleeding exacerbated by anticoagulation.
• So OAC sustains intracerebral hematome formation but does not cause it.
Case fatality

• Fatality = hematoma expansion
• Hematoma expansion results of vessel tissue pressure gradient and shear forces. (10)
• This pressure is highest in the early stages after vessel rupture and then gradually decreases.
Case fatality = Hematoma expansion

- In patients not on OAC, hematoma expansion occurs in 30% to 40% of patients within 3 to 6 hours after onset.
- In patients taking VKAs, hematoma expansion is approximately 54% first hours but often it is delayed.

A 64 YO woman
History of AF on VKA
Admission INR = 6
• DOACs +ICH
✓ There is limited data on the frequency of hematoma expansion on DOACs.
✓ It has been reported that hematoma expansion in ICH is the same even for patients on VKAs or on DOACs.
✓ Anticoagulant reversal should be undertaken as soon as possible
Particular case:
59 YO man
History of FA+ diabetes
TRT: Xarelto 15mg

Hematoma + hemorrhagic transformation of acute ischemic stroke
3/Reversal of anticoagulation related to ICH

1) Selection of the appropriate coagulation test
   - VKAs are monitored by using the international normalized ratio (INR) which is based on prothrombine time (PT)
     \[
     \text{INR} = \frac{\text{patients PT}}{\text{laboratory reference PT}}
     \]
   - DOACs
     - Dabigatran: the thrombine time is the most sensitive
       A normal test in case of ICH excludes the presence of clinically relevant dabigatran.
     - Rivaroxaban, apixaban and edoxaban have a greater effect on the PT
       Anti factor Xa is not widely used.
2) Reversal of OACs

- VKAs: VitK
  - PCC
  - FPP

Vit K: VitK IV within 20 to 30 mn to avoid anaphylactoid reactions.

PCC: Prothrombin Complex Concentrate which contains 4 or 3 factor format (VII, IX, X and prothrombine or IX, X and prothrombine) 25-50 UI/kg IV

- FFP
  - PCC is superior than FPP:
    - rapid normalisation of INR
    - Reduction of hematoma expansion
  - Vlla: avoided
DOACs
- Dabigatran: Idarucizumab (praxbind) is a fragment of humanized antibody (5g IV bolus)
- Rivaroxaban, Apixaban and Edoxaban
  Andexanet (Andexxya): recombinant variant of human factor Xa

Recommendations
- Plasma concentration of Dabigatran ≤ 30ng/ml  No reversal
  Or APTT ratio ≤ 1,2

- Plasma concentration of Rivaroxaban ≤30 ng/ml  No reversal
  Or PT ratio ≤ 1,2
In practice

1) In patients with ICH + OAC
   Vit K: 5-10 ng IV
   PCC: 30-50 UI/kg if INR > 1.2

2) In patients with ICH + DOACs
   It is difficult to determine the drug levels because of their relatively short half lives
   Idarucizumab (5g):
   PCC (50 UI/kg): reversal of rivaroxaban, apixaban and edoxaban
   Pending availability of andexanet.
Take home messages

• Intracerebral hemorrhage is the most serious complication in patients taking oral anticoagulation
• The severity is related to hematoma expansion
• Generally hematoma expansion occurs more frequently in patients taking VKAs and can be delayed from onset bleeding
• At today there is limited data on the frequency of ICH and its complications related to the use of DOACs
• Anticoagulant reversal should be undertaken as soon as possible for both (VKAs and DOACs)
References


