The Novel Oral Anticoagulants - An Update for the Interventional Radiologist

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Purpose

DVT, PE, stroke and MI are leading causes of morbidity and mortality worldwide. Therefore treatment of and prophylaxis against thrombosis is a priority. There has been a huge dependency on the orally ingested warfarins and the parenterally administered heparin derivatives over the last 50 years. New oral anticoagulants have emerged onto the market will soon change this dependency. Dabigatran, rivaroxaban and apixaban are orally ingested with predictable pharmacology and have comparable anticoagulant effects to the traditional agents. Their use will grow exponentially in the coming years and interventional radiologists are encountering increasing numbers of patients taking them. It is therefore essential for interventional radiologists to have a thorough understanding of the pharmacology, uses and possible complications of these new drugs in order to appropriately manage patients taking them in the periprocedure setting.

Methods and Materials

Objective

This poster will provide a brief review of the three major novel anticoagulants - dabigatran, rivaroxaban and apixaban - for the interventional radiologist. The uses of these novel drugs will be discussed along with key pharmacodynamic and pharmacokinetic properties. The implications of the pharmacological properties of these drugs will be considered in the periprocedural setting for patients undergoing radiological intervention. This will include the review of pre and post procedure dosing, periprocedural laboratory monitoring, requirements for bridging anticoagulation and options for reversing anticoagulant effect. A guideline will also be proposed for the periprocedural management of the new oral anticoagulants.

Results

The Novel Oral Anticoagulants

The two main classes of new oral anticoagulant agent each target a single step in the coagulation cascade (Fig. 1), thus having more specific and predictable anticoagulant effects than the traditional agents(1). A summary of the properties of the novel oral anticoagulants can be found in the table in Fig.2.
1. Direct Thrombin Inhibitors - Dabigatran

Thrombin has a profound effect on the coagulation cascade and the direct thrombin inhibitors bind to thrombin's active site blocking its interaction with fibrin. Dabigatran is the main oral thrombin inhibitor available.

2. Factor Xa inhibitors

Factor Xa has a role as rate limiting factor in thrombin production and amplification and is an attractive target for new anticoagulants. There are two major oral factor Xa inhibitors currently in widespread use, rivaroxaban and apixaban.

Periprocedural Management of Patients Receiving New Oral Anticoagulant Therapy

Periprocedural management of anticoagulant therapy involves reducing the anticoagulant effect to negate significant haemorrhage, whilst minimising the risk of a thrombo-embolic event occurring at this time. The residual anticoagulant effect should be low or negligible in procedures considered to have a high risk of bleeding or in procedures where even minimal haemorrhage can have devastating consequences (e.g. neurological interventions). A mild to moderate residual anticoagulant effect can be tolerated in procedures where the risk of bleeding is low. A drug's residual effect is linked directly to its elimination half life. 50% of a drug's effect remains after one half life, 25% after two half lives, and so on until after five half lives only 3.125% of a drug's effect remains. A drug's residual effect is moderately reduced after 2-3 elimination half lives (25 - 12.5%) and low to negligible after 4-5 elimination half lives (6.25 - 3.125%)(2). Thus the time to stop an anticoagulant before a procedure is dependent upon two factors - the desired anticoagulant effect at the time of the procedure, and the elimination half life of the anticoagulant. In summary, the anticoagulant should be held for 4-5 elimination half lives prior to high bleeding risk procedures producing a low to negligible effect. Prior to low bleeding risk procedures the anticoagulant should be held for 2-3 elimination half lives producing a mild to moderate anticoagulant effect. The table in Fig. 3 demonstrates a summary of pre-procedural management of the new oral anticoagulants.

Periprocedural Laboratory Monitoring

The predictable pharmacokinetics of the new anticoagulants make periprocedural laboratory monitoring unnecessary in most cases. If assessment of anticoagulant effect is required, rivaroxaban and apixaban are best assessed with anti Xa levels whilst the ecarin clotting time and thrombin time are most reflective of dabigatran(3).
Reversing Anticoagulation in Patients Requiring Urgent Intervention

All such cases should be discussed with a haematologist. The relatively short elimination half lives of the new oral anticoagulants mean that the mainstay of reversal is discontinuation of the medication. This is usually enough to reduce the anticoagulant effect sufficiently that procedures can take place\(^{(4)}\). Options for reversal are limited if a patient requires immediate intervention. Prothrombin complex concentrates, containing coagulation factors II, VII, IX and X, have shown promise in the laboratory setting for all of the new anticoagulants but there is a deficiency of clinical studies.

Restarting Anticoagulation

Studies using novel oral anticoagulants for thrombotic prophylaxis after orthopaedic surgery recommend commencing half to full prophylactic dose the evening of surgery followed by full prophylactic dose the day after surgery. This produced low bleeding rates and satisfactory anticoagulant effect \(^{(5)}\). It is reasonable to extrapolate that for procedures with a low to moderate bleeding risk, commencing half to full daily dose on the evening after the procedure will not significantly increase bleeding and will also minimise the period the patient is without anticoagulant cover. In order to minimize bleeding in procedures considered to have a high risk of haemorrhage, a delay of 24 - 48 hours should be allowed before restarting anticoagulants.

Bridging Anticoagulation

In contrast to warfarin therapy, the new anticoagulants are unlikely to require any bridging anticoagulation due to their relatively short elimination half life and rapid onset of action. Only in patients with high thromboembolic risk who are undergoing procedures with a high bleeding risk should it be contemplated. Bridging should take the form of very short half life medications such as heparin infusions.

Images for this section:
Fig. 1: The final common pathway of the coagulation cascade
**Table 1 - Summary of the properties of the new oral anticoagulants**

<table>
<thead>
<tr>
<th>Property</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name</strong></td>
<td>Pradaxa</td>
<td>Xarelto</td>
<td>Eliquis</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Thrombin/IIa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Half life (hr)</strong></td>
<td>12 - 17</td>
<td>5 – 9</td>
<td>8 - 11</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6.5%</td>
<td>80 – 90%</td>
<td>30 – 90%</td>
</tr>
<tr>
<td><strong>Time to peak plasma concentration (hrs)</strong></td>
<td>0.5 - 2</td>
<td>0.5 – 3</td>
<td>1 - 3</td>
</tr>
<tr>
<td><strong>P450 metabolism</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>P-glycoprotein</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
<tr>
<td><strong>Renal Clearance</strong></td>
<td>80-90%</td>
<td>65%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Hepatic clearance</strong></td>
<td>10%</td>
<td>35%</td>
<td>75%</td>
</tr>
<tr>
<td><strong>Monitoring Required</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Potential Monitoring Assays</strong></td>
<td>Ecarin Time/aPTT</td>
<td>PT</td>
<td>-</td>
</tr>
<tr>
<td><strong>Dose Adjustment in Moderate Renal Impairment</strong></td>
<td>50% dose reduction</td>
<td>Caution advised</td>
<td>No</td>
</tr>
<tr>
<td><strong>Use in severe renal impairment</strong></td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Indicated</td>
</tr>
<tr>
<td><strong>Dose Adjustment for Weight</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Antidote available</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prophylactic dose</strong></td>
<td>110 – 220mg OD</td>
<td>10mg OD</td>
<td>2.5mg BD</td>
</tr>
<tr>
<td><strong>Therapeutic dose</strong></td>
<td>150mg BD</td>
<td>20mg OD</td>
<td>-</td>
</tr>
</tbody>
</table>

**Fig. 2:** Summary of properties of novel oral anticoagulants
### Table 2 - Summary of peri-procedural management of the new oral anticoagulants

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Dabigatran (T 1/2 = 12-17hrs)</th>
<th>Rivaroxaban (T 1/2 = 5-9hrs)</th>
<th>Apixaban (T ½ = 8-11hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Expected Bleeding Risk:</td>
<td>Hold 24 hrs pre procedure</td>
<td>Hold 36 hrs pre procedure</td>
<td>Hold 24-36 hrs pre procedure</td>
</tr>
<tr>
<td>Mild/moderate anticoagulant effect acceptable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Expected bleeding Risk/Neurological Intervention:</td>
<td>Hold 48 hrs pre procedure</td>
<td>Hold 72 hrs pre procedure</td>
<td>Hold 24-36 hrs pre procedure</td>
</tr>
<tr>
<td>No/minimal anticoagulant effect required</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Normal renal Function (Fx) = CrCl >50ml/min
*Impaired renal Function (Fx) = CrCl 30-50ml/min
*Severely impaired renal function (Fx) = CrCl <30ml/min

**Fig. 3:** Summary of peri-procedural management of patients taking the novel oral anticoagulants
Conclusion

Discussion

These new oral anticoagulants promise to eliminate many of the deficiencies and flaws of the traditional anticoagulant agents and interventional radiologists are already encountering these medications with increasing frequency. Currently little information is available for interventional radiologists regarding periprocedural management of these medications. This poster provides an outline of the medications, their pharmacology and proposes periprocedural management guidelines.

References

References


Personal Information