Reversing the New Oral Anticoagulants
Not as Complicated as You Think

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It wasn’t that long ago that the patients we saw in the emergency department who were on long-term anticoagulation were all on warfarin. We shook our heads when the 86-year-old patient on warfarin presented with a fall from the nursing home for the third time in as many months, but at least we knew how to measure warfarin’s therapeutic effect and how to reverse it when the CT scan revealed an intracranial hemorrhage.

The PCCs provided an alternative for the reversal of warfarin’s anticoagulant effect without the need for cross matching and with a much smaller volume of infusion.

Then dabigatran (Pradaxa), a direct thrombin inhibitor, gained FDA approval in 2010, followed in rapid succession by the factor Xa inhibitors rivaroxaban (Xarelto) in 2011, apixaban (Eliquis) in 2012, and edoxaban (Savaysa) in 2015. We called these the novel oral anticoagulants (NOACs), and we fretted about how to measure, let alone reverse, their anticoagulant effects. Many now embrace the term direct oral anticoagulants (DOACs) because these agents are no longer new to the market. They may not be the new kids on the block anymore, but many of us are still unclear about the options available when emergency reversal of these agents is needed in a patient with major bleeding.

First, let’s answer the question of what constitutes major bleeding. What we’re really asking is which patient presentations require rapid reversal. A formal definition has been proposed as “symptomatic bleeding in a critical area of origin, such as intracranial, intraspinal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in the hemoglobin level of 2.0 g/l or more, leading to transfusion of two or more units of blood or red cells.” (Expert Rev Hematol 2016;9[1]:37.)

Patients requiring emergent surgical intervention constitute another group in which rapid reversal is indicated. Most procedures performed in the emergency department don’t require reversal, but lumbar puncture is an exception. Fortunately, diagnostic lumbar punctures are at relatively low risk for hemorrhagic complication, and most can be performed the next day. Given these facts and the short half-lives of the DOACs, stopping these drugs for 24 hours is usually sufficient to allow for reversal of their effect for this purpose. (Am J Emerg Med 2016;34[11]:14.)

Traditional laboratory measures of anticoagulation (i.e., aPTT and PT/INR) have little value in the long-term monitoring of the DOACs, but they may be of some use in the emergency department. Dabigatran may prolong the aPTT, but the correlation with its anticoagulant effect is not linear, especially at supratherapeutic concentrations. Nevertheless, at therapeutic serum levels, dabigatran should prolong the aPTT. The Xa inhibitors typically prolong the aPTT only if present at supratherapeutic levels. The PT/INR should be elevated from dabigatran only if its serum level is three to five times above its normal therapeutic concentration. As for the factor Xa inhibitors, both rivaroxaban and edoxaban may cause an elevation of the PT/INR at therapeutic concentrations, with apixaban only mildly affecting the PT/INR levels. (West J Emerg Med 2015;16[1]:11; West J Emerg Med 2016;17[3]: 264.)

If the decision is made for emergent anticoagulation reversal for a patient on a DOAC, it must be known which specific agent the patient is taking and the timing of his last dose. The reversal strategies differ between dabigatran and the factor Xa inhibitors.
Characteristics of Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Direct thrombin</td>
<td>Direct factor</td>
<td>Direct factor</td>
<td>Direct factor</td>
</tr>
<tr>
<td></td>
<td>inhibitor</td>
<td>Xa inhibitor</td>
<td>Xa inhibitor</td>
<td>Xa inhibitor</td>
</tr>
<tr>
<td>Half Life</td>
<td>12-14 hours</td>
<td>5-13 hours</td>
<td>8-15 hours</td>
<td>9-11 hours</td>
</tr>
<tr>
<td>Elimination with dialysis</td>
<td>Yes</td>
<td>Very little</td>
<td>Very little</td>
<td>Modest</td>
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Emergent reversal

- Idarucizumab (Praxbind) 2.5g IV X2, given not more than 15 min. apart
- Alternatives if idarucizumab is unavailable:
  - PCC 50u/kg IV
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  - rVIIa 90mcg/kg IV
  - Tranexamic acid 1 g IV load, then 1 g IV over 8 hrs
  - Desmopressin 0.3 mcg/kg SQ or IV
  - Activated charcoal 50-100 g PO/NG if ingestion time <2 hrs
  - Hemodialysis

Idarucizumab (Praxbind) was approved by the FDA in 2015, and is the agent of choice for reversing dabigatran. This monoclonal antibody irreversibly inhibits dabigatran, and is given as two IV boluses of 2.5 g in rapid succession. Idarucizumab will reverse the anticoagulant effect of dabigatran within minutes. (N Engl J Med 2015;373(6):511) If idarucizumab is unavailable, several other less effective reversal options are available:

- Activated charcoal at a dose of 50-100 g can be given IV/PO to decrease absorption of the drug in the gut. This is an option if the last dose of dabigatran was taken less than two hours prior to presentation.

Hemodialysis is effective at removing dabigatran, and will eliminate approximately two-thirds of all that is present in the serum in four hours. (Neurocrit Care 2016; 24(1):6.)

- PCCs may be given to try to raise the levels of the coagulation factors that have been inhibited by the DOACs. Three-factor PCCs (Profilnine and Bebulin in the United States) contain factors II, IX, and X, and four-factor PCCs (Kcentra in the United States) contain factors II, VII, IX, and X, as well as protein C and protein S. Four-factor PCCs are preferred over the three-factor PCCs in this setting. (Crit Care Med 2016;44(12):2251.) It should be noted that the use of PCCs to reverse the effect of DOACs is based only on studies that used animals and healthy human volunteers; no studies have been carried out in the clinical setting.

- Activated prothrombin concentrate (FEIBA) and recombinant factor VIIa (Novoseven) may also be tried. The downside of these agents is their relatively high rates of thromboembolic complications. (Curr Opin Anaesthesiol 2014; 27(4):409.)

- Desmopressin and tranexamic acid, both hemostatic drugs, may also be given. Tranexamic acid inhibits fibrinolysis by inhibiting the binding of plasmin to fibrin. Desmopressin stimulates the release of von Willebrand factor and increases the production of factor VII. No studies to date have looked at the efficacy of these drugs in this setting, but their cost and overall risks of administration are low. (West J Emerg Med 2016;17(3):264.)

The Factor Xa Inhibitors

Note that rivaroxaban, apixaban, and edoxaban all conveniently have “xa” in their names. Unlike dabigatran, there is no specific reversal agent for the Xa inhibitors at this time. We are pretty much left with the same less-than-ideal options listed for dabigatran, with two caveats. Hemodialysis is not an effective form of elimination for rivaroxaban and apixaban, but it may be moderately effective for edoxaban. Use of PCCs for reversal of the Xa inhibitors may be more effective when used for dabigatran.

The Future

This article would not be complete if we didn’t mention the promising reversal agents that are currently undergoing clinical trials in the pursuit of FDA approval: andexanet alfa and ciraparantag.

Andexanet alfa is a recombinant modified human factor Xa decoy protein that binds and removes factor Xa inhibitors. Given by IV bolus or infusion, its effect is noted in five minutes, with a peak effect lasting two hours. It reverses the anticoagulant effect of all three Xa inhibitors as well as unfractionated heparin, low molecular weight heparins, and possibly fondaparinux.

Ciraparantag, also known as aripazine, is touted as a “universal antidote” for anticoagulants. It is a synthetic molecule capable of binding dabigatran, all three factor Xa inhibitors, unfractionated heparin, low molecular weight heparins, and fondaparinux. It is given as a single IV bolus, with reversal effects noted in 30 minutes and lasting up to 24 hours. (EMN)

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