Overview of Direct Thrombin Inhibitors: With an Emphasis on Monitoring and Urgent Reversal Strategies

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For many decades, the heparins and vitamin K antagonists (VKAs, e.g., warfarin) have served as the primary pharmacologic means for preventing thromboembolism in at-risk patients. However, the use of drugs within these two traditional anticoagulant classes is being partially superseded by medications that possess more specific mechanisms of action. One of the most important classes of these new drugs is known as the direct thrombin inhibitors (DTIs).

DTIs bind reversibly and directly to one or two domains on the thrombin molecule. Thus, they interfere with thrombin’s two primary roles: (1) to generate fibrin clots and (2) to activate platelets. These new agents offer similar, and in some cases better, efficacy than other antithrombotic drugs. Moreover, they are associated with comparable-to-reduced hemorrhage risk, fewer food and drug interactions, and no need for therapeutic monitoring in most situations.

The first four DTIs to be approved by the Food and Drug Administration – argatroban, bivalirudin, desirudin, and lepirudin (note: lepirudin was removed from the US market in 2012) – are administered intravenously (IV) and/or subcutaneously (SC) and possess relatively short half-lives (t1/2). The use of these parenteral drugs is limited to relatively few indications involving hospitalized patients. Therefore, while they have played a meaningful role in improving anticoagulation safety, their overall scope of use has remained restricted compared to that of the orally administered VKAs. In 2010, however, this changed when dabigatran was approved by FDA as the first oral DTI.

Key Points

- Unlike the heparins and VKAs:
  - DTIs achieve their antithrombotic effect by binding thrombin directly and specifically; and
  - A patient’s renal status should be considered when selecting DTIs.
- The use of DTIs is increasingly being applied to indications previously treated exclusively by the heparins and VKAs.
- Three of the four DTIs currently available in North America are administered parenterally, whereas the fourth (dabigatran) is given orally.
- Monitoring options, when needed, are varied.
- None of the DTIs have well-defined antidotes, making their rapid reversal (i.e., in the event of bleeding or impending surgery) problematic.
Overview of Direct Thrombin Inhibitors

associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. Unlike the VKAs, however, for which vitamin K and 4-factor prothrombin complex concentrates (PCCs) serve as effective reversal agents, no well-defined antidote for bleeding associated with dabigatran (or other DTIs) currently exists.4 Dabigatran has a plasma t1/2 of approximately 12-14 hours and is cleared by both the kidneys (80%) and liver (20%).

A key advantage of this drug is that monitoring is typically not needed other than during active bleeding. In such instances, testing options include the activated partial thromboplastin time (aPTT), Ecarin clotting time (ECT), and thrombin time (TT). As noted above, the most effective means for urgent reversal have not been well delineated, though differing experts have suggested the use of hemodialysis, diuresis, activated charcoal (if given soon after drug ingestion), 4-factor PCCs, recombinant factor VIIa (rFVIIa), and/or plasma transfusions.1, 4, 7

ARGATROBAN (ARGATROBAN) – This IV drug was initially approved by FDA in 2000 for the prophylaxis or treatment of thromboses in patients with heparin-induced thrombocytopenia (HIT). In 2002, FDA expanded its approval to include patients undergoing percutaneous coronary intervention (PCI), who are experiencing or at risk for HIT. Its plasma t1/2 is approximately 45 minutes and it is cleared via the liver.1 Monitoring options include the aPTT (the first choice for guiding dosage adjustments) and activated clotting time (ACT) tests.1, 2 No specific antidotes exist, though rFVIIa, hemodialysis, and/or hemoperfusion have been used. Currently, discontinuation of the drug plus the application of locally directed hemostasis serve as the primary “counter-agent” until drug concentrations fall to sufficiently low levels for spontaneous bleeding to resolve.1, 2

BIVALIRUDIN (ANGIOMAX®) – This IV drug, approved by FDA in 2000, is indicated for patients: (1) with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA); (2) undergoing PCI with provisional use of glycoprotein IIb/IIIa inhibitor; and (3) with, or at risk of, HIT, undergoing PCI. It should be used in conjunction with low-dose aspirin. Its plasma t1/2 is approximately 25 minutes and it is cleared primarily via the liver.1 Monitoring options include the ACT (the first choice as an indicator for when to make dosing adjustments), aPTT, and ECT tests.1, 2 See “Argatroban” for discussion on drug reversal.

Direct Thrombin Inhibitor Comparisons

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Argatroban (Argatroban®)</th>
<th>Bivalirudin (Angiomax®)</th>
<th>Desirudin (Iprivask®)</th>
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<tbody>
<tr>
<td>Half Life</td>
<td>12-14 hrs</td>
<td>45 min.</td>
<td>25 min.</td>
<td>60 min. (IV) 120 min. (SC)</td>
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<tr>
<td>Metabolism</td>
<td>Kidneys (80%); liver (20%)</td>
<td>Liver</td>
<td>Liver</td>
<td>Kidneys</td>
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<td>Indications</td>
<td>Non-valvular A-fib: Reduce stroke and systemic embolism risk</td>
<td>HIT: Prophylaxis and treatment, including patients undergoing PCI</td>
<td>PCTA with unstable angina</td>
<td>DVT prophylaxis for elective hip replacement</td>
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References