Rapid Reversal of Novel Anticoagulant and Antiplatelet Medications in General Surgery Emergencies

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KEYWORDS

• Nonvitamin K antagonist oral anticoagulants • Reversal agents
• Perioperative management • Emergent • Urgent

KEY POINTS

- Nonvitamin K antagonist oral anticoagulants (NOACs) are a new class of medications that present challenges in reversal.
- The emergent nature must be determined in every situation, because it will guide the reversal strategy and help determine risk stratification.
- Most NOACs do not have an antidote. Providers must consider other alternatives to mitigating the effect of NOACs.

INTRODUCTION

In the past decade, a new drug class – nonvitamin K antagonist oral anticoagulants (NOACs) – have been rapidly introduced and popularized. For patients, the benefits of these drugs are stable doses without the need for frequent laboratory monitoring. Clinically, these medications are as effective as vitamin K antagonists (VKAs) in preventing stroke and systemic embolic events in nonvalvular atrial fibrillation and preventing and treating venous thromboembolism (VTE).[1–4] Moreover, the risk of bleeding is similar to or less than VKAs with NOACs.[2] Specifically, they are of less risk of intracranial bleeding.[2] Although the phase III trials of each of the drugs were performed without an antidote available, the mortality rates of major bleeding while taking a NOAC were the same or less than those taking VKAs.[5]

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DABIGATRAN

In October of 2010, dabigatran, the first NOAC was introduced.[6] Its mechanism of action is to directly inhibit thrombin, thus preventing thrombus development.[6] Initially it was only approved for the reduction of stroke and embolic events in nonalvular atrial fibrillation; its scope was expanded to include treatment and reduction in the risk of recurrent VTE and prophylaxis of VTE in patients undergoing hip or knee replacement.[6] It is a prodrug, and estimated bioavailability is 3% to 7%.[6] It has a relatively low protein-binding capability at 35%.[6] Dabigatran is dosed twice a day, 150 mg except for as prophylaxis during hip and knee replacements, where 110 mg is given the first day and 220 mg each day thereafter.[6]

The half-life of dabigatran is 12 to 18 hours (**Table 1**).[6] It peaks after 2 to 4 hours.[6] It is primarily eliminated by the kidneys. When administered intravenously, dabigatran is 80% cleared by the kidneys. When given orally, only 7% is excreted in urine, 86% in the feces.[6] Activated partial thromboplastin time (aPTT) or ecarin clotting time (ECT) can assess for dabigatran's activity. These and thrombin time (TT) may be prolonged while taking dabigatran.

Idarucizumab was developed specifically as a reversal agent for dabigatran. It binds to dabigatran with a 350 times higher affinity than thrombin.[7] It is a humanized monoclonal Fab antibody fragment. The dose is 5 g intravenously.[7] It has a 47-minute half-life and a terminal half-life of 10.3 hours.[7] Furthermore, hemodialysis can remove dabigatran, but the data are limited. Protamine and vitamin K are not expected to affect the drug's activity. Prothrombin complex concentrate (PCC) and recombinant factor VIIa may be used but have not been studied. Dabigatran may be restarted immediately following an operation or invasive procedure. Finally, platelet administration should be undertaken in thrombocytopenia and when long-acting antiplatelet medications are involved.

RIVAROXABAN

Rivaroxaban is a factor Xa inhibitor[8] approved for use by the US Food and Drug Administration (FDA) in November 2011 to reduce the risk of stroke and embolic events in nonvalvular atrial fibrillation, treat VTE and reduce the recurrent risk, and VTE prophylaxis during hip or knee replacements.[8] It does not require antithrombin III or other cofactors, and it is not a prodrug.[8] Its bioavailability is strictly dose dependent; for the 10 mg dose, its estimated bioavailability is 80% to 100%.[8] Rivaroxaban

Table 1
Non-vitamin K antagonist oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Half-life	12–18 h	5–9 h	12 h	5.8–10.7 h	19–27 h
Antidote	Idarucizumab	Andexanet[a] Ciraparantag[b]	Andexanet[a] Ciraparantag[b]	Andexanet[a] Ciraparantag[b]	Andexanet[a] Ciraparantag[b]
Adjuncts	PCC, recombinant factor VIIa	PCC	PCC, aPCC (FEIBA), recombinant Factor VIIa, activated charcoal	PCC, aPCC (FEIBA), recombinant factor VIIa	No data
Dialyzable	Yes	No	No	No	No data

[a] In ongoing phase III trial.
[b] In phase II trial.