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Review

Non–vitamin K antagonist oral anticoagulant reversal: hope is on the horizon

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Abstract

BACKGROUND: Non–vitamin K oral anticoagulants have become an attractive alternative to warfarin when patients require anticoagulation. Until recently, one of the biggest challenges to these agents was the lack of specific reversal of their anticoagulation when bleeding occurs or urgent/emergent procedures are required.

DATA SOURCES: This article is a narrative review of peer-reviewed publications with particular attention to authors that are experts in the field, society guidelines, and government publications.

CONCLUSIONS: Development of several drugs has led to agent-specific reversal. Idarucizumab has gained approval in the United States for reversal of dabigatran. Andexanet alfa has completed promising phase III trials for the reversal of factor Xa inhibitors. Aripazine (PER977) has shown promise as a universal reversal agent against non–vitamin K antagonist oral anticoagulants and heparin products.

Since the development of the next generation of oral anticoagulants, clinicians have faced difficulties when urgent or emergent reversal of the non–vitamin K antagonist oral anticoagulants (NOACs) is necessary. Options for correcting the anticoagulant effects of NOACs were limited and nonspecific. The risks of thromboembolic complications due to these agents' significant prothrombotic nature and uncertain efficacy present a challenge. Until recently, NOACs had no specific reversal agent. Several medications appear promising in addressing the issue of NOAC anticoagulant reversal.

NOACs were first approved in the United States in 2010. With their ease of administration and lack of routine coagulation testing, they have rapidly become integrated in thromboembolic risk reduction and treatment for several conditions. From 2010 to 2013, NOACs comprised 62% of all new oral anticoagulant prescriptions for atrial fibrillation in the United States.[1] These agents became popular because of attractive characteristics including ease of daily or twice a day oral administration, short half-lives, predictable pharmacokinetics that do not require routine anticoagulant effect monitoring, and limited food and drug interactions.[2] The efficacy of these agents appears to be similar to older anticoagulants for their approved indications, with similar bleeding complication rates.[3]

Two distinct classes of these agents exist: the direct thrombin inhibitor dabigatran (Pradaxa; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) and factor Xa (fXa) inhibitors including apixaban (Eliquis; Bristol-Myers Squibb, New York, NY), rivaroxaban (Xarelto; Janssen Pharmaceuticals, Raritan, NJ), and edoxaban (Savaysa; Daiichi Sankyo, Parsippany, NJ). Each drug has a slightly different elimination pathway, half-life, and potentially

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relevant clinical laboratory testing for anticoagulant effects.[4] These properties and approved indication for use are summarized in Table 1. One characteristic of all these agents is a short half-life that may prove very beneficial compared with traditional oral vitamin K antagonists (VKA) when faced with bleeding or the need for emergent or urgent procedures.[5]

Nonspecific reversal agents

Several agents have been studied in animal models or healthy volunteers to address the issue of NOAC reversal. These studies have not evaluated the clinical effectiveness of bleeding abatement in patients prescribed NOACs, or the increased thrombotic risk in patients who need anticoagulation.[6] Administrating these agents is off-label for NOAC anticoagulation effect reversal. The clinician must weigh the potential risks and benefits when prescribing these medications, in particular the risk of thromboembolic complications.[4]

The prothrombin complex concentrates (PCCs) are nonspecific reversal agents that have been found to reverse the anticoagulant effect of NOACs. These agents are concentrated, plasma-derived products that contain several clotting factors in varying amounts. Several preparations are available, including 3 factors (containing factors II, IX, and X) and 4 factors (containing factors II, VII, IX, and X). All approved PCCs in the United States contain nonactivated factors with the exception of one: factor VIII inhibitor bypass activity (FEIBA; Baxter Healthcare, Deerfield, IL), which contains the previously mentioned 4 factors including factor VII in active form. Activation of the nonactive factors occurs through the inherent coagulation cascade once the agent is administered. These agents may also contain heparin, antithrombin, protein C, and/or protein S to decrease thrombotic risks.[7]

The 2012 CHEST Antithrombotic Guidelines recommend PCCs over fresh-frozen plasma for the reversal of VKA in the event of severe bleeding.[8] However, data supporting the use of PCCs to reverse NOAC-associated anticoagulation are limited and confusing. Studies have found varying levels of effectiveness depending on the laboratory or the clinical parameter measured.[6] One hypothesis regarding PCCs' effectiveness in correcting NOAC-induced coagulopathy is the administration of large amounts of factors II and X.[7,9] Activated 4-factor PCC (30 to 80 U/kg) may be preferred for reversing dabigatran, whereas 4-factor PCC (25 to 50 U/kg) may be preferred for Xa inhibitors.[10,11] With the use of these agents, thrombotic complications can occur; the true incidence of risk in patients using NOACs is unclear. Meta-analysis by Dentali et al[12] examining the risk of thromboembolic events when VKA-treated patients received PCC for reversal yielded a 1.4% risk.

In a recent retrospective review, Grandhi et al[13] examined the use of 4-fator PCC in patients with intracranial hemorrhage. Their cohort included 16 patients on rivaroxaban and 2 patients on apixaban. After receiving PCC, only one had progression of their hemorrhage. One patient suffered a thrombotic complication roughly 24 hours of receiving PCC. The in-hospital mortality was 33%, 4 patients had care withdrawn and 2 patients died of respiratory complications due to aspiration.

Recombinant factor VIIa has been examined as a possible reversal agent with variable effectiveness.[14] The high risk of thromboembolic events when used off-label

Table 1 Non–vitamin K oral anticoagulant properties

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Mechanism of action	DTI	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Tmax	.5–2 hours	1–3 hours	2–4 hours	1–2 hours
Half-life	12–17 hours	8–15 hours	7–13 hours	10–14 hours
Clearance	Renal 80% Bile 20%	Hepatic 66% Renal 33%	Hepatic 75% Renal 25%	Hepatic 50% Renal 50%
Laboratory assay effects				
PT	Not useful	Useful	Possibly useful	Useful
aPTT	Useful	Not useful	Not useful	Possibly useful
ACT	Useful	Not useful	Not useful	N/A
ECT	Useful	N/A	N/A	N/A
TT	Most useful	N/A	N/A	N/A
Chromographic anti-Xa	N/A	Most useful	Most useful	Most useful
Approved indications				
NVAF	Yes	Yes	Yes	Yes
Acute VTE treatment	Yes	Yes	Yes	Yes
Prevention recurrent VTE	Yes	Yes	Yes	
Prevention VTE in hip/knee arthroplasty		Yes	Yes	

ACT = activated clotting time; aPTT = activated partial thromboplastin time; DTI = direct thrombin inhibitor; ECT = ecarin clotting time; N/A = not applicable; NVAF = nonvalvular atrial fibrillation; PT = prothrombin time; Tmax = time to maximum concentration; TT = thrombin time; VTE = venous thromboembolism.

Adapted with permission from Yorkgitis et al.[4]