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Reversal of novel oral anticoagulants

Elsayed Abo-Salem and Richard C Becker

The development of a new generation of non-vitamin K oral anticoagulants represents a potential breakthrough in the management of patients with thrombotic diseases, disorders and conditions. While a large and growing body of evidence from large-scale clinical trials and registries supports a favorable safety profile, having a means to rapidly reverse their anticoagulant effects represents an unmet need among practicing clinicians. Several targeted reversal agents are currently in development and the early results are promising. Idarucizumab is a monoclonal antibody that can immediately and specifically reverse dabigatran. Andexanet alfa is a recombinant modified factor Xa that can bind and reverse oral and parenteral factor Xa inhibitors, including rivaroxaban, apixaban and edoxaban, and low molecular weight heparin. Aripazine is a small molecule that can reverse the action of factor Xa inhibitors and possibly dabigatran as well through non-covalent binding and charge–charge interactions.

Address
Division of Cardiovascular Health and Disease, University of Cincinnati College of Medicine, Heart, Lung and Vascular Institute, Cincinnati, OH, USA

Corresponding author: Becker, Richard C (Beckerrc@ucmail.uc.edu)

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Introduction

For decades, vitamin K antagonists (VKA) were the only approved option for oral anticoagulation. Although this class of drugs is one of the most effective in the cardiovascular field, only 50% of patients with an indication for long term anticoagulation receive a prescription and complete therapy [1]. Novel oral anticoagulants (NOACs), also referred to as target-specific oral anticoagulants and non-vitamin K oral anticoagulants represent a potential breakthrough in anticoagulation pharmacology due to their predictable dose-response relationship without the need for routine monitoring and dose titration and fewer drug–drug and food–drug interactions compared to VKAs [2]. Some of NOACs are also more effective than VKAs in stroke prevention among patients with non-valvular atrial fibrillation, or associated with lower risk of major bleeding. Each agent has been shown to significantly reduce the likelihood of intracranial hemorrhage.

Despite several favorable properties and an overall excellent performance in both large-scale, randomized trials and post-marketing registries, the uptake of NOACs has been relatively modest and a concern has been raised among the clinical and lay communities about the lack of an antidote or effective anticoagulation reversal strategy should the need arise [3,4].

Non-specific reversal of NOACs

The pharmacology of NOACs is summarized in Table 1. Each agent has a comparatively short half-life (average 7–12 hours) compared with VKAs. Warfarin has a half-life of 36–42 hours. The anticoagulant activity dissipates after 4–5 half-lives, and withdrawal of anticoagulation with supportive care are often effective therapies for mild and moderate bleeding among patients with normal renal function. Dabigatran is cleared from the circulation primarily by renal mechanisms; accordingly, hemodialysis is a potential option for the management of moderate-to-severe bleeding. Initiation of hemodialysis does require central access and only 50% of the drug is removed after 4 hours of dialysis [5].

Severe, life-threatening bleeding associated with hemodynamic instability or acute organ dysfunction requires immediate reversal of anticoagulation. Volume resuscitation and appropriate control of bleeding source(s) are the main stay of therapy currently. Activated charcoal can decrease the absorption of NOACs, when administered within 2–3 hours of drug intake [6,7].

Fresh frozen plasma does not reverse the anticoagulation of dabigatran and is, at most, only partially effective in reversing the anticoagulant effect of direct Xa inhibitors. In addition, large volume transfusion of FFP increases risk of volume overload. The efficacy of prothrombin complex concentrates (PCCs) in the reversal of either direct thrombin or factor Xa inhibitors has not been evaluated in large-scale clinical trials.

Recombinant factor VIIa and factor eight inhibitor bypassing activity (FEIBA) decreased bleeding times of dabigtran and rivaroxban in animal bleeding models [8,9]. Nonactivated 4-factor PCCs decreased bleeding time in a dabigatran rabbit bleeding model, but did not correct thrombin or ecarin clotting times among healthy volunteers [10,11••]. Prolonged prothrombin time and endogenous thrombin lag time induced by rivaroxaban

Table 1

Pharmacokinetics and reversal of new oral anticoagulants

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Mechanism	Direct factor IIa inhibitor	Direct factor Xa inhibitors		
t_{max} (hours)	1–3	2–3	2–4	1–2
Protein bound	35%	87%	95%	20%
Vd (L)	60	21	50	300
Excretion	Renal	Renal/hepatic	Renal/hepatic	Renal
*T*1/2 (hours)	12–17	8–15	9–13	8–10
Dialyzable	Yes	No	No	No
Drug interaction	P-gp inhibitors	P-glycoprotein inhibitors &/or CYP3A4 inhibitors		P-gp inhibitors
Monitoring	Thrombin clotting time Ecarin clotting time[a]		Anti-Xa activity[b]	
FFP	Not effective		Not effective	
PCC	Partially effective?[c]		Partially effective?[c]	
Target reversal	Idarucizumab Aripazine		Andexanet alfa Aripazine	

[a] Normal TT or aPTT suggests a low plasma dabigatran level.
[b] Prothrombin time is prolonged, but dependents on reagents used.
[c] Activated PCC may be more effective, but there are no large-scale clinical trials, and there is a potential risk of thrombosis.

in healthy volunteers were immediately corrected with 4-factor PCCs (50 IU/kg) [11••]. Four-factor PCC (50 IU/kg) also reduced bleeding duration associated with edoxaban in a human punch biopsy bleeding model, though prothrombin time was only partially corrected [12•].

Targeted reversal drugs

Idarucizumab (BI655075-Dabi-Fab)

Idarucizumab is a humanized monoclonal antibody fragment (FAB, molecular weight is 47.8 kDa) that tightly binds and irreversibly inhibits dabigatran in a 1:1 ratio. The affinity of idarucizumab to dabigatran is 350 times the affinity of dabigatran to thrombin. In vitro and in vivo animal studies revealed an immediate and complete reversal of dabigatran's anticoagulant activity at equimolar concentrations after single bolus dose of idarucizumab. The drug did not interact with other thrombin substrates, coagulation factors or impact platelet activity [13]. In addition and despite its molecular structure idarucizumab does not possess thrombin-like activity, and unlike nonspecific reversal agents has not, in the studies performed to date, caused an 'over-correction' as assessed by thrombin generation parameters [14]. The efficacy is also not affected by solutions used for resuscitation in a pig model of hemorrhagic shock [15].

Idarucizumab is 100 times larger than dabigatran and the volume of distribution of the former or idarucizumab-dabigatran complex is significantly lower than dabigatran alone. The half-life is 45 min in healthy volunteers and elimination occurs primarily by a renal route. The efficacy and safety in patients with advanced chronic kidney disease is unknown, though animal studies have suggested efficacy since both dabigatran and idarucizumab are expected to accumulate and allow concomitant neutralization [16].

No serious adverse events were reported among healthy volunteers in a double blinded placebo controlled phase II trial [17•]. The median serum dabigatran concentrations in this study were similar to levels reported in the RE-LY trial. An infusion (over 5 min) of 1, 2 and 4 g resulted in a reduction of dilute thrombin time by 74%, 94% and 98%, respectively. Similar responses were observed as determined by activated thromboplastin time (aPTT), ecarin clotting time and thrombin time measurements. [18]. Reversal was maintained over 72 hours with 2 g or higher doses of idarucizumab. Serum dabigatran concentrations remained elevated albeit inactive and in a bound state to the Fab fragment. Minor adverse reactions included skin irritation and erythema at the site of drug administration, dizziness, asthenia and flu-like symptoms. Idarucizumab vials contain sorbitol, and there is a potential risk of adverse events, including hypoglycemia, vomiting and metabolic acidosis, in patients with hereditary fructose intolerance.

Idarucizumab is currently being studied in a multicenter, observational phase III trial (RE-VERSE AD) which is designed to enroll 300 subjects on dabigatran with a clinical indication for anticoagulation reversal, including uncontrollable/life threatening bleeding (group A) or need for emergency surgery/invasive procedure (group B) [19] (clinicaltrials.gov NCT02104947). An interim analysis of 90 subjects who received a total of 5.0 g (2.5 g/50 mL × 2 doses) was performed. The median investigator reported time to cessation of bleeding was 11 hours in group A. Normal intraoperative hemostasis was achieved in 92% of group B subjects. The all-cause

mortality rate was 20% and more than half of deaths were secondary to co-existent medical illness and occurred within 48 hours. Although idarucizumab is not believed to have a direct procoagulant effect, reversal of anticoagulation is expected to unmask an existing propensity for thrombosis carried by underlying conditions such as atrial fibrillation and venous thromboembolism [20••].

Andexanet alfa (r-antidote-PRT064445)

Andexanet alfa is a recombinant modified factor X molecule (factor X decoy) that possesses a specific binding site for factor X/Xa inhibitors. It lacks the membrane binding γ-carboxylglutamate domains and catalytic site, and therefore does not exert a procoagulant effect [21]. The drug can reverse the anticoagulant activity of direct factor Xa inhibitors in a dose-dependent manner. Andexanet alfa also retains its ability to bind antithrombin III and can reverse antithrombin III-mediated indirect factor Xa inhibitors, including low molecular weight heparins and fondaparinux [22].

In a rivaraoxaban-treated rabbit model of liver laceration, andexanet alfa decreased blood loss by 85%. This correlated with a reduction in peak factor Xa activity, prothrombin time and aPTT. The plasma levels of free (active) factor Xa inhibitors decreased immediately after antidote infusion, although total rivaraoxaban level increases due to redistribution of drug from tissue to the plasma pool and binding with andexanet alfa [21]. Andexanet Alfa was also more effective than 4-factor PCC in an animal model of bleeding.

Several randomized, double-blind and placebo-controlled trials in healthy volunteers investigated the efficacy and safety of various andexanet alfa doses in reversal of direct and indirect factor Xa inhibitors. ANNEXA-A and ANNEXA-R trials included older healthy volunteers after treatment with apixaban or rivaroxaban, respectively. Anti-factor Xa activity of, apixaban and rivaroxaban was immediately reversed after a bolus injection of 400 mg and 800 mg, respectively. Thrombin generation increased to normal without a rebound effect in the andexanet alfa arm. There were no thrombotic events in these trials. Reversal was maintained for 2 hours after a bolus injection and for a longer duration with a continuous infusion of 4 mg/min for rivaroxaban and 8 mg/min for apixaban. The published studies have thus far included a modest number of healthy subjects [23–25,26••]. Trials of factor Xa inhibitor reversal with andexanet alfa among patients with severe bleeding are currently enrolling patients (NCT02329327).

Aripazine (PER977, ciraparantag)

Aripazine is a synthetic small molecule that can bind, non-covalently, and reverse the action of unfractionated and low molecular weight heparins, direct factor Xa inhibitors and direct thrombin inhibitors. It does not bind to either other coagulation factors or to albumin [27]. Ex vivo studies employing human plasma treated with rivaroxaban or apixaban showed an ability of aripazine to reverse the anti-factor Xa activity of direct factor Xa inhibitors in a dose-dependent fashion [28].

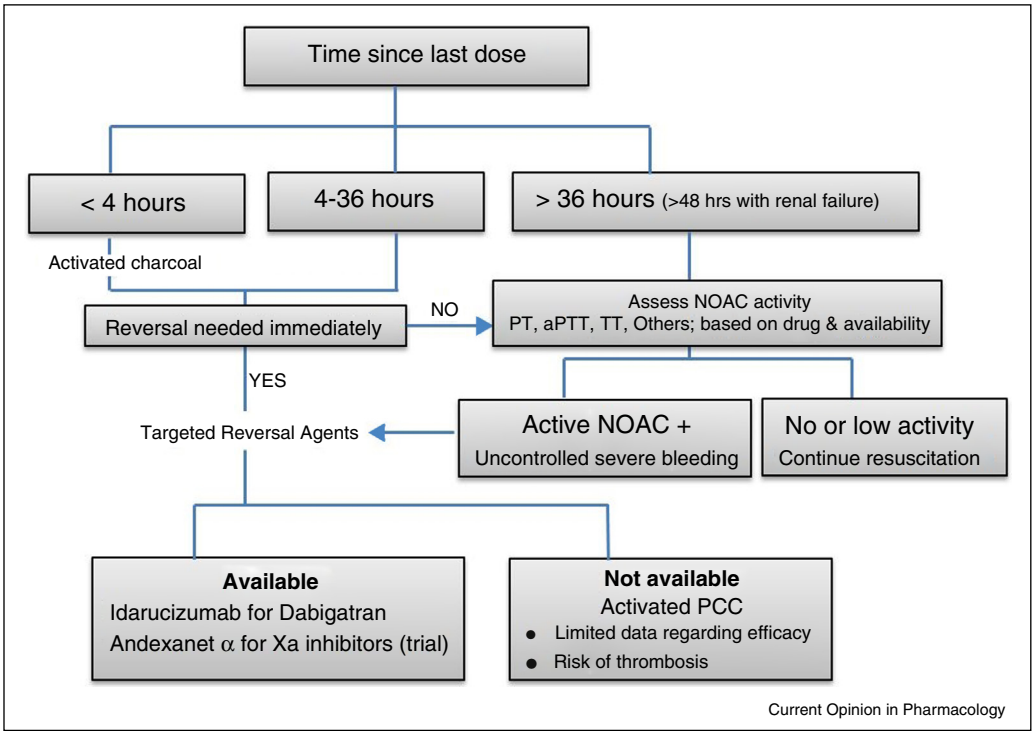
In a rat tail transection model, aripazine reduced blood loss with NOAC including factor Xa inhibitors and direct thrombin inhibitors (dabigatran), with a reduction in PT and aPTT, respectively. Aripazine did not have procoagulant properties or affect coagulation measures in animal models without anticoagulation [28]. In a trial among healthy volunteers treated with edoxaban, a single dose of aripazine (100 and 300 mg doses) resulted in a reduction in whole blood clotting time to baseline in less than 10 min. Reversal was maintained for 24 hours [29]. The clotting time in the placebo arm reached baseline levels in 12–15 hours. Aripazine remains in an early phase of development.

The mechanism of aripazine action is not completely understood. In a rabbit model of bleeding with liver laceration, aripazine resulted in a 76% reduction of blood loss [30]. However, the anti-factor Xa activity, PT and aPTT did not change significantly after aripazine injection, compared with andexanet alfa despite a similar degree of reduction in blood loss [30]. Aripazine use in animal bleeding models without prior anticoagulation reduced bleeding by 23%. In an in vitro study, platelet activation with aripazine was observed [31]. This will require further evaluation if clinical development continues.

FDA approval process

The drug approval process through the United States Food and Drug Administration (FDA) is traditionally viewed as lengthy, expensive and complex. Only 10% of the drugs find their way from phase I to FDA approval, and the average duration of development is 9 years. *Breakthrough Therapy Designation* is an accelerated approval route for innovative therapies to treat serious illness, when preliminary data support the likelihood of improved clinical outcome(s) and there is no existing standard of care. This path to approval was initiated in July 2012 and, since that time, 24 drugs have been approved through this mechanism-from a total of 308 requests. The process includes intensive FDA guidance on drug development and an expedited review process. Idarucizumab (Praxbind®, manufactured by Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut, United States) was granted a break through designation in April 2014 and was approved for human use by FDA on October 16, 2015 for emergency reversal of dabigatran anticoagulant. Praxbind® is supplied in vials, each containing 2.5 g/50 mL of idarucizumab. Andexanet alfa, manufactured by Portola Pharmaceuticals (San Francisco, CA, United States), was submitted for break through designation in November 2013 and also as an *orphan drug therapy* in February 2015. It is not currently approved for human use as a reversal agent.

Figure 1



Management of serious or life-threatening bleeding in patients receiving NOAC therapy is presented in this figure, in addition to standard of care; withholding anticoagulation, volume resuscitation and proper management of bleeding source(s) and comorbid conditions. The clinical benefit of activated or 4-factor prothrombin complex concentrates (PCCs) has not been demonstrated among patients receiving non-vitamin K oral anticoagulants who experience bleeding.

Potential candidates for targeted reversal therapy

A decision to reverse anticoagulation in a patient who is either at risk for or who has experienced a prior thrombotic or thromboembolic event must be made after carefully consideration of potential benefits and risks. One should consider reversal in the following patients and clinical settings: firstly, severe bleeding that results in hemodynamic compromise, organ dysfunction or a need for massive blood transfusion, secondly, patients within 24 hour of receiving an anticoagulant who require emergency surgery or an invasive procedure known to be associated with a significant risk of bleeding. Other factors that must be considered prior to reversal include the time since a last dose of a NOAC, indication for anticoagulation and risk of thrombosis, drug interactions, associated renal or hepatic dysfunction and local or systemic factors that increase the risk of poor outcomes with bleeding, for example, advanced age. A suggested management algorithm reversal of NOAC activity appears in Figure 1.

Conclusion

The results of both early and late phase studies employing targeted reversal agents for NOACs are thus far promising for safety and efficacy. Pathways for expedited FDA approval of these drugs and post-approval studies will determine their ability to rapidly, effectively and safely restore hemostasis. Whether a readily available strategy of reversal will increase the number of at risk patients who receive anticoagulant therapy awaits further population-wide assessment. One should expect the cost of reversal agents to be high and careful patient selection will be of utmost importance.

Conflict of interest statement

None declared.

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