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A review of reversal of oral anticoagulants, old and new, in major bleeding and the need for urgent surgery

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Abstract

Oral anticoagulants, old and new, are effective therapies for prevention and treatment of venous thromboembolism and reduction of stroke risk in patients with atrial fibrillation. However, blocking elements of the clotting cascade carries an inherent risk of bleeding. Also, anticoagulated patients sometimes require urgent surgery or invasive procedures. This has led to the emergence of a body of scientific literature on the reversal of anticoagulation in these two settings. Traditionally, vitamin K antagonists (VKAs), which indirectly inactivate clotting factors II, VII, IX and X (and natural anticoagulant proteins C and S), had been the mainstay of oral anticoagulation for half a century. Only a few years ago, the US Food and Drug Administration (FDA) approved a specific VKA reversal agent, 4-Factor Prothrombin Complex Concentrate (4F-PCC). The last decade has seen the rise of non-Vitamin K oral anticoagulants (NOACs), which target specific factors, i.e. Factors IIa and Xa. Investigators have rapidly developed reversal agents for these agents as well, idarucizumab for the Factor IIa inhibitor dabigatran (Pradaxa) and andexanet alfa for the entire class of Factor Xa inhibitors (FXaIs), currently four drugs: rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa) and betrixaban (Bevyxxa). Clinicians still use off-label PCC for reversing FXaIs in some settings, and a universal reversal agent, ciraparantag, remains in development. This review summarizes the safety and efficacy of these reversal agents in the setting of anticoagulant-associated major bleeding and the need for urgent surgery.

Keywords

Anticoagulant; Reversal; Major bleeding; Non-Vitamin K oral anticoagulants; Direct oral anticoagulants; Vitamin K antagonists; Warfarin; Coumadin; Rivaroxaban; Apixaban; Dabigatran; Andexanet alfa; Idarucizumab; Kcentra; 4-factor prothrombin complex concentrate

Introduction

Clinicians have used oral anticoagulants to mitigate thrombotic risk for more than half a century. Beginning with vitamin K antagonists (VKAs), such as warfarin, discovered in spoiled sweet clover at the beginning of the last century [1], clinicians have sought to steer

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their patients between the two pathologic states of bleeding and thrombosis. A natural consequence of anticoagulant therapy is bleeding risk, which can be severe and life threatening, but bleeding is generally easier to treat than thrombosis. Thrombotic complications can present clinically as venous thromboembolisms (VTE) such as deep vein thrombosis and pulmonary embolism but also arterial thrombosis such as ischemic stroke and myocardial infarction. Tilting the balance toward bleeding has led to great improvements in clinical outcomes for patients at risk of these diseases. For example, VKAs reduce stroke risk by two-thirds in patients with atrial fibrillation [2].

VKAs, while effective, had some less than desirable characteristics. These included long half lives, the need for frequent testing of prothrombin time/International Normalized Ratio (INR), multiple dietary and drug interactions, and a small but devastating risk of intracranial hemorrhage (ICH), the most feared consequence of anticoagulant therapy. This led to the development of non-vitamin K oral anticoagulants (NOACs), also called direct oral anticoagulants (DOACs) over the last decade. These drugs targeted specific clotting factors (Factors IIa and Xa) rather than the broader approach of VKAs. VKAs, by inhibiting the enzyme Vitamin K epoxide reductase, reduce levels of Factors II, VII, IX and X and the natural anticoagulant Proteins C and S. The NOACs as a class are as safe and effective as VKAs and possibly more so, have simpler dosing, few diet or drug interactions, require no INR checks and are associated with less intracranial hemorrhage [3]. They are rapidly replacing VKAs as the standard of care in prevention and treatment of VTE and prevention of stroke in patients with non-valvular atrial fibrillation (though a significant percentage of these patients were still taking VKAs in 2018) [4]. VKAs remain the standard for patients with mechanical heart valves.

Clinicians must deal with the major bleeding complications and the need for urgent surgical or other invasive procedures in anticoagulated patients, whether VKAs or the NOACs. This has necessitated a field of anticoagulant reversal research over the last decade, studying tilting the delicate balance back toward thrombosis just long enough to stop the bleeding or facilitate the surgery. There are approved specific reversal agents for VKAs, i.e. 4-Factor prothrombin complex concentrates (4F PCCs), and the lone currently marketed direct thrombin inhibitor (DTI), dabigatran (Pradaxa), i.e. idarucizumab (Praxbind). The U.S. Food and Drug Administration (FDA) approved andexanet alfa (AndexXa) as a reversal agent for the Factor Xa inhibitors (FXaIs), rivaroxaban (Xarelto) and apixaban (Eliquis), in May 2018. The European Medicines Agency (EMA), after receiving a positive opinion from its Committee for Medicinal Products for Human Use (CHMP) in February 2019, was to rule on the drug in May 2019. In the period from NOAC approvals to andexanet approval, a small body of evidence emerged on using PCC off label for the reversal of FXaIs. PCC makers have not pursued trials to seek regulatory approvals for this practice. Also, a universal reversal agent, ciraparantag, remains in development, but has not yet been studied in major bleeding or urgent surgery patients.

This review is a summary of VKA and NOAC reversal agents' safety and efficacy in major bleeding and urgent surgical intervention up to 2019.

Of note, trials of NOAC reversal agents idarucizumab and andex-anet are single cohort as there were no accepted standard-of-care control agents for comparison. Also, placebo arms were considered unethical in bleeding patients and those in need of urgent surgery. However, this has made it difficult to contextualize the results of these trials such as the morbidity and mortality, hemostatic efficacy and thromboembolic event rate (TEE rate). The warfarin reversal trials with 4F PCC were able to use plasma as a control. While plasma as a reversal agent has little evidence to support it, it was widely used in warfarin reversal for decades and was an accepted standard of care [5].

The International Society of Thrombosis and Hemostasis (ISTH) criteria [6], defines major bleeding as an acute 2-g hemoglobin (2 g/dl) drop or bleeding into a critical organ such as intracranial hemorrhage. Researchers study patients in need of urgent surgery in a separate cohort due to differences in patient populations and the methods of measurements of hemostatic efficacy. In the dabigatran reversal study, investigators studied two cohorts under one protocol. In the warfarin reversal trials, investigators studied the two cohorts in independent protocols, one for major bleeding and one for urgent surgery. In the FXaI reversal study, researchers enrolled only major bleeding patients, and surgery remains unstudied with this agent.

The key outcomes in reversal studies are hemostatic efficacy, measured either by biomarkers or clinical scales or both, and thromboembolic events (TEEs), venous such as VTE and arterial such as stroke, systemic embolism or myocardial infarction, in addition to mortality.

Methods

This review is unstructured and based on the published major developments in oral anticoagulant reversal since the seminal warfarin reversal trials with 4F-PCC [7, 8]. While researchers have published other important work in this area, much of it is beyond the scope of this article, which is meant to update clinicians who deal with oral anticoagulant reversal in major hemorrhage and the need for urgent surgery.

Review

Direct thrombin inhibitor reversal

Oral DTIs present a remarkable example of development of a specific reversal agent. The FDA approved dabigatran in 2010, the first of the NOACs (excepting ximelagatran, a previous DTI pulled from the market for liver toxicity). Five years later, the FDA approved the monoclonal antibody fragment antigen binding (Fab), idarucizumab, for the reversal of the effects of dabigatran. This was notably rapid in terms of the usual time intervals for drug development. Boehringer Ingelheim, the maker of dabigatran, developed idarucizumab, and it is specific to that drug. It has no role in reversal of any other anticoagulant. It has 350 times more affinity for dabigatran than the thrombin (Factor IIa)-dabigatran interaction, and it binds both free and thrombin bound drug to neutralize its activity [9].

In several non-bleeding cohorts, e.g. healthy young volunteers with normal renal function, older adults and those with moderate renal impairment, idarucizumab completely reversed

dabigatran's anticoagulant effects without thromboembolic complications [9]. Interim analysis of The ReverseAD trial involving 90 patients with major hemorrhage or in need of urgent surgical intervention [9], formed some of the basis for the approval of the drug, but since then Pollack and colleagues published the full cohort analysis of 503 patients [10].

ReverseAD enrolled 301 patients with major bleeding (Cohort A) and 202 patients in need of urgent surgery (Cohort B) [10]. Based on either dilute thrombin time or ecarin clotting time, the primary outcomes, the median maximum percentage reversal of dabigatran from two 2.5 g bolus infusions of idarucizumab (no more than 15 min apart) was 100% (95% confidence interval, 100 to 100). In Cohort A, 137 patients (45.5%) presented with gastrointestinal bleeding and 98 (32.6%) presented with intracranial hem-orrhage; among the patients who could be assessed, the median time to the cessation of bleeding was 2.5 h. In Cohort B, the median time to the initiation of the intended procedure was 1.6 h; periprocedural hemostasis was assessed as normal in 93.4% of the patients, mildly abnormal in 5.1%, and moderately abnormal in 1.5%. At 90 days, thrombotic events had occurred in 6.3% of the patients in Cohort A and in 7.4% in Cohort B, and the mortality rate was 18.8% and 18.9%, respectively [10]. There was no clinical hemostatic efficacy primary outcome as in other reversal trials, and using a drug level as a primary outcome in a trial of an antibody to that drug might seem tautological.

Factor Xa inhibitor reversal

Shortly after the approval of dabigatran, rivaroxaban, the first of the oral FXaIs, was marketed. It was quickly followed by apixa-ban and edoxaban and most recently betrixaban. Concurrent with this raft of approvals, Portola Pharmaceuticals (maker of betrixaban) began developing the andexanet alfa program [11]. Andexanet is a recombinant FXa protein with two important modifications. The serine active site, which binds to and cleaves prothrombin to thrombin, has been substituted with an alanine, inactivating the catalytic domain [11]. Also, the glutamic acid (GLA) residue at the opposite end of the molecule has been cleaved. This keeps andex-anet from complexing with native Factor Va and competing with native FXa, which would create an anticoagulant effect. The serine to alanine substitution at the active site keeps andexanet from creating a prothrombotic effect (by cleaving prothrombin to thrombin). Andexanet still avidly binds to FXaIs, becoming a biological decoy, sweeping up the inhibitor so native FXa can function in the clotting cascade [11].

Andexanet underwent an extensive pre-clinical program in several animal models followed by several cohorts of non-bleeding volunteers taking various FXaIs [11–16]. No thromboembolic complications were reported and no neutralizing antibodies developed to FXa. (Such antibody development could potentially create an iatrogenic hemophilia.) Andexanet has been studied in phase 3, double-blind, placebo-controlled studies as a single bolus or a bolus plus 2-h infusion in nonbleeding healthy older adults (50–75 years) treated with apixaban or rivaroxaban [16]. Andexanet was administered as a bolus plus 2-h infusion due to the approximately 1 h half-life of the drug. In the apixaban group, anti-FXa activity was reduced by 94% in subjects ($n = 24$) who received an andexanet bolus versus 21% in participants ($n = 9$) who received placebo (P 0.001). The concentration of unbound apixaban was reduced by 9.3 ng/mL versus 1.9 ng/mL (P 0.001) Thrombin generation was fully

restored within 2–5 min in 100% versus 11% of subjects (P 0.001) [16]. In the rivaroxaban group, anti-FXa activity was reduced by 92% in subjects (n = 27) who received an andexanet bolus versus 18% in subjects (n = 14) who received placebo (P 0.001), and the concentration of unbound rivaroxaban was reduced by 23.4 ng/mL versus 4.2 ng/mL (P 0.001). Thrombin generation was fully restored in 96% versus 7% of subjects (P 0.001) [16]. When andexanet was administered as a bolus plus 2-h infusion, these effects were sustained in subjects treated with apixaban and rivaroxaban. Though transient increases in levels of D-dimer and prothrombin fragments 1 and 2 (F1.2) occurred in a subgroup of subjects, raising a concern for prothrombotic effect, this normalized within 24–72 h [16].

The final FDA approval step in the andexanet program was the ANNEXA4 trial, a single cohort of patients with major bleeding on FXaIs (including the indirect FXa inhibitor enoxaparin). Investigators published the final cohort in 2019 [17]. (They published an interim analysis in 2016, analyzing 67 patients predominantly with gastrointestinal and intracranial hemorrhage, which preceded FDA approval in May 2018 prior to trial completion on an accelerated pathway [18].) The ANNEXA4 final cohort evaluated 352 patients who had acute major bleeding within 18 h after administration of a FXaI. The patients received a bolus of andexanet, followed by a 2-h infusion. Bleeding was predominantly intracranial (in 227 patients [64%]) or gastrointestinal (in 90 patients [26%]), with 10% other bleeding. In patients who had received apixaban, the median anti-factor Xa activity decreased from 149.7 ng per milliliter at baseline to 11.1 ng per milliliter after the andexanet bolus (92% reduction; 95% confidence interval [CI], 91–93); in patients who had received rivaroxaban, the median value decreased from 211.8 ng per milliliter to 14.2 ng per milliliter (92% reduction; 95% CI, 88–94). Excellent or good hemostasis occurred in 204 of 249 patients (82%) who could be evaluated. Within 30 days, death occurred in 49 patients (14%) and a thrombotic event in 34 (9.7%). Reduction in anti-factor Xa activity was not predictive of hemostatic efficacy in the general study population but was modestly predictive in patients with intracranial hemorrhage, (AUC 0.64: 0.53–0.74).

In the absence of a specific reversal agent, many clinicians use off-label 3 and 4 factor PCC to reverse FXaIs [19]. Factor levels are normal in patients on FXaIs, so the mechanism of flooding the system with so many different clotting factors to reverse an inhibitor of only one is not well understood. The pre-clinical data to support this practice are from animal studies, small cohorts of nonbleeding volunteers and studies of edoxaban and rivaroxaban reversal in a human thigh punch biopsy model [20–24].

A few cohorts of bleeding FXaI patients given PCC have been published. The evidence is somewhat conflicting in Majeed et al. [25], Shulman et al. [26], Gerner et al. [27], and Arachchillage et al. [28]. Schulman and Majeed applied clinical hemostatic efficacy scales finding acceptable rates similar to andexanet alfa, but the cohorts were small (66 and 84 patients respectively), and lacked the rigor of adjudication and FDA oversight of ANNEXA4. Arachchillage et al., a prospective registry, did not formally assess hemostatic efficacy, making a comparison difficult. Gerner et al., a retrospective cohort of 190 intracerebral hemorrhage patients, took a different approach, analyzing the correlation between PCC administration and lack of hematoma volume expansion. Investigators found no correlation, nor did they find one with mortality or functional outcome. The closest

attempt at a head to head trial is the ongoing ANNEXA-I trial (NCT03661528) of andexanet versus “usual care” in intracranial hemorrhage patients on a FXaI. (Usual care in many settings will be some formulation of PCC.) However, this trial launched at the beginning of 2019 and will take several years to complete. Neither andexanet nor PCC has been studied prospectively in large groups of patients needing urgent surgery.

Vitamin K antagonist reversal

Early last century the first coumarin derivatives were isolated from spoiled sweet clover after an outbreak of hemorrhagic disease in Wisconsin cattle [1]. First used as a rodenticide, these compounds were eventually tested in humans with prothrombotic conditions, which inevitably led to bleeding complications. The most etiological reversal agent was Vitamin K. However, even given intravenously this agent took hours or more to allow the liver to ramp up production of the Vitamin K-dependent clotting factors II, VII, IX, X and proteins C and S. This made Vitamin K alone inadequate for truly life-threatening hemorrhagic scenarios, which led to the practice of also giving plasma, in hopes of more quickly supplementing factor levels. Despite widespread use, the efficacy of plasma for urgent VKA reversal has never been established. Plasma has several well-known drawbacks including time delays for ABO blood-typing and thawing of frozen plasma, large volumes and long infusion times to reach the factor levels necessary to correct coagulopathy, risk of pathogen transmission, risk of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO), leading causes of transfusion-related deaths [29–32]. PCCs, originally developed to treat hemophilia, offered an alternative. Many were approved elsewhere in the world for treatment of VKA-associated major bleeding and in the setting of need for urgent surgery and began appearing in guidelines. But it was not until 2013, after the first large randomized, plasma-controlled trials of a 4F PCC were completed [7,8], that the FDA approved the first PCC for VKA reversal in the United States, KCentra. These trials illustrated some of the difficulties in studying major bleeding, which include presentations as varied as intracranial hemorrhage and hematuria. The trials were designed as tests of non-inferiority to plasma, with secondary tests for superiority if non-inferiority was met, and the co-primary outcomes were rapid reduction of the INR and clinical hemostatic efficacy [7, 8]. All patients were also to be given Vitamin K.

KCentra investigators developed an a priori, intricate clinical hemostatic efficacy scale across the many different types of bleeding. (It has subsequently been used in modified form in both ReverseAD, as a secondary outcome [9, 10], and AN-NEXA4 [17, 18], as a primary outcome). The major bleeding trial found 4F PCC superior to plasma in INR reduction and noninferior in clinical hemostatic efficacy [7] and the urgent surgery trial found PCC superior on both measures [8]. TEE rates and deaths combined from both trials, 388 patients (4F-PCC: $n = 191$; plasma: $n = 197$) were reported in detail in follow up publications [33, 34]. The rates were remarkably similar, 14 TEEs with 4F-PCC (7.3%) and 14 with plasma (7.1%); 13 deaths with 4F-PCC (6.8%) and 13 with plasma (6.6%) [33, 34].

One additional randomized trial [35], though stopped early, provided additional support for the superiority of 4F PCC (in this case Octaplex, which is in a separate clinical trial randomized with KCentra in urgent surgery and is seeking FDA approval [36]) over plasma

in intracerebral bleeding. Fifty-Four patients were randomly assigned (26 to FFP and 28 to 4F-PCC) and 50 received study drug (23 FFP and 27 4F-PCC). Safety concerns with the plasma group resulting from an early analysis caused the trial to be terminated at 50 patients. Two (9%) of 23 patients in the FFP group versus 18 (67%) of 27 in the 4F-PCC group reached the primary endpoint of INR 1.2 or lower within 3 h of treatment initiation (adjusted odds ratio 30.6, 95% CI 4.7–197.9; $p = 0{\cdot}0003$). 13 patients died: eight (35%) of 23 in the FFP group (five from hematoma expansion, all occurring within 48 h after symptom onset) and five (19%) of 27 in the PCC group (none from hematoma expansion), the first of which occurred on day 5 after start of treatment. Three thromboembolic events occurred within 3 days (one in the FFP group and two in the 4F-PCC group), and six after day 12 (one and five).

The universal reversal agent

Ciraparantag (formerly PER977) a small, synthetic, water-soluble, cationic molecule that is designed to bind specifically to unfractionated heparin and low-molecular-weight heparin through noncovalent hydrogen bonding and charge-charge interactions [37]. It binds in a similar way to the FXaIs, edoxaban, rivaroxaban and apixaban, and to the DTI dabigatran [37]. It has been studied in animal models and non-bleeding healthy normal subjects on edoxaban and LMWH [38,39]. The utility and simplicity of such an agent is apparent, but the true test of reversal agents is how they perform in the clinical setting of major hemorrhage or urgent surgery.

Summary

Idarucizumab should be used in patients on dabigatran (and only dabigatran) with major bleeding or in need of urgent surgery. For warfarin reversal, there is little remaining role for plasma, except perhaps in relatively stable patients who can sustain the volume load, i.e. those without congestive heart failure or compromised renal function. 4F PCC along with Vitamin K should be used for most patients on Warfarin requiring rapid reversal for surgery or major hemorrhage including all intracranial hemorrhage and any patient at imminent risk of hemorrhagic death. For major bleeding on FXaIs, andexanet alfa has the most evidence for effective and safe reversal. Off-label use of PCCs for FXaI reversal rests on less evidence but may be reasonable if andexanet is not available. Neither has a prospective evidence base in urgent surgery. Ciraparantag would be a versatile reversal agent, but it has not been tested in bleeding patients.

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