Management of bleeding in patients receiving non-vitamin K antagonists

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ABSTRACT

Anticoagulation with non-vitamin K antagonists (Non vitamin K oral anticoagulant (NOACs)) including dabigatran, rivaroxaban, apixaban and edoxaban is at least as effective as warfarin, has fewer drug and food interactions and does not require monthly monitoring. Although major bleeding with NOACs is infrequent, there remains concern about the ability to effectively treat episodes of major bleeding. New agents have been developed that are capable of providing rapid reversal of the anticoagulation effect of NOACs. Idarucizumab normalises the dilute thrombin time and the ecarin clotting time, both of which are elevated with dabigatran. Andexanet alfa reduces increased anti-factor Xa activity seen with the use of rivaroxaban and apixaban. A universal reversal agent is in development. These agents, unlike agents to reverse the anticoagulation effect of vitamin K antagonists, appear to reverse the specific NOAC anticoagulant. The development of reversal agents is a major advancement in managing bleeding in the era of NOACs. Future studies will be required to determine the impact on important clinical outcomes.

INTRODUCTION

In randomised clinical trials, the risk of major bleeding involving non-vitamin K antagonists ranged from 1.4% to 3.6% per year.[1–5] Life-threatening or critical bleeding occurred less frequently, between 0.3% and 1.45% per year.[1 3 4] The introduction of agents capable of rapid and complete reversal of the anticoagulant effect of the NOACs makes these agents even more attractive for use in the prevention of thromboembolic events. This review will provide a state-of-the art review of the specific reversal agents.

ASSESSMENT AND DIAGNOSIS

Tests to assess anticoagulation effect of NOACs

There are some situations in which knowledge of an anticoagulant effect may improve outcomes. For example, periodic monitoring of an anticoagulant effect might improve compliance. However, the ability to measure an anticoagulant effect may also be helpful in the management of the patient with major bleeding. A rapidly available and accurate test might determine if a reversal agent is required. In a patient who receives a NOAC and is being considered for a surgical procedure, knowledge of the anticoagulation effect might influence the timing of surgery.

Tests to assess the efficacy of direct thrombin inhibitors

The dilute thrombin time (dTT) and the ecarin clotting time (ECT) can estimate the anticoagulation effect of dabigatran. In a pooled analysis, the thrombin time was too sensitive with dabigatran concentrations as little as 25 ng/mL and as high as 150 ng/mL exceeding the limits of detection.[6] To overcome this limitation, the dTT and ECT have been used to detect wide ranges of drug concentrations. There is a good correlation between dabigatran concentration and dTT or ECT when dabigatran concentrations are >50 ng/mL.[6] The dTT is commercially available for use. The ECT is currently being used in research settings. Dabigatran levels and unbound dabigatran levels have also been used in research settings. Since the half-life of the direct thrombin inhibitors is around 12 hours, these tests need to be interpreted with the knowledge of the time of intake of last dose.

Tests to assess efficacy anti-factor Xa inhibitors

Anti-factor Xa inhibitors apixaban, edoxaban and rivaroxaban inconsistently affect the Prothrombin time (PT) and activated partial thromboplastin time (aPTT). Both agents prolong the PT and there is a linear relationship with drug concentration, but sensitivity is too poor to detect therapeutic drug concentrations.[6] A prolonged PT always suggests the presence of the drug, whereas the PT can be normal despite the patient being on therapy. The drug can still be at therapeutic levels despite the PT being normal. Factor Xa inhibitors also prolong the aPTT although in a non-linear fashion and hence the aPTT is not suited to assess drug efficacy.

Chromogenic anti-factor Xa assays have been used to assess the therapeutic effect of these agents, similar to its use in monitoring for therapeutic levels of heparin and low molecular weight heparin (LMWH). Multiple studies have found a linear response between anti-factor Xa activity and drug levels of both rivaroxaban and apixaban.[6] The high degree of sensitivity makes this a reasonable agent to assess for anticoagulant effect of anti-factor Xa inhibitors. However, there are limitations. The assay must be calibrated to specific factor Xa inhibitors. The results of the assay are to be interpreted based on the timing of the last dose.

TREATMENT

General management of major bleeding with NOACs

Current anticoagulation guidelines endorse fluid and blood resuscitation, in addition to analysis of haemoglobin, renal function and a coagulation assessment.[7] In patients with major bleeding who

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last received dabigatran within 2 hours prior to presentation, activated charcoal can help decrease drug absorption from the gut. Dabigatran can be removed via haemodialysis and is an option to remove drug from circulation in patients with symptomatic bleeding.

Reversal of anticoagulation in patients on oral anticoagulation can be achieved by administration of a specific reversal agent or by repletion of factors. Repletion of factors with the use of non-activated prothrombin complex concentrates (PCCs), activated PCCs (aPCCs, FEIBA) and recombinant factor VII can be considered for patients with major bleeding, but without much supportive evidence of clinical effectiveness from randomised trials. Non-specificity in the mechanism of action, the possibility of prothrombotic risk and lack of consistency in normalisation of coagulation parameters have made PCCs a less than ideal agent for use in patients with major bleeding on NOACs.

A special situation involves the case of intracerebral haemorrhage (ICH). Haematoma expansion occurs in 73% of patients with ICH, often as early as 1 hour after the initial CT scan.[8 9] Each 1 mL increase in ICH volume from baseline is associated with 1% increased risk of death.[8] The American heart association (AHA)/American stroke association (ASA) guidelines for the management of spontaneous ICH recommend immediate correction of coagulopathy in patients with ICH.[10]

Specific antidotes for dabigatran

Idarucizumab is a humanised monoclonal antibody, which binds to dabigatran, with a higher affinity than the binding of dabigatran to thrombin, thereby neutralising the anticoagulant effect.[11–13]

In preclinical studies, idarucizumab was found to have an extremely high affinity for dabigatran, about 350 times stronger than the affinity for thrombin and no activity in coagulation or platelet aggregation[13] (figure 1). The antibody fragment demonstrated immediate reversal of dabigatran-induced anticoagulant effects as measured by thrombin time and activated partial thromboplastin time.[13] A single bolus injection of idarucizumab was shown to neutralise steady-state levels of dabigatran within 1 min, and this neutralisation was maintained over a 25 min course despite a continual infusion of dabigatran.[13] Another

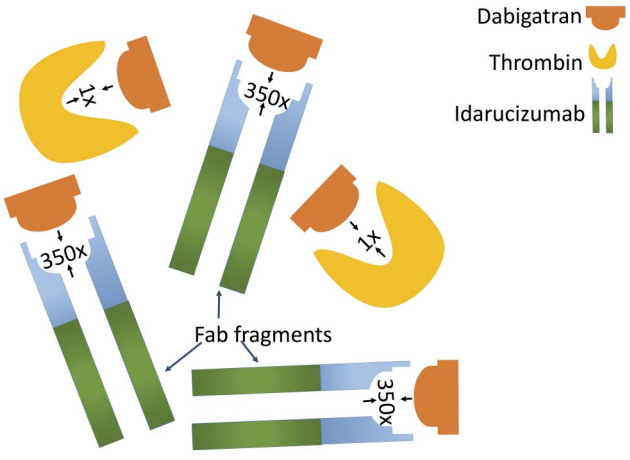

Figure 1 Schematic representation of the mechanism of action of idarucizumab. Antigen binding site (blue region in the Fab fragment) on idarucizumab binds to dabigatran (orange) with 350 times affinity than thrombin (yellow). This increased affinity is the mechanism behind removal of thrombin-bound and thrombin-unbound dabigatran and reverses the anticoagulation effect.

preclinical study was performed in a porcine model and showed a reduction in bleeding in dabigatran and trauma-induced bleeding.[14]

Following the success in the preclinical setting, a phase I study[11] of healthy volunteers was conducted to investigate the safety, tolerability and pharmacokinetics of idarucizumab.[12] The majority of adverse events reported were headache and skin irritation, but no major events were reported in either the placebo or study drug arm. Adverse events were not specific to a group, with almost 45% of subjects receiving placebo reporting events and 36% of patients in the idarucizumab arm reporting events.

Idarucizumab has a high affinity for dabigatran and can bind both free and thrombin-bound dabigatran to neutralise the anticoagulant effect.[13] Idarucizumab was found to reach peak plasma concentrations shortly after a 5 min infusion, and the effect was seen up to 24 hours.[11 12 15]

Food and Drug Administration approval of idarucizumab was based on these preclinical trials as well as the Reversal Effects of Idarucizumab on Active Dabigatran study (REVERSE AD).[16] The interim study results included two groups of patients: those needing anticoagulation reversal for serious bleeding (group A, n=51) and those needing an urgent surgical procedure (group B, n=39). In group A, the predominant aetiology of bleeding was either gastrointestinal (20 patients) or intracranial (18 patients). A total dose of 5 g of idarucizumab was administered intravenously, given in two equal aliquots less than 15 min apart. In the study, idarucizumab normalised the ECT and dTT in 88–98% of patients who received the drug. Idarucizumab also decreased the concentration of detectable unbound dabigatran. The anticoagulant effect of dabigatran was completely reversed within minutes of receiving the drug.

The other endpoint studied was haemostasis achieved in patients belonging to group B at the time of the surgical procedure. Thirty-three of 36 patients (92%) had normal intraoperative haemostasis.

In the entire study, 18 of 90 patients (20%) died including five deaths due to fatal bleeding. Seven deaths occurred in the first day after treatment (two in group A and five in group B) and were mainly related to shock and haemodynamic aetiologies. One patient had new intracranial bleeding. Deaths occurring within 4 days of treatment were thought to be due to the initial bleeding event.

After administration of a reversal agent, there is a concern about an increase in thrombotic events. Deep venous thrombosis (DVT) with pulmonary embolism occurred in two patients (one with a left atrial thrombus). A DVT occurred in one other patient without a pulmonary embolism. One patient in the study had a non-ST segment myocardial infarction and another patient suffered an ischaemic stroke. All of the reported thrombotic events occurred when antithrombotic therapy was not restarted after reversal.

The REVERSE AD study illustrates the effectiveness of idarucizumab in rapidly and effectively reversing the anticoagulant effect of dabigatran. However, the death rate was high, illustrating the poor prognosis of patients with NOAC-associated major bleeding. Since the study was not placebo-controlled, it cannot be determined if idarucizumab could be related to death, especially with the theoretical concern of increased thrombotic events. In addition, a large number (22 of 90) of patients who were bleeding had normal clotting parameters on initial evaluation, and only 1/3 had taken dabigatran within 12 hours of entry into the study. The last intake of dabigatran was self-reported and was not available. This raises the issue of a need for a rapidly available assay to determine an anticoagulant effect

of this NOAC to accurately determine which patients need a reversal agent. Finally, the endpoint of the study was reversal of anticoagulant effect, but will major clinical events be reduced? Additional studies will need to be performed before this important question could be answered.

The apparent lack of a hypercoagulant effect with idarucizumab was shown in normal volunteers when idaucizumab reversed the anticoagulant effect of dabigatran as measured by the dTT, ECT and assays of endogenous thrombin potential (ETP).[11 17] Idarucizumab use was associated with a reduction in ETP, which returned to baseline values but did not exceed baseline values prior to dabigatran ingestion, supporting the absence of procoagulant effect of idarucizumab.[11 17] In another study, reinitiation of dabigatran 24 hours after the infusion resulted in a similar therapeutic anticoagulation effect in both idarucizumab and placebo arms.[17]

Specific antidotes for factor Xa inhibitors (rivaroxaban, apixaban and edoxaban)

Andexanet alfa is a recombinant modified human factor Xa decoy protein (figure 2). The protein is an inactive factor Xa receptor due to the lack of membrane binding γ-carboxyglutamic acid domain and a serine mutation in the thrombin-generating protease enzyme.

Preclinical studies performed in rodent model and rabbit model have shown that andexanet alfa does not have any anticoagulant effect as it does not bind to native factor Xa.[18] This is despite some similarity in the receptor complex of andexanet alfa (factor Xa decoy) with factor Xa receptor. The decoy receptor binds to the unbound drug in plasma. The factor Xa inhibitor is sequestered by andexanet and rendered inactive. As a result, the active drug is not available to bind to the native Xa receptor leading to an increase in endogenous factor Xa activity. This makes it a drug that can serve as an antidote to apixaban, rivaroxaban, edoxaban and LMWH. The therapeutic effect of factor Xa inhibitors can be assessed by using the anti-factor Xa activity.[6] The effect of an antidote-like andexanet alfa thus can be assessed by normalisation of these parameters.

The effect of andexanet alfa was tested in vivo in a rat model.[18] Andexanet alfa corrected the whole blood International normalized ratio (INR) values after rivaroxaban and apixaban administration.[18] Preclinical data using a rabbit liver laceration model showed the reversal effect seen in the haemostasis models correlated with decrease in unbound rivaroxaban and apixaban as well as decrease in anti-factor Xa activity.[19] These studies established the efficacy of andexanet alfa as a reversal agent for factor Xa inhibitors and led to Study in Older Subject to Evaluate the Safety and Ability of Andexanet Alfa to Reverse the Anticoagulation Effect of Apixaban (ANNEXA A) and Study in Older Subject to Evaluate the Safety and Ability of Andexanet Alfa to Reverse the Anticoagulation Effect of Rivaroxaban (ANNEXA R) phase II studies.

ANNEXA A[20] and R[20] are two placebo-controlled randomised control studies evaluating the reversal efficacy of andexanet alfa in healthy volunteers receiving apixaban and rivaroxaban, respectively. Healthy volunteers aged 50–75 years were randomised in 3:1 (ANNEXA A) and 2:1 (ANNEXA R) ratio to andexanet alfa or placebo. In view of the half-life of andexanet being 1 hour, two dosing strategies were compared in the trial. Part 1 was an intravenous bolus dose only regimen and part 2 was an intravenous bolus dose followed by continuous infusion to extend the duration of action in view of the short half-life of andexanet. Participants on rivaroxaban needed higher bolus dose (800 mg) compared with apixaban (400 mg). This dosing was based on both phase II studies and the fact that rivaroxaban achieves higher plasma concentration and has increased volume of distribution.[20] The primary study endpoint was change in anti-factor Xa activity.

The results of ANNEXA A and ANNEXA R studies showed that andexanet alfa rapidly reversed rivaroxaban-induced and apixaban-induced changes in factor Xa activity. The onset of action was within 2–5 min after administration and was sustained for the period of infusion. The anti-factor Xa levels returned to placebo levels between 1 and 3 hours after cessation of the infusion. There was a >90% reduction in anti-factor Xa activity in both apixaban and rivaroxaban arms. There was a decrease in the measured concentration of unbound apixaban and unbound rivaroxaban with andexanet alfa administration.

No increase in thrombotic events was noted with use of reversal agent. No serious adverse drug reactions were noted. Andexanet alfa being a recombinant protein has a potential for generating antibody response. No immune response against andexanet or factor X/Xa was noted. Participants tested negative for neutralising antibodies to andexanet alfa or factor X/Xa up to 45 days after exposure.

Unlike the REVERSE AD study where idarucizumab was tested in clinical setting in a phase III trial, the ANNEXA A and R trials were performed in healthy volunteers (age 50–75 years).

ANNEXA 4, a phase III study, evaluated the safety and efficacy of andexanet in patients with acute major bleeding who were receiving one of the four factor Xa inhibitors (apixaban, rivaroxaban, edoxaban and LMWH).[21 22] The interim results of the study were recently published.[22] Patients received an andexanet bolus followed by a 2-hour infusion of the drug. For patients who had taken apixaban or rivaroxaban more than 7 hours before the administration of andexanet, the bolus dose

Figure 2 Schematic representation of the differences between factor Xa receptor and andexanet alfa. Factor Xa receptor and andexanet alfa are structurally similar. Andexanet alfa lacks the membrane binding γ-carboxyglutamic acid and has a mutated protease. These characteristics make it a decoy and the receptor cannot generate any thrombin but retains the ability to bind to factor Xa inhibitors.

was 400 mg and the infusion dose was 480 mg. For patients who had taken enoxaparin, edoxaban or rivaroxaban 7 hours or less prior to the administration of the bolus dose or for patients in whom the timing of the last dose was unknown, the bolus dose was 800 mg and the infusion dose was 960 mg. Two primary endpoints were studied: the per cent change in anti-factor Xa activity and rate of good haemostatic efficacy at 12 hours after the infusion. Patients were followed for 30 days. Thirty-two of 67 patients were on rivaroxaban, 31 were on apixaban, 4 were on enoxaparin. No patient was on edoxaban even though the inclusion criteria allowed patients to be included. The site of haemorrhage was gastrointestinal in 49% and intracranial in 42%. Thirty-seven of 47 patients had good haemostasis. Eighteen per cent of patients in the study had thrombotic events. Four patients had events within 3 days of andexanet infusion and eight patients between 4 and 30 days. The rate of prothrombotic events was higher when compared with the REVERSE AD study using idarucizumab. The rates of reinitiation of anticoagulation after the bleeding event were lower in the ANNEXA 4 study compared with REVERSE AD. The lower rate of reinitiation could have led to higher thrombotic events. Fifteen per cent of the patients died during the study from both cardiovascular and non-cardiovascular causes. The study is still ongoing and final results are awaited.

Other agents in development: a universal antidote

Aripazine (PER977, Ciraparantag) is a small, synthetic, water-soluble, cationic molecule, which binds to unfractionated heparin and LMWH through non-covalent hydrogen bonding and charge–charge interactions.[23] PER 977 has also been shown to bind to NOACs including edoxaban, rivaroxaban and apixaban and dabigatran. The results of a phase II study were published as a correspondence.[23] In healthy volunteers, 60 mg dose of edoxaban was administered, followed by intravenous PER977 3 hours later. Whole blood clotting times were significantly reduced within 10–30 min after PER977 administration and the effect was sustained up to 24 hours. There is no information regarding the adverse effects.

CONCLUSION

Bleeding is an inevitable risk with use of all anticoagulants, and the ability to manage major and life-threatening bleeding makes anticoagulants more attractive. Unlike agents like vitamin K, fresh frozen plasma and PCC, reversal agents are now being developed, which quickly and completely reverse the anticoagulant effect with NOACs. Future studies will determine if important outcomes are improved with effective therapy for major bleeding.

Main messages

- Anticoagulation effect of dabigatran and factor Xa inhibitors is measured with dilute thrombin time and anti-factor Xa activity, respectively, although these assays are not widely available.
- Idarucizumab is a specific agent for reversing the anticoagulation effect of dabigatran.
- Andexanet alfa is a specific agent for reversal of anticoagulation effect of apixaban, rivaroxaban, edoxaban and enoxaparin.

Current research questions

- What is the role of testing for anticoagulant effect in patients presenting with bleeding on NOACs?
- What is the effect of reversal agents on outcomes?
- What is the cost-effectiveness of use of reversal agents?

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Self assessment questions

1. Idarucizumab is an antibody fragment.
2. Dilute thrombin time is a test to assess efficacy of apixaban.
3. Anti-factor Xa activity measures effect of dabigatran.
4. Andexanet alfa is a reversal agent for rivaroxaban and apixaban only.
5. Aripazine is a potential universal antidote that can reverse heparin, dabigatran, edoxaban, apixaban and rivaroxaban.

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Answers

1. True
2. False
3. False
4. False
5. True