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Antidotes for the new oral anticoagulant drugs!

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Abstract:

The introduction of direct oral anticoagulant drugs has added a new dimension to the management of thrombotic and cardiovascular diseases. Although clinical useful, the use of these drugs has been associated with bleeding complications of varying magnitude. Until recently, there was no antidote available for the control of bleeding associated with DOAC's. Such traditional approaches as the use of blood products and mechanical methods have been used to control bleeding in past. Molecular approaches have resulted in the development of specific antidotes for the oral anti-Xa and anti-IIa drugs. Andexanet alfa is a molecularly modified recombinant human factor Xa which is developed as an antidote for rivaroxaban and apixaban. Praxbind is an antibody which neutralizes dabigatran. Both agents have approved by the FDA and the European Medicine Agency, while these two agents are valuable in the management of bleeding with DOAC's, their use is associated with various adverse responses. Since both agents are proteins, antibody generation and interactions with endogenous proteins may also contribute to some of the observed adverse effects. The clinical data on their use is rather limited and additional studies are warranted to optimize their use. A global antidote, Ciraparantag, (PER977) is also developed for the neutralization of DOAC's. Both the activated and non-activated forms of prothrombin complexes are reportedly effective as an antidote for DOAC's. Additional studies are needed to develop guidelines for the safe use of antidotes to minimize the observed complications with the use of antidotes.

Keywords:

Antidotes, oral anticoagulant drugs, pharmacology

Anticoagulation is widely utilized for the treatment and prevention of thrombosis in more than seven million patients annually in the United States. Despite the need for anticoagulation, many groups of patients are not treated with anticoagulation due to the fear of bleeding complications. An additional serious consideration among patients receiving anticoagulants is disruption of therapy in the event of emergency surgery or invasive procedures resulting in elevated risk of thrombosis. In the United States for the 12 months ending June 2013, among patients treated with anticoagulants enoxaparin, rivaroxaban, apixaban and dabigatran, it is estimated that approximately 300,000 patients experienced bleeding with approximately 106,000 emergency room and 68,000 hospital admissions. Although protamine sulfate may be useful in the case of heparins until recently there was no antidote available for dabigatran, rivaroxaban and apixaban. Using advanced molecular approaches specific antidotes of dabigatran namely praxbind and for the anti-Xa agent's specific antidote, andexanet alfa are developed. Other agents for the control of bleeding which have been used include prothrombin complex concentrates (activated and non-activated), recombinant factor VIIa and a universal antidote, ciraparantag.

Dabigatran was the first direct oral anticoagulants approved in 2010 and is a factor IIa inhibitor. Whereas apixaban, betrixaban, edoxaban and rivaroxaban represent factor Xa inhibitors. Since these

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new anticoagulants inhibit the blood from clotting normally, patients taking these agents may be at risk of serious and catastrophic bleeding.

Praxbind is an antidote developed for the neutralization of the effects of dabigatran (the active moiety of Pradaxa). Praxbind can be used to rapidly stop the anticlotting effect of dabigatran, before emergency surgery or in case of life-threatening bleeding. Praxbind is comprised of the active substance idarucizumab which is a monoclonal antibody fragment. A monoclonal antibody is a type of protein that has been designed to recognize and attach to a specific structure (called an antigen). Praxbind works by attaching strongly to dabigatran and forming a complex in the blood. This readily stops dabigatran's anticoagulant effects. Praxbind has been investigated in three main studies involving 141 healthy adults who previously received dabigatran. In these studies, volunteers received either praxbind or placebo, after treatment with dabigatran for 3.5 days, results showed that praxbind was able to completely neutralize dabigatran anticoagulant effect within 5 minutes of use. In a still ongoing trial, an interim analysis showed similar results in 123 patients who had uncontrolled bleeding or required emergency surgery while using dabigatran. Most patients in the study were taking dabigatran to prevent stroke due to atrial fibrillation. These studies showed that praxbind effectively neutralize the anticoagulant effect of dabigatran rapidly which sustained for longer period of time.

Andexanet alfa (Annexxa), is a recombinant protein that acts as a decoy for the direct oral FXa inhibitors apixaban and rivaroxaban. As a result, andexanet alfa neutralizes the anticoagulant effect of these inhibitors. It is projected that andexanet alfa will also neutralize the effects of other factor Xa inhibitors such as betrixaban and edoxaban. The effects of the therapy with andexanet alfa were studied in 352 patients for safety and 167 patients for efficacy. Clinical efficacy is based upon reversal of anti-Xa activity in healthy volunteers and interim results of study in patients with life-threatening bleeding. Andexanet alfa enabled the reversal of the apixaban and rivaroxaban anticoagulant effect within minutes of its administration.

Ciraparantag (aripazine) is a synthetic drug which is under investigation as a universal antidote for a number of anticoagulant drugs, including oral factor Xa inhibitors and factor IIa inhibitors, parenteral low molecular weight heparins and unfractionated heparin. Based on experimental studies, this substance binds directly to anticoagulants via hydrogen bonds from or to various parts of the molecule. Clinical studies have shown that ciraparantag acetate doses of ≥100 mg exhibited complete and sustained reversal of both steady-state apixaban and rivaroxaban in age-matched healthy volunteers as measured by whole blood clotting time (WBCT). In previous clinical trials, ciraparantag had shown complete and sustained reversal of the DOAC, edoxaban, and the LMWH, enoxaparin, following a single intravenous bolus dose, as measured by WBCT. While the safety profile of ciraparantag is consistent with previous trials; the most common adverse events observed were transient mild facial flushing and dysgeusia. No pro-coagulant signals were observed in any clinical trials to date.

Prothrombin complex concentrates (PCC) such as KCentra and activated prothrombin complex concentrates such as FEIBA have also been used for the neutralization of the newer oral anticoagulant drugs. FEIBA at a dosage of 25 – 50 U/kg has found to be effective in reversing the effects of newer oral anticoagulant drugs. Some recent reports have shown that lower dosage can also be effective. KCentra, a four factor PCC can also be used at a 50 U/kg dosage. Additionally, recombinant factor VIIa (Novoseven) has also been used in severe bleeding control. These drugs were approved long before the use of newer antidotes such as the praxbind and andexanet alfa, moreover their cost of the plasma-based drugs is much cheaper than the newer antidotes.

Although, the antidote currently available for the management of bleeding with new oral anticoagulant drugs are useful in managing severe bleeding complications. These antidotes have certain adverse effects which have not been fully explored. Thrombotic complications with the use of both praxbind and andexanet alfa have been reported. The thrombotic event within 30 days of reversal are much higher with andexanet alfa (10%) in comparison to praxbind (4.8%). Some of these complications have been severe and resulted in mortality outcome. Andexanet alfa is a decoy protein and still retains some of the biologic properties, it has been shown to interfere with the TFPI, AT and thrombomodulin. Thus, it may create endogenous thrombotic environment. Praxbind is an antibody and forms complexes endogenously which may have some adverse effects. Since both of these are proteins, neutralizing antibodies may also be formed. The thrombogenicity of activated prothrombin complex concentrate is also a complication which requires close monitoring, similarly PCC's have thrombogenic effects which are relatively mild. Ciraparantag reportedly have allergic reactions and may lead to anaphylactoid reactions. The FDA has approved both andexanet alfa and praxbind following fast tracking path in order to provide clinician an antidote, however this approval was based on limited clinical data and incomplete adverse reaction profile review. The cost of the newer antidotes is rather high. In the case of andexanet alfa, it is $58,000 per reversal (800 mg bolus + 960 mg infusion, $3,300

per 100 mg vial) which is higher than reversal agents for other DOAC agents. For the dabigatran reversal, the cost of 2.5 g vials is nearly $3500. The cost of FEIBA can range from $ 3500 – 5000. KCentra is approximately the same as FEIBA. Therefore, these drugs are relatively costly, and their use is strictly controlled by internal audit units in the hospitals.

A full study report of the use of andexanet alfa to treat bleeding associated with FXa inhibitors reported that within 30 days, 49 (14%) patients died in a cohort of 352 patients. Thirty-four of these patients had thrombotic events. Of these, 11 patients encountered thrombotic event within 5 days after andexanet alfa therapy, 11 had an event with in 6 to 14 days, and 12 had an event between 13 and 30 days. Myocardial infarction, ischemic stroke, and deep venous thrombosis (DVT) were recorded as major thrombotic complications.[1] In other studies, a transient reduction in tissue factor pathway inhibitor (TFPI) activity was reported after andexanet alfa therapy.[2] Since TFPI is a major inhibitor of TF-VIIa complex, a decrease in its activity may lead to increased thrombogenesis. Andexanet alfa also reverses the anticoagulant effects of low-molecular-weight heparin and fondaparinux by competing with FXa for binding with antithrombin.[3,4] It is plausible that andexanet alfa treatment may also inhibit the endogenous heparan sulfate glycosaminoglycan (GAG) complexes with endothelium-bound antithrombin.[5] Additionally, andexanet alfa may also modulate protease activated receptor functions and interact with thromboodulin (TM). Taken together, andexanet alfa produces additional effects on endogenous modulators which regulate hemostasis, including TFPI, antithrombin, TM and GAG, and may also influence other heparin-like mediators. Thus, besides neutralizing the anti-Xa agents, andexanet alfa may promote a procoagulant environment by disrupting hemostasis at multiple sites.[6]

In a recent study, the effect of andexanet alfa on the neutralization profile of various FXa inhibitors was investigated using anticoagulant and thrombin generation (TG) assays.[7] Individual aliquots of normal human plasma containing 1 mg/mL of apixaban, betrixaban, edoxaban, and rivaroxaban, were supplemented with saline or andexanet alfa at a concentration of 100 ug/mL. Clotting profiles include prothrombinase-induced clotting time, activated partial thromboplastin time, and prothrombin time. Factor Xa activity was measured using an amidolytic method. Thrombin generation was measured using a calibrated automated thrombogram. Differential neutralization of all 4 anticoagulants was noted in the activated clotting time and other clotting tests. The FXa activity reversal profile varied with an observed decrease in apixaban (22%), betrixaban (56%), edoxaban (28%), and rivaroxaban (49%). Andexanet alfa also led to an increased TG in comparison to saline. The peak thrombin was higher (40%), area under the curve (AUC) increased (15%), whereas the lag time (LT) decreased (17%). Andexanet alfa added at 100 ug/mL to various FXa supplemented systems resulted in reversal of the inhibitory effects, restoring the TG profile; AUC, LT, and peak thrombin levels were comparable to those of unsupplemented samples. Andexanet alfa is capable of reversing anti-Xa activity of different oral FXa inhibitors but overshoots thrombogenesis in both the saline and FXa inhibitor supplemented systems. The degree of neutralization of Xa inhibitor is specific to each agent.

In the RE-VERSE AD trial with idarucizumab, the adverse reactions reported in ≥5% of patients were GI related. Of the 503 dabigatran-treated patients in the entire study period, 101 patients died, 19 within the first day after idarucizumab dosing; which are reported to be due to complications of the other co-morbidities. Of the 33 of 503 patients reported thrombotic events, 11 patients within 5 days after treatment with idarucizumab and 22 patients 6 days or more after treatment with this antidote. Most of these patients were not treated with any antithrombic therapy and the observed thrombotic complications were attributed to other co-morbities. Patients administered with dabigatran have underlying disease predisposing them to thromboembolic events. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease.[8]

Since both the andexanet alfa and idaruzizumab are proteins in nature these agents may generate antibodies which have not been extensively investigated. The immunogenic potential of andexanet alfa has been briefly reported in an internal document of the 145 subjects treated with andexanet alfa, 17% showed low titer of antibodies to andexanet alfa. In the ANEXXA4 study, 6% of the 98 patients developed antibodies to andexanet alfa with in 30 days after treatment, however none of these were neutralizing antibodies. Antibodies with cross reactivity for FX and FXa have not been detected in the healthy subjects or in bleeding patients.[9] However this internal data is very limited and additional information on systematic screening of these antibodies is warranted. Moreover, repeated administration of andexanet alfa to patients treated before may also provide some insight into the existence of long-term antibodies. Anti-idarucizumab antibodies were detected in 5.6%, but in most patients, these antibodies either preceded idarucizumab dosing or were of low titer. Two serious anaphylactic reactions and one hypersensitivity reaction were reported.[10] It seems that the magnitude of antibody generation for these agents is underreported and warrants accurate reporting on patients treated with these agents.

Although, the need for an antidote for the new oral anticoagulant drug such as the FXa and FIIa inhibitors, is timely and will be helpful in using these agents more freely by clinicians, however there is adequate data that the use of these agents is associated with thrombogenesis. Patient with pre-existing thrombophilia and other predispositions to thrombosis may be more prone to develop severe thrombotic complications. Thus, these antidotes should be used with caution and the dosage need to be optimized and carefully monitored in order to avoid adverse outcomes. Moreover, the selection of a specific DOAC for the treatment of different population groups should be taken into account the pharmacological profile of each of the individual drug and patients on physiologic predispositions.

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Conflicts of interest

There are no conflicts of interest.

References

1. Connolly SJ, Crowther M, Eikelboom JW, *et al*. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med 2019;380:1326-35.
2. Lu G, Hollenbach SJ, Baker DC, Tan S, Hutchaleelaha A, Curnutte JT, *et al*. Preclinical safety and efficacy of andexanet alfa in animal models. J Thromb Haemost 2017;15:1747-56.
3. Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz JI, *et al*. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. J Thromb Haemost 2016;14:623-7.
4. Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. Thromb Haemost. 2015; 113:931-42.
5. Li L, Bonventre JV. Endothelial glycocalyx: not just a sugar coat. Am J Respir Crit Care Med 2016;194:390-3.
6. Sartori M, Cosmi B. Andexanet alfa to reverse the anticoagulant activity of factor Xa inhibitors: a review of design, development and potential place in therapy. J Thromb Thrombolysis 2018; 45:345-52.
7. Siddiqui F, Tafur A, Ramacciotti LS, Jeske W, Hoppensteadt D, Ramacciotti E, Iqbal O, Fareed J. Reversal of Factor Xa Inhibitors by Andexanet Alfa May Increase Thrombogenesis Compared to Pretreatment Values. Clin Appl Thromb Hemost 2019; 25:1076029619863493.
8. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, *et al*. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med 2017;377:431-41. doi: 10.1056/NEJMoa1707278.
9. Portola Pharmaceuticals. Andexxa (coagulation factor Xa (recombinant), inactivated-zhzo): US prescribing information. 2018. http://www.fda.gov/. Accessed 15 May 2018.
10. Connors JM. Antidote for Factor Xa Anticoagulants. N Engl J Med 2015;373:2471-2. doi: 10.1056/NEJMe1513258.