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DOAC Reversal Agents

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Abstract

Direct oral anticoagulant (DOAC) drugs revolutionized the anticoagulant market and pose an attractive alternative approach to the treatment and prevention of VTE, as well as the prevention of stroke in atrial fibrillation (A. Fib) patients. DOAC agents include dabigatran etexilate (PRADAXA), rivaroxaban (XARELTO), apixaban (ELIQUIS), and edoxaban (SAVAYSA). Dabigatran etexilate functions mechanistically as a direct thrombin inhibitor, whereas rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors. These agents are more expensive when compared to warfarin therapy (classic Vitamin K antagonist), but have fewer monitoring demands, fewer food interactions, and may offer a more patient-friendly outpatient dosing regimen.[1] One unique characteristic of DOACs is the ability for DOAC anticoagulation effects to be rapidly reversed. DOAC specific reversal agents (idarucizumab, andexanet alfa, and ciraparantag) have recently become available or are currently undergoing phase 2 and 3 trials. This review article will focus on specific reversal agents and some of their characteristics.

Managing DOAC therapy around invasive procedures involves consideration of the current patient situation. Clinicians should take into consideration the urgency of the procedure and determine whether it is possible to delay invasive operations.[1] For patients who are on a DOAC due to recently having an invasive operation, the risk of recurrent VTE is highest during the first 3 months post operation.[1] For elective procedures, clinicians should first consider whether the procedure can be delayed until a time that the patient may not require a DOAC, or is at least several months after the initial event due to the risk of recurrence.[1] For patients requiring long-term anticoagulation or who cannot delay a procedure, clinicians must assess the risks and benefits of the abrupt therapy interruption. When therapy interruption is necessary, the cessation and resumption of the DOAC around the elective procedure is determined according to bleeding risk, renal function, and DOAC half-life.[1]

As with all anticoagulant drugs, bleeding is a major complication that can develop and cause life threatening hemorrhagic conditions to arise. Where DOACs have previously failed to match warfarin is in the category of rapid reversal, possibly explaining why many prescribers may be partial to warfarin. Vitamin K or fresh frozen plasma infusion have functioned as warfarin reversal agents during episodes of bleeding or hemorrhage, but there has not been a reversal agent for the DOAC agents in the cases when rapid reversal has been needed (traumatic bleeding, emergency surgery, hemorrhage etc).[2] Typically, due to the short half-lives of DOAC agents, relatively abrupt discontinuation of these medications can suffice in eventually reversing their effects.[3] In times of emergency, when discontinuation reversal will not be enough, it is essential that alternative reversal strategies target individual DOAC agents while taking into consideration the urgency of the situation. Thus, several agents have been developed over the last several years to meet this need. These agents will likely be used clinically in patients with life-threatening bleeding such as intracranial hemorrhage and retroperitoneal bleeding, as well as in patients requiring emergency/immediate surgery.[4] This review looks to compare characteristics of DOAC reversal agents, that are both FDA approved as well as currently undergoing phase 2 and 3 studies.

Idarucizumab (Praxbind)

Idarucizumab received FDA approval in October 2015 as a reversal agent that rapidly neutralizes the anticoagulant effect of dabigatran. Idarucizumab is a monoclonal antibody fragment that binds directly to dabigatran with an extremely high affinity.[4] The affinity of idarucizumab for dabigatran is approximately 350-fold stronger than the affinity of dabigatran for thrombin.[4] This allows idarucizumab to be highly specific to dabigatran, prevent binding to other thrombin substrates (factors V, VIII, or XIII, fibrinogen, von Willebrand factor, protease-activated receptor 1, and protein C), as well as having no effect on platelet aggregation.[4] In the Phase III RE-VERSE AD prospective cohort study, 90 patients were divided into two groups.[5]

Group A included patients with uncontrollable/life threatening bleeding that required a reversal agent, and group B patients included those who required an invasive procedure/surgery within the next 8 hours.[5] Patients received 5 g of intravenous idarucizumab, which was administered as two 50-ml bolus infusions, each containing 2.5 g of idarucizumab, no more than 15 minutes apart.[5] The median plasma concentration of unbound dabigatran at baseline was 84 ng/mL in group A and 76 ng/mL in group B.[5] In samples obtained after the first vial of idarucizumab was administered, the concentration of unbound dabigatran was less than 20 ng/mL; a level that produced a negligible anticoagulant effect (in all but one patient).[5] These levels were maintained for roughly 24 hours.[5]

Uses: Dabigatran reversal prior to emergency surgery
Dose: 5 grams IV given in two separate doses of 2.5 grams no more than 15 minutes apart.[6]
Time of onset: "immediately" decreasing the plasma concentrations of dabigatran after IV with complete bleeding cessation in 11.4 hours.[4]
Negative aspects: coagulation correction as soon as 1-4 hours after Praxbind injection; may consider a second dose.[4]
Warnings/Side effects: Patients with known hypersensitivity reactions with idarucizumab or any components of its formulations should be evaluated against the potential benefit of emergency dabigatran reversal.[6] Thromboembolic risk in patients after dabigatran reversal; reinitiate dabigatran 24 hours after idarucizumab reversal.[6]

Andexanet alfa

Andexanet is a recombinant modified human factor Xa decoy protein that retains no enzymatic activity within the human body, but retains the ability to bind factor Xa inhibitors at the active site with high affinity.[7] The efficacy and safety of andexanet alfa on apixaban and rivaroxaban anticoagulation reversal was assessed in the ANNEXA-A and ANNEXA-R trials. Participants in the ANNEXA-A study received apixaban orally where as participants in the ANNEXA-R study received rivaroxaban orally.[7] After achieving max plasma concentration of apixaban, andexanet was administered as an intravenous (IV) bolus or as an IV bolus with or without continuous infusion.[7] After achieving max plasma concentration of rivaroxaban, andexanet was administered as an intravenous bolus or as an equivalent intravenous bolus followed by a continuous infusion.[7]

Anti–factor Xa activity was rapidly reduced and thrombin generation was rapidly restored (within 2 to 5 minutes) to a greater extent after administration of a bolus of andexanet than after administration of placebo, both in the apixaban study and in the rivaroxaban study (p-value <0.001 in both studies).[7] After administration of the andexanet bolus was completed, the reversal of anti–factor Xa activity persisted for 2 hours and thrombin generation increased to above the lower limit of the normal range within 2 to 10 minutes.[7]

The study claimed that there were no serious or severe adverse events, no thrombotic events, as well as no neutralizing antibodies present.[7] Non-neutralizing

antibodies against andexanet were detected in 17% of patients who received andexanet and tended to appear within 15 to 30 days after andexanet administration.[7] Hypersensitivity reactions could be a cause of a severe adverse reaction in future trials. The ongoing ANNEXA-4 phase 3b–4 study is evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor–associated acute major bleeding.[7] Andexanet alfa received FDA approval for "Breakthrough Therapy" designation in November 2013 and orphan drug status in February 2015. "Breakthrough therapy" designation is similar to a fast track designation.[9] In order to meet this criteria, preliminary clinical evidence must demonstrate that the drug may have substantial improvement on at least one clinically significant endpoint over available therapies.[9]

In conclusion, andexanet adds a specific and rapidly acting antidote that is being developed for urgent reversal of factor Xa inhibitor anticoagulant activity.[7] The ability of andexanet to reverse anticoagulation in participants undergoing anticoagulation therapy with apixaban, rivaroxaban, edoxaban, or enoxaparin makes it a potential widespread antidote for direct and indirect factor Xa inhibitors.[7] The rapid onset and offset of action of andexanet paired with the ability to administer it as a bolus or as a bolus plus an infusion may provide flexibility with regard to the restoration of hemostasis when urgent factor Xa inhibitor reversal is required.[7]

Uses: Rapid acting antidote for direct and indirect factor Xa inhibitor anticoagulant medications

Doses: 400-960mg IV bolus or bolus plus infusion.[7]

Time of Onset: Thrombin generation restored 2-5 minutes after bolus dosing.[7]

Warnings/side effects: In one study, one patient developed hives.[7] No other severe side effects or thrombotic events were reported.

Ciraparantag

Ciraparantag (PER977) is a small, synthetic, water-soluble molecule designed specifically as an IV reversal agent targeting DOACs and heparins.[4] It has been shown to form a complex with larger molecules such as unfractionated heparin and LMWH, as well as with smaller molecules such as fondaparinux, apixaban, edoxaban, rivaroxaban, and dabigatran and inhibits antithrombin interaction.[4] Ciraparantag exhibits no binding to plasma coagulation factors or albumin therefore exhibiting no procoagulant effect.

Ciraparantag was investigated in a double-blind, placebo-controlled, dose-escalation trial involving 80 healthy volunteers.[4] Trial participants were randomly assigned to cohorts to receive single-dose IV ciraparantag 5, 15, 25, 50, 100, 200, or 300 mg or placebo.[4] Study participants received oral edoxaban 60 mg followed by single dose IV ciraparantag or a placebo 3 hours later at edoxaban max concentration.[4] Edoxaban administration increased whole blood clotting time (WBCT) by 37% over the baseline value.[4] Participants receiving ciraparantag 100, 200, or 300 mg expressed a decreased WBCT to within 10 percent above the baseline value in 10 minutes or less, suggesting a full

reversal of anticoagulant effects, and values remained in that window for 24 hours.[4] One recognizable limitation of a universal reversal agent is that it may interfere with the emergency use of an anticoagulant during a procedure for patients requiring heparins for extracorporeal life support or cardiopulmonary bypass support.[2] Research is also required to determine when anticoagulation can be restarted after ciraparantag administration. Ciraparantag received fast-track status from the FDA in April 2015 and is currently undergoing additional phase II trials under Perosphere Inc, with Phase III clinical trials planned for the future.[4,8]

Conclusion

These agents provide a method of anticoagulant reversal for patients who cannot wait for an extended period of time post DOAC discontinuation in order to undergo a procedure. These situations include patients with life-threatening bleeding such as intracranial hemorrhage and retroperitoneal bleeding, as well as in patients requiring emergency/immediate surgery to "safely" undergo surgery without an extensive risk of bleeding.

Clinicians will need to have unmistakable evidence supporting that the patient is truly in immediate need of a rapid anticoagulant reversal agent to justify one being used. The need for these agents in the moment will have to be significant, as these agents will be relatively costly. Clinicians will also have to become familiar with new guidelines and treatment regimens. The ability to rapidly reverse DOAC therapy may positively influence the confident use of them more frequently in the clinical setting. Hospital pharmacies will need to accommodate the storage requirements for these new agents by preparing/maintaining proper refrigeration and inventory management. Hospitals will also have to consider modifying/programming "smart-pump" infusion devices for these agents.

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