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Reversal of Oral Anticoagulants a Narrative Review

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ABSTRACT

Abbreviations: VTE: Venous Thromboembolism; VKA: Vitamin K Antagonists; NVAF: Nonvalvular Atrial Fibrillation; DOAC: Directly Acting Oral Anticoagulants; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PT: Prothrombin Time; INR: International Normalised Ratio; DTT: Diluted Thrombin Time

Introduction

Anticoagulants have long been used for prevention and treatment of arterial and venous thromboembolism (VTE). Vitamin K antagonists (VKAs), especially warfarin, were used for decades as the only available oral anticoagulants. Recently, non–vitamin K antagonist oral anticoagulants (Directly acting oral anticoagulants; DOACs) have been approved and used as alternatives to warfarin. DOACs are now indicated for prevention of stroke risk that may result from nonvalvular atrial fibrillation (NVAF), and for VTE treatment and prophylaxis. Currently, the most used DOACs are Dabigatran etexilate, Rivaroxaban, Apixaban and Edoxaban. DOACs have been found to be associated with lower or comparable risk of stroke, systemic embolism, major bleeding, and death when compared with warfarin. In contrast to warfarin, DOACs have been proved to have a more predictable therapeutic effect and hence no specific routine laboratory monitoring are required for patients receiving these agents. Moreover, DOACs have fewer drug-drug interactions risk and no dietary restrictions are needed as in case of warfarin. Since their introduction, DOACs have had the disadvantage of the absence of a specific antidote to reverse their anticoagulant effect in case of uncontrolled bleeding or emergency surgery. However, more recently, two of the new reversal agents (Idarucizumab and Andexanet alfa) have been approved for reversal of dabigatran and FXa inhibitors. Also, ciraprantag, which is still under trial, is expected to be a broad-spectrum reversal agent for many of the commonly used anticoagulants [1,2] (Figure 1).

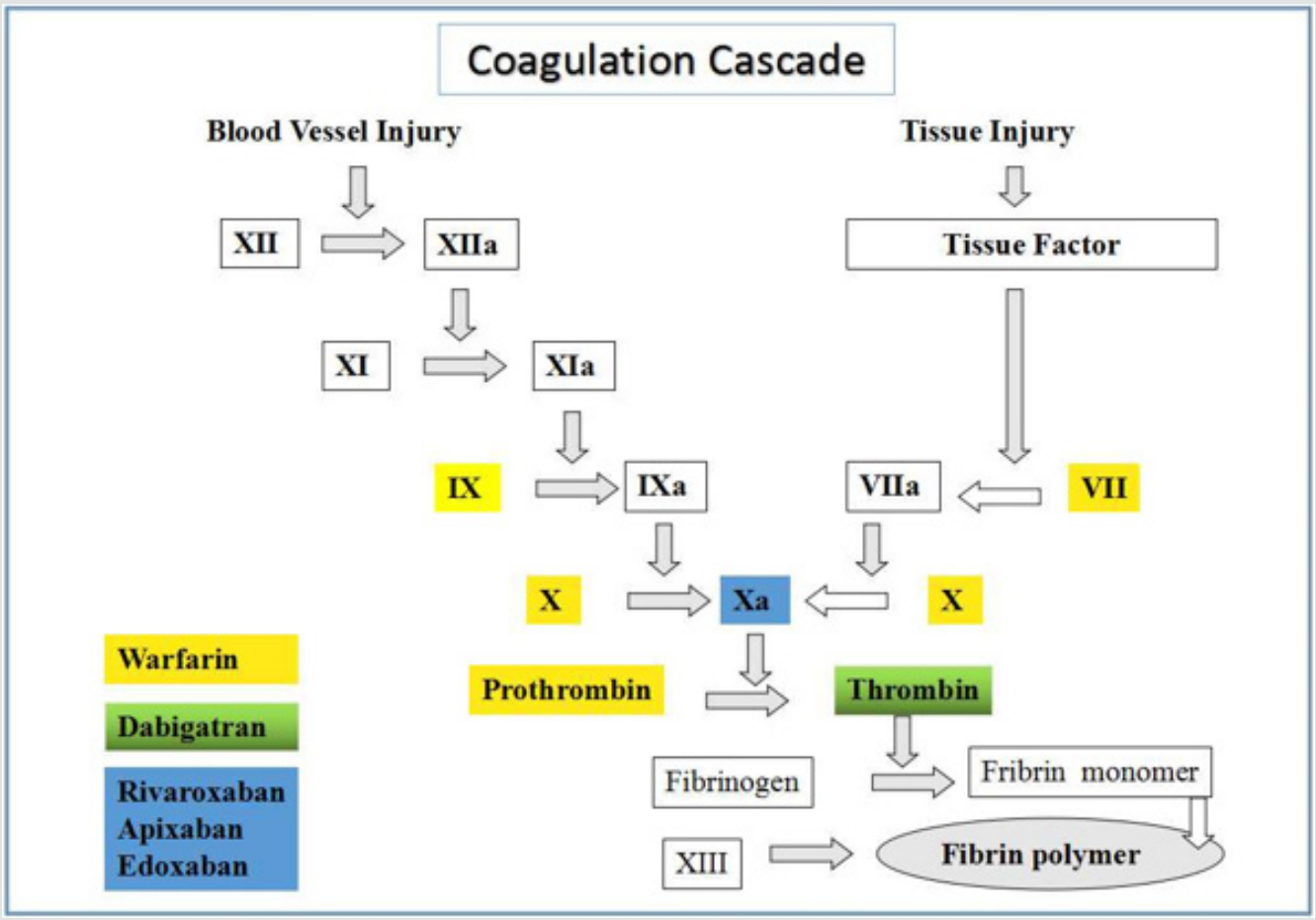

Figure 1: Coagulation cascade and sites of action of oral anticoagulants.

Pharmacological Properties of Commonly Used Oral Anticoagulants

Warfarin: Warfarin achieves its anticoagulant activity by inhibiting hepatic synthesis of vitamin K-dependent clotting factors "II, VII, IX, and X". These factors are produced in the liver as precursor forms which are activated, using vitamin K as a cofactor, by carboxylation of their glutamic acid residues. Maximum anticoagulant effect may not be achieved before 4–5 days. Owing to its high-water solubility, it is rapidly absorbed from gastrointestinal system and hence has high bio-availability and reaches its maximal blood concentrations about 90 minutes after oral administration. Up to 99% of warfarin circulates bound to plasma proteins and mainly undergoes hepatic metabolism by the cytochrome P450 system. Warfarin has high susceptibility to drug-drug interactions. Its metabolism is affected by multiple other drugs, particularly those that inhibit or induce cytochrome P450. Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, potentiate the anticoagulant effect of warfarin through displacement of warfarin from its protein binding sites and through inhibition of platelet function [1,3].

Dabigatran Etexilate (Pradaxa)

Dabigatran etexilate is a highly specific and competitive direct thrombin inhibitor. It is a pro-drug, with a very low bioavailability (3-7%), which is converted to its active form by serum esterases. It reaches its peak plasma level within 2 to 3 hours following oral administration, with a rapid onset of action (1–2 h) and a short half-life in healthy subjects (12–17h). Dabigatran is not a substrate of CYP450 enzymes but is subject to conjugation forming pharmacologically active acyl glucuronides. After oral administration, 7% of dabigatran is recovered in urine and 86% is excreted in feces. Of the proportion of the drug reaching blood, 80% is eliminated by the kidneys [2,4].

Rivaroxaban (Xarelto)

Rivaroxaban is a selective competitive direct inhibitor of factor Xa. It is rapidly absorbed from gastrointestinal tract with 80 to 100% bioavailability for the 10 mg dose and around 66% for the 20 mg dose. It reaches its peak plasma concentration within 2 to 4 hours after oral administration with a half-life of 9 to 13 hours. It has a high plasma protein binding of 92 to 95% and it undergoes

oxidative degradation and hydrolysis in the liver. More than half of the orally administered rivaroxaban is excreted as inactive metabolites in urine and feces. While more than one-third of the drug is excreted unchanged in urine [3,5].

Apixaban (Eliquis)

Apixaban is, like Rivaroxaban, a competitive direct inhibitor of factor Xa. It is absorbed throughout gastrointestinal tract with a bioavailability of 50%. It achieves its maximum plasma concentration in 3 to 4 hours after oral administration with a half-life of 12 hours. It has high plasma protein binding of 87% and is predominantly metabolized via CYP3A4 in the liver. Apixaban is eliminated through urine and feces with renal excretion accounts for more than 25% of its total clearance [3,6].

Edoxaban (SAVAYSA)

Edoxaban is another reversible direct factor Xa inhibitor. The usual recommended dose is 60 mg once daily and should be reduced to 30 mg in patients with creatinine clearance less than 50 ml/minute. Notably, it showed reduced efficacy to protect against ischemic stroke in non-valvular atrial fibrillation patients with creatinine clearance more than 95 ml/ minute. It is rapidly absorbed and reaches peak plasma concentration within 1–2 h with a half-life of 9 to 11 hours. Up to 50% of edoxaban is eliminated by the kidneys [3,7]. All DOACs are substrates for P-glycoprotein (P-gp) transport. Rivaroxaban Apixaban and Edoxaban are substrates for cytochrome P450 (CYP 3A4). Therefore, concomitant medications that are inducers or inhibitors of these pathways should be evaluated for the potential to interact.

Measurement of Coagulation Effect

Warfarin increases the prothrombin time (PT) and the international normalised ratio (INR). Regular measurement of INR levels in patients receiving warfarin is an essential component of their management. Therefore, warfarin anticoagulant effect can be reliably evaluated by measuring the INR. One of the clinical advantages of DOACs is their predictable anticoagulant effect which makes it possible to administer them in fixed doses without the need of routine laboratory monitoring. Unlike warfarin, there is no specific reliable method to measure the anticoagulant activity of DOACs. Both quantitative and qualitative tests for DOACs assessment exist. Quantitative assessment of DOACs, by measuring Direct Thrombin Inhibitors (DTIs) and Activated Factor X inhibitors (FXaIs), are not commonly available in most hospitals. On the other hand, qualitative tests to measure DOACs activity are more easily accessible.

For dabigatran, diluted thrombin time (dTT) is the most sensitive test which measures direct activity of thrombin. Hemoclot is a measure of dTT with specific calibrators for dabigatran. A dTT level of more than 200 ng/mL after 12 hours of the last dose is correlated with a higher risk of bleeding. Both activated partial thromboplastin time (aPTT), and ecarin clotting time (ECT) can also be used. An aPTT level of ≥2 or ECT ≥3 times the upper limit of normal may be associated with increased risk of bleeding. Regarding factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), measurement of anti-factor Xa activity by chromogenic assays is the most specific indicator of their anticoagulant effect. They also affect the PT and aPTT to varying degrees. All factor Xa inhibitors cause prolongation of the PT. Although its sensitivity depends on the reagents used and the particular factor Xa inhibitor, a normal PT value usually excludes any residual anticoagulant effect produced by one of these drugs. Activated partial thromboplastin time (aPTT) prolongation is also affected by variability of assays. aPTT could be useful for measuring anticoagulation effect of rivaroxaban. On the other hand, there is not much data available for edoxaban and apixaban. Overall, there is no available definite studies to associate a level of specific coagulation parameter with the bleeding risk of any of the DOACs [1,8].

Strategies for Anticoagulation Reversal in Oral Anticoagulants Associated Bleeding

Generally, assessment of bleeding severity is the key factor in managing uncontrolled bleeding. While minor to moderate bleeding could be managed symptomatically, life-threatening bleeding should be managed promptly and aggressively. Regardless of the degree of bleeding severity, supportive care and discontinuation of the anticoagulant drug remain the mainstay of management. The source of bleeding should be investigated, and general supportive measures should be applied for the aim of stopping the bleeding and resuscitating the patient. General supportive measures include mechanical compression, surgical or endoscopic hemostasis, and fluids and blood products resuscitation. Once specific reversal agents are available, they should be used accordingly. Activated charcoal can be used if a recent dose of the medication has been received within less than 2 hours. Hemodialysis can also be considered for removal of dabigatran, especially in patients with renal impairment [9].

Non-Specific Haemostatic Agents

If no specific reversal agent is available, the following non-specific haemostatic agents can be used for reversal of excessive bleeding.

Recombinant factor VIIa (NovoSeven)

It acts by by activating factor X to initiate thrombin generation and can be given by a dose of 90 mcg/kg. Its use is associated with high risk of thrombotic complications [10].

Prothrombin Complex Concentrate (PCC)

It contains the 4 vitamin K-dependent factors (II, VII, IX and X)

in addition to proteins C and S. It was developed for management of warfarin-induced uncontrolled bleeding, but further studies showed its effectiveness in controlling life-threatening haemorrhage resulted from the use of DOACs. Its usual dose is ranging between 25 to 50 IU/Kg. Different available types of PCC include the following:

- Four-factor prothrombin complex concentrate (Beriplex, Octaplex) contains large amounts of non-activated vitamin K-dependent factors II, VII, IX and X.
- Three-factor prothrombin complex concentrate (Profinine SD, Bebulin VH) contains smaller amounts of non-activated factor VII relative to II, IX and X.
- Activated prothrombin complex concentrate (FEIBA NF) contains activated factor VII in addition to factors II, IX and X [10].
- Fresh Frozen Plasma: It contains all coagulation factors in lower concentrations than in factor concentrates preparations. It can be used as a last resort for controlling bleeding in case of unavailability of specific antidotes and factor concentrates. The recommended dose is 15 ml/Kg [11].
- Human fibrinogen concentrate: Although it is effectively used to control bleeding in some conditions such as hypofibrinogenemia and dissiminated intravascular coagulation, its use has not been proved to be effective in reversal of anticoagulation in bleeding patients on oral anticoagulants [10].

Specific Antidotes

Phytomenadione (vitamin K1): Phytomenadione is the specific reversal agent used for warfarin. It is usually used in combination with prothrombin complex or fresh frozen plasma for management of major bleeding in patients on warfarin. The presence of vitamin K is essential for synthesis of prothrombin, factor VII, factor IX and factor X in the liver. A dose of 5–10 mg IV is able to reverse the anticoagulant effect of warfarin in most patients, however, it takes around 24 hours to work. That is why vitamin K cannot be used as a sole measure to control warfarin related uncontrolled bleeding [9].

Idarucizumab (PRAXBIND): Praxbind (idarucizumab) was granted approval by Food and Drug Administration (FDA) in 2015 and its efficacy was proved by the RE-VERSE AD clinical trial in 2017 [12]. It is a humanized monoclonal antibody fragment (Fab) that binds non-competitively to Dabigatran with 350 times greater affinity than thrombin. It is indicated in patients treated with Dabigatran when reversal of the anticoagulant effects of dabigatran is needed. The recommended dose of PRAXBIND is 5 g which is given in two divided doses with no more than 15 minutes apart. Thrombotic complications are considered the most serious side effects of using Idarucizumab, as reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Patients with Hereditary Fructose Intolerance could have risks of serious adverse reactions due to Sorbitol Excipient used in the drug. Other reported less serious adverse effects are headache, constipation, and nausea [13,12].

Andexanet Alfa (ANDEXXA): The FDA approved the drug in May 2018. Andexanet alfa is a recombinant modified human Factor Xa (FXa) protein that binds competitively to direct FXa inhibitors to reverse their action. Its efficacy has been proved, in the recent ANNEXA-4 study, for reversing anticoagulant activity of rivaroxaban and apixaban [14]. In spite of data regarding its activity against edoxaban, unfractionated heparin and low-molecular-weight heparins, its efficacy is still under ongoing clinical trial [15]. It is administered as an intravenous (IV) bolus of 400-800mg, with a target rate of 30 mg/min, followed by continuous infusion 4-8mg/min. for up to 120 minutes. Side effects range from urinary tract infections, pneumonia, up to life-threatening thromboembolic events [16].

Ciraparantag: It is a promising drug, though, it has not been approved yet for medical use. It is a synthetic small molecule (512 Da) that binds to heparins and oral FXa and IIa inhibitors through hydrogen bonding. It is expected to be used as a broad-spectrum antidote to Dabigatran, FXa inhibitors (Rivaroxaban, Apixaban, Edoxaban), Fondaparinux and heparin [1]. Single IV dose of 100 to 300 mg of ciraparantag demonestrated full reversal of edoxaban anticoagulation within 10–30 minutes of administration and its effect sustained for 24 hours [17] (Figure 2).

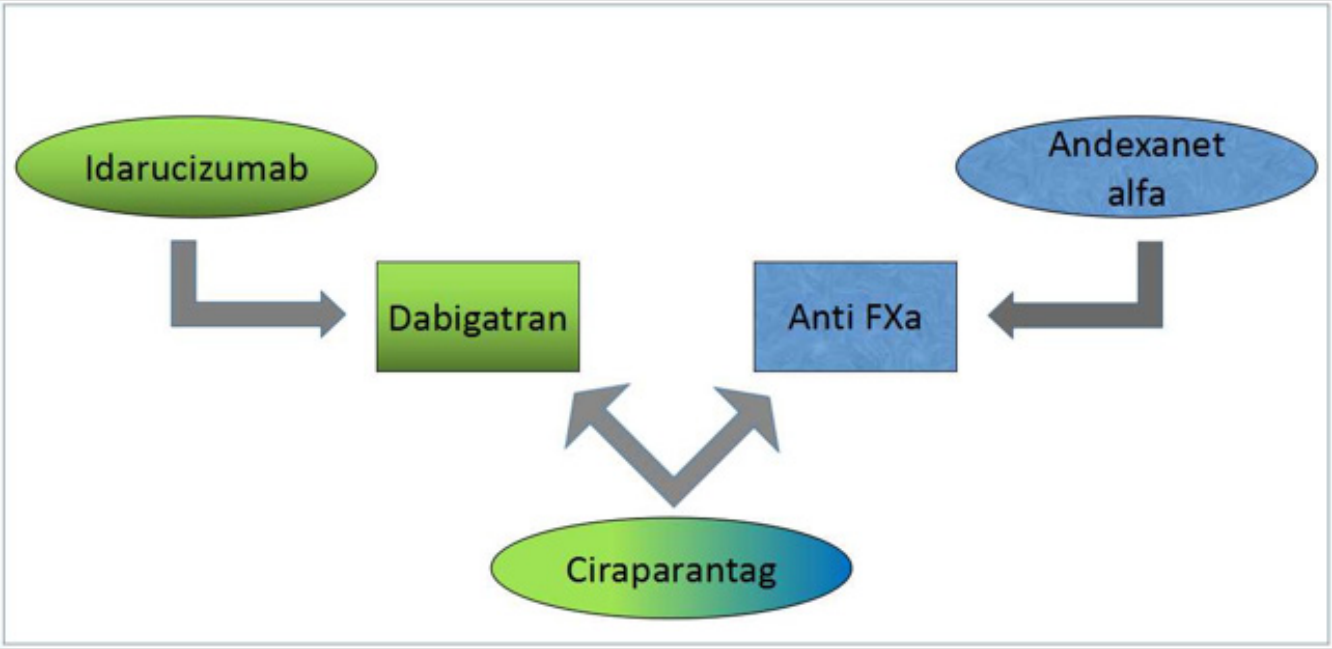

Figure 2: Specific reversal agents for DOACs.

Summary

I. In clinical practice, there is still widespread uncertainty on how to manage uncontrolled bleeding in patients receiving DOACs.

II. Although a few specific reversal agents for DOACs have been approved for clinical use, they still are not widely available.

III. Knowledge of time of last ingestion of the DOACs and renal function is critical to managing these patients.

IV. Laboratory measurements of anticoagulant effect of DOACs are challenging and mostly inconclusive. .

V. Idarucizumab and andexanet alfa have been approved as specific antidotes to rapidly reverse the effects of dabigatran and anti FXa respectively, while ciraparantag is still under trial.

VI. Prothrombin concentrate and FVIIa may be considered in life-threatening bleeding.

VII. Multidisciplinary approach should be followed in managing patients on oral anticoagulants perioperatively.

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