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TRENDS IN ANTICOAGULANT THERAPY: AN INSIGHT INTO NOVEL ORAL ANTICOAGULANTS

Tintu C. Sunny*, Rosmin Jacob, K. Krishnakumar and Carolin Antony

Department of Pharmacy Practice, St. James College of Pharmaceutical Sciences, Chalakudy, Kerala, India.

***Corresponding Author: Tintu C. Sunny**

Department of Pharmacy Practice, St. James College of Pharmaceutical Sciences, Chalakudy, Kerala, India.

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ABSTRACT

Anticoagulants are the cornerstone therapy for many thromboembolic diseases. Theses drugs bring their action by reduce the rate of fiber in formation and indicated to prevent thrombus extension and embolic complications. Traditionally, heparin is given as parenteral anticoagulant, whereas warfarin is given as oral anticoagulant. In the last several years, 4 noval oral anticoagulants are approved by FDA includes dabigatran (2010), rivaroxaban (2011), apixaban (2012) and edoxaban (2015). In Randomized clinical trials and observational studies shows that the efficacy and safety of DOACs for stroke prevention in patients with atrial fibrillation have been shown to be comparable or superior to warfarin. Clinical development paves way for the emergence of novel oral anticoagulants. Because of their ease of use and favorable pharmacodynamic profile, the older agents are replaced by the newer ones. However, these agents are not free of adverse events. Hemorrhage is most commonly occurring adverse event. When taken into consideration the overall OAC utilization pattern remained steady. In the starting of 2010, there is a gradual decrease in warfarin use with corresponding increase in the use of direct oral anticoagulants.

KEYWORDS: Anticoagulants, oral anticoagulants, DOAC.

INTRODUCTION

When considering the scenario in high-income countries thromboembolic diseases are the main cause of disability and death. And the incidence of thromboembolic diseases is also dramatically increasing in middle- and low-income countries.

There are two types of clots that is arterial clots and venous clots. Arterial clots are usually formed at the sites of vascular injury under high shear rates and are responsible for myocardial infarction and stroke, venous clots lead to venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT). Anticoagulant agents should be regarded as a vital therapeutic tool in the management of these patients as blood hypercoagulability have an important role in thrombogenesis.[1,2]

Over 17.5 million losses occur in each year due to Cardiovascular diseases and this regarded as most worldwide epidemic disease.[3,4] Oral anticoagulant drugs are mainly prescribed to treat this condition.[5]

Thrombus extension and embolic complications are prevented by using anticoagulants. They act by reducing the rate of fiber in formation and they have the capability to prevent devastating medical complications. Anticoagulants are mainly indicated in the treatment of pulmonary embolism (PE), deep vein thrombosis (DVT), prosthetic heart valve, myocardial infarction (MI), unstable angina, defibrination syndrome, rheumatic heart disease, extra corpuscular circulation, retinal vessel thrombosis, hemodialysis and vascular surgery.[6,7]

Era of Novel Anticoagulants

Over the past 20 years, there is a tremendous growth in anticoagulant therapy. A number of antithrombotic compounds such as low-molecular-weight heparins, direct thrombin inhibitors like argatroban, bivalirudin, lepirudin, and desirudin, and indirect factor Xa inhibitors such as fondaparinux, were introduced and these compounds have relatively specific targets within the coagulation pathway. These drugs are costlier than oral vitamin K antagonists and they require parenteral administration. Apart from this, the newer anticoagulants have numerous peculiarity over unfractionated heparin. Thus despite of disadvantages, for most patients requiring chronic anticoagulation, VKAs are the only therapeutic option.[8]

Traditionally, heparin is given as parenteral anticoagulant and warfarin is given as oral anticoagulant. But in recent years there is tremendous growth in anticoagulant therapy and there is an urge to develop

more efficacious drugs which ultimately result in emergence of newer anticoagulants. Introduction of these drugs helps to overcome medical problems associated with warfarin therapy as it is a narrow therapeutic range drug and it require routine laboratory monitoring.[9,10]

Food and Drug Administration (FDA) approved warfarin to prevent ischemic stroke in AF patients. In order to prove its effectiveness and safety a wide varieties of studies were carried out. For decades, warfarin has been more often prescribed as OAC.[11,12,13] However, warfarin use is related with harmful issues these results in poor medication compliance. The problems associated with warfarin therapy includes complex dose–response relationship that requires close monitoring of the laboratory values, a number of drug–food interactions that require avoidance of certain foods or drugs, and a risk of bleeding.[14,15,16]

In most of the study, the drug warfarin has proved as an oral anticoagulant, still found that 40–60% of patients who are eligible and should receive it not prescribed with warfarin, and of those patients who are treated with warfarin, the serum warfarin levels only achieved a time in therapeutic range (TTR) equal to INR 2–3 about 55–60% of the time. This indicate there is a need for achieving better anticoagulation in patients as only about 1 in 4 patients are adequately anticoagulated with warfarin, for anticoagulation, physicians have sometimes use antiplatelet therapy like aspirin or clopidogrel and this will lead to doubling of the risk of thromboembolic events.[17]

Dabigatran, rivaroxaban, apixaban, edoxaban are the 4 DOACs that are recently approved by FDA. In October 2010, dabigatran is the first DOAC was approved and marketed as Pradexa by Boehringer Ingelheim pharmaceuticals. In november 2011 rivaroxaban approved as Xarelto, by Janssen pharmaceuticals. Bristol-Myers Squibb pharmaceuticals introduce apixaban as Eliquis and it is approved by FDA in December 2012 and in early 2015 edoxaban approved by FDA and it is marketed as Savaysa by Daiichi Sankyo pharmaceuticals. Randomized clinical trials and observational studies reveals that the efficacy and safety of novel oral anticoagulants were superior to warfarin.[18]

These 4 oral agents have unique mechanism of action than VKAs that is they produce their anticoagulant effect by inhibiting a single activated clotting factor, either thrombin (factor IIa) or factor Xa. This is totally different from VKAs, as they bring their action by alter the hepatic synthesis of multiple clotting proteins whereas DOACs are act by directly antagonizing a single target in the clotting pathway.[8]

Features of Doac

Dabigatran

Dabigatran is a prodrug and its bioavailability is 6.5%. the main advantage of the drug is presence of food not affect the absorption. Tmax is 0.5-2 hours and the biological half life is 12-14 hours. Its metabolism is very low. Dabigatran is mainly excreted by renal route that is 85% and 6% excreted through feces. The usual dose given is 2*150 mg or 2*110mg.

Rivaroxaban

It is not a prodrug. Presence of food affect the absorption of drug. when administer <15mg of drug its bioavailability is 80-100%. if the dose is ≥15 mg and the patients on fasting the bioavailability is 665%. if the dose is ≥15 mg and the drug administer after food intake the bioavailability is 100%. Tmax is 2-4 hours and the biological half life is 5-9hours in case of young patients, if the patients are older the half life is 11-13 hours. its metabolism is high. Rivaroxaban is mainly excreted by renal route that is 33% unchanged and 33% as metabolite. 33% excreted through feces as metabolite. The usual dose given is 1*20mg for patient having atrial fibrillation. In case of DVT-PE the dose is 2*15(21Days then) 1*20mg.2*2.5 mg is the usual dose given in case of POST ACS.

Apixaban

Apixaban is not a prodrug and its bioavailability is 50%. the main advantage of a the drug is presence of food not affect the absorption. Tmax is 3-4 hours and the biological half life is 12hours. its metabolism is very high. Apixaban is mainly excreted through feces that is 27% and 27% excreted through renal route. The usual dose given is 2*5 mg or 2*2.5mg.

Edoxaban

Edoxaban is not a prodrug. and its bioavailability is 62%. the main advantage of the drug is presence of food not affect the absorption. Tmax is 1.5 hours and the biological half life is 10-14 hours. Its metabolism is very low. Apixaban is mainly excreted through feces that is 60% of absorbed drug 70% excreted unchanged. and 35% excreted through renal route. The usual dose given is 1*60mg.[19]

Indications of DOACs

In prevention and treatment of thrombosis, the introduction of direct oral anticoagulants was an important therapeutic advance. DOACs include the dabigatran, which is direct thrombin inhibitor and the anti-Xa agents include rivaroxaban, apixaban and edoxaban. stroke and systemic embolisms can be prevented by the use of DOACs in adults with NVAF. The ischemic or hemorrhagic stroke, and all-cause mortality are better controlled by the administration of DOACs than VKAs.[20] DOAC have been a mainstay in the prevention of VTE after a major elective orthopedic surgery and in the secondary prevention and treatment of VTE.[21] Other indications of DOACs are still investigated like use of DOAC in acute coronary syndrome.

Advantages of DOACs

New Oral Anticoagulants have Potential advantages over VKAs. They are:

- There is no need for bridging therapy as sudden onset of action
- Anticoagulant effect can be easily controlled as their biological half life is short
- There is no need of dietary restrictions like warfarin because of limited food interactions.
- The number of drugs which interact with DOACs are less.
- Routine coagulation monitoring is not necessary
- Easy to predict anticoagulant effect.

Disadvantages of DOACs

- Poor patient compliance due to high cost.
- If required, no monitoring is possible.
- There is no specific antidote to treat toxicity.
- In case of renal impaired patients and elderly more than 80 years warfarin is the drug of choice, If glomerular filtration rate is 15–30 mL/min as it cause serious bleeding events.[22]

Laboratory Tests

Due to lack of sensitivity, routine coagulation tests like activated partial thromboplastin time (aPTT) or prothrombin ratio (PR), are not suitable in the clinical settings. The absence of clinically active blood levels of dabigatran is related to a normal thrombin clotting time (TCT). The effect of heparin manily monitored by using the plasma anti- Xa assay, it is also applicable to exclude clinically active blood levels of rivaroxaban or apixaban, when anti-Xa activity is below 0.1 IU/ml. Fixed doses of DOACs can be administered for the long time without routine coagulation monitoring because DOACs are developed to be used without any biological monitoring.[19]

Risks Of Doacs

Overall bleeding risk under DOACs

Intracranial hemorrhage and gastrointestinal bleeding are clinically significant bleeding events under DOACs treatment. These events are remarkable and also common under VKA treatment. The main risk factor associated with this is age. The Elderly patients are more prone to these bleeding complications.[21] especially in patients over 75 years of age, with severe renal and liver function impairment, low body weight (<60 kg), diabetes, history of gastrointestinal bleeding, hypertension, or receiving concomitant systemic treatment by strong inhibitors of CYP3A4 and P-gp.[19]

There are some controversies regarding overall bleeding risk associated with DOAC therapy. Some observational studies reveal that overall bleeding risk in patients treated with DOACs is comparable with VKAs, whereas some studies states there is a reduction in overall bleeding in patients receiving DOACs. This marks a decline in the risk of intracranial hemorrhage.[23,24]

Gastrointestinal bleeding risk under DOACs

The patients treated with anticoagulants shows that gastrointestinal bleeding risk at a rate of 1.5–5% in each year. It is more prevalent in older people because of associated comorbidity as well as Polypharmacy. The anti platelet and non steroidal anti-inflammatory are the drugs which shows interactions with anticoagulant drugs and they cause serious bleeding events.[25,26] In comparison with VKA, the incidence of gastrointestinal bleeding is less in patients who are treated with direct oral anticoagulants.[27]

Providing direct oral anticoagulants (DOACs) was a new treatment modality in nonvalvular atrial fibrillation (NVAF) and venous thromboembolic disease care. The bleeding risk associated with DOACs studied extensively to safety associated with their use. Ruff CT et al. randomized four pivotal controlled trials including 71,863 patients with atrial fibrillation (AF) stated that DOACs are equal and not superior, to vitamin K antagonists (VKAs) in preventing stroke with a survival benefit.[20] But when considering the adverse events associated with the treatment of DOACs, the overall bleeding risk is lower, especially a lower risk of intracranial hemorrhage.[19]

David Deutsch et al. conducted six randomized controlled trials with 26,997 patients to prove the efficiency and safety of DOAC, in the management of deep vein thrombosis (DVT) and pulmonary embolism (PE). The study discloses that the efficiency of DOAC and heparin are equal. when considering the safety profiles, the overall bleeding risk is less but the occurrence of gastrointestinal bleeding is very high.[19]

CONCLUSION

For the past few years, there is a signaled growth in anticoagulant therapy, particularly by integrating DOACs. Clinical development paves way for the emergence of novel oral anticoagulants. Because of their ease of use and favorable pharmacodynamic profile, the older agents are replaced by the newer ones. However these agents are not free of adverse events. Hemorrhage is most commonly occurring adverse event. The clinician should have thorough knowledge and understanding about its pharmacology, dosing, monitoring and toxicity. It is mandatory to overcome intercepting and averting problems.

When compared to injectable anticoagulants the patient compliance and adherence is more with the newer oral anticoagulants. The newer OACs like apixaban, rivaroxaban and dabigatran are considered as potential candidates for future anticoagulant therapy. When taken into consideration the overall OAC utilization pattern remained steady. In the starting of 2010, there is a gradual decrease in warfarin use with corresponding increase in the use of direct oral anticoagulants.

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