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Overview of The New Oral Anticoagulants: Novel Oral Anticoagulants

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ABSTRACT

Novel oral anticoagulants commonly known as NOACs are the non vitamin k antagonist oral anticoagulants which are newer the market .It has displaced vitamin k antagonist oral anticoagulants mainly Warfarin for many indications .Novel oral anticoagulants are a main class of drug of choice to prevent stroke in patients with non valvular atrial fibrillation and to prevent and treat venous thromboembolism. Two classes of NOACs are currently available : Direct thrombin inhibitors such as Dabigatran and the Direct inhibitors of Xa factor such as Rivaroxaban ,Apixaban and Edoxaban. Compared to vitamin K antagonist oral anticoagulants, these drugs have a fixed dosing with no need for INR monitoring ,a wider therapeutic range, rapid onset and short half lives and few drug and food interactions.

KEY WORDS : Novel oral anticoagulants ,Vitamin K antagonist ,Direct thrombin inhibitor ,Direct Xa factor inhibitor ,Dabigatran, Rivaroxaban, Edoxaban, Apixaban, Venous thromboembolism ,Non valvular atrial fibrillation.

INTRODUCTION

Thromboembolic disease are of Major clinical concern due to their high prevalence and consequences and are often fatal .Treatment of venous and arterial thrombotic events represents a major medical challenge , and the development of anticoagulants represents a revolution in the medicine .

During the past 60 years ,Vitamin K antagonists which includes coumarin derivatives such as warfarin and acenocoumarol ,Despite its proven effectiveness ,there are several disadvantages including a narrow therapeutic range ,drug-drug interactions ,food-drug interactions ,slow dose-adjustment time, and genetic variability in the enzymes involved in its metabolism, and to assure that a therapeutic INR is maintained. So that NOACs developed to address some of the disadvantages of vitamin K antagonists, it has a predictable anticoagulant response ,making regular laboratory monitoring unnecessary. Anticoagulation with NOACs is achieved quickly ,reaching peak plasma concentrations 1-4 hours following oral administration, it have fewer drug-drug and drug-food interactions and also dosage adjustment is not required ,these are administered in fixed doses, except when a patient has a functional disorder of the liver or kidney.

NOACs include four drugs ,of which dabigatran was the first to be FDA approve in 2010 ,it is a direct thrombin inhibitor .Rivaroxaban, apixaban and edoxaban fall under direct factor Xa inhibitors that were approved by FDA on 2011,2014 and 2015, respectively .

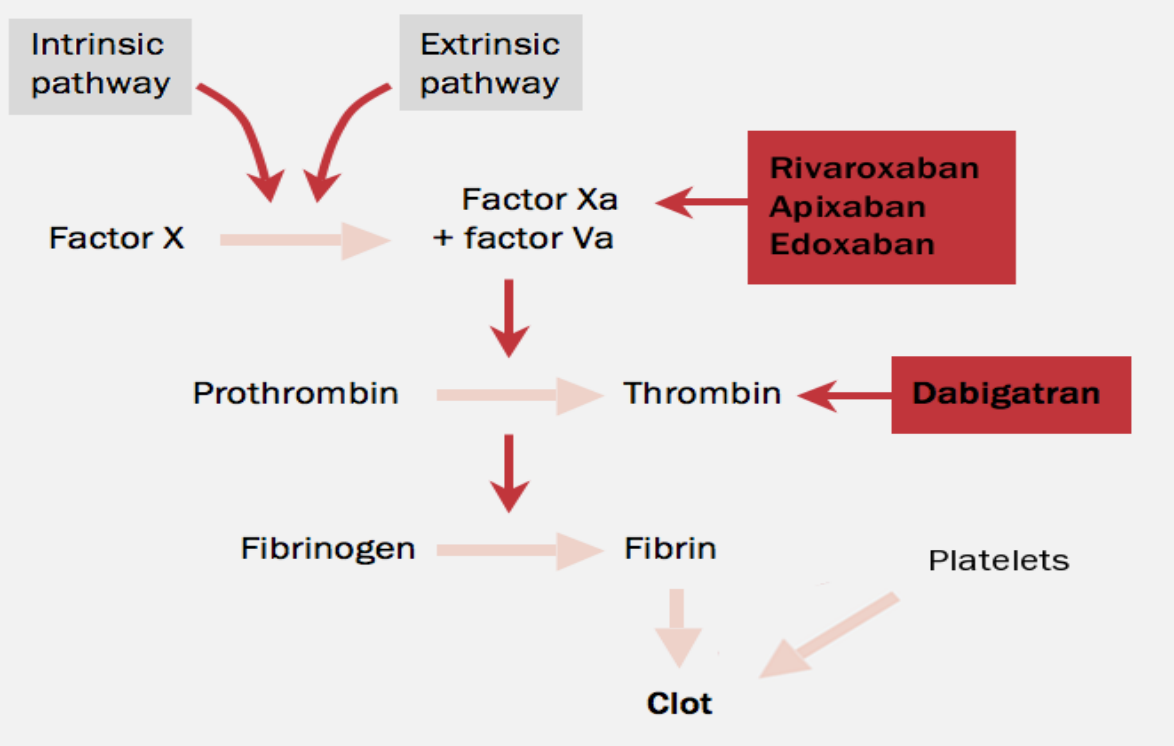
NOVEL ORAL ANTICOAGULANTS

The new oral anticoagulants represent novel direct acting medications that are selective for one specific coagulation factor, either thrombin or activated factor Xa. These drugs have recently been approved for the prevention of venous thromboembolism in patients after elective hip or knee arthroplasty, non valvular atrial fibrillation and pulmonary embolism.

BLOOD CLOTTING MECHANISM

The coagulation cascade is triggered by release of tissue factor from tissue trauma or vascular injury . These factor forms a complex with factor VIIa in the presence of calcium and cleaves clotting factors X and IX to their activated forms. The prothrombinase complex cleaves prothrombin to factor thrombin. Thrombin is responsible for clot formation by fibrin polymerization ,platelet receptor activation ,endothelium activation and activation of factors V,VIII,XI and XIII. Anticoagulant agents can inhibit thrombogenesis by altering various pathways within the clotting cascade or by targeting thrombin directly ,attenuating thrombin generation . Indirect inhibitors ,however , target and bind to naturally occurring plasma cofactors , such as antithrombin , catalyzing their interaction with clotting enzymes.

HOW THE DRUG WORKS ?



NOACs act by two different mechanisms ,based on this it is classified as direct thrombin inhibitor and direct factor Xa inhibitor .The former category inhibits coagulation by directly binding to thrombin and prevents the formation of fibrin by restricting thrombin from breaking fibrinogen. The latter group inhibits factor Xa which is trypsin -like serine protease that plays a critical role in blood clotting cascade. It has a principal position in linking the intrinsic and extrinsic pathways to the final common coagulation pathway. These agents bind directly to factor Xa and prevent them from cleaving prothrombin to thrombin.

DABIGATRAN

Dabigatran was the first approved NOAC ;it was approved by FDA in 2010.A new oral, direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin and thereby prevents clot formation and it is indicated to reduce the risk of stroke and systemic embolism in patients with non valvular atrial fibrillation. It is a product of the prodrug (dabigatran etexilate) of dabigatran, which is rapidly transformed to dabigatran after oral ingestion and hepatic processing. Oral bioavailability of dabigatran is low (6%-7%), half life is about 12-14 hours. The primary route for elimination is renal. Recommended doses are 110 mg and 150 mg twice daily.

RIVAROXABAN

Rivaroxaban is the second NOAC approved by FDA in 2011 .It is a selective direct inhibitor of factor Xa which is formed by both intrinsic and extrinsic coagulation pathways.This prevention of thrombin formation from prothrombin is needed to prevent the conversion of fibrinogen to fibrin .It is rapidly absorbable and has a high bioavailability (60%-80%).Approximately 30% of rivaroxaban is excreted unchanged in the urine and through fecal elimination. Metabolism occurs in the liver. Recommended dose is 20 mg once daily.

APIXABAN

Apixaban is another NOAC that is a reversible direct Xa antagonist .It exerts a similar anticoagulant activity as rivaroxaban ,by the direct inhibition of factor Xa, which is formed by both intrinsic and extrinsic coagulation pathways. This prevention of thrombin formation from prothrombin is needed to prevent the

conversion of fibrinogen to fibrin. Apixaban is the third NOAC that was approved by FDA in 2014.It is rapidly absorbed after oral administration and its bioavailability is about 66%.It is metabolized in liver. Recommended dose is 5 mg twice daily.

EDOXABAN

Edoxaban is an oral direct ,specific inhibitor of factor Xa with approximate 10,000 fold selectivity for factor Xa over thrombin. It was approved by the FDA in 2015 for the prevention of stroke and non-central-nervous-system systemic embolisms .It is rapidly absorbed, and its bioavailability is about 58.3% . This drug has dual mechanisms of elimination ,approximately one third is eliminated via the kidneys and the reminder via feces. A daily dose of 60 mg is preferred.

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
Target	Thrombin	Factor xa	Factor xa	Factor xa
Dosage	Capsule	Tablet	Tablet	Tablet
Prodrug	Yes	No	No	No
Dose	110 mg& 150 mg	20 mg	5 mg	60 mg
Bioavailability	6%-7%	60%-80%	66%	58.3%
Half life	1.5-2 hours	2.5-4 hours	3 hours	1.5 hours
Onset of action	12-14 hours	7-13 hours	8-15 hours	9-11 hours
Route of elimination	80% renal	70% renal	25% renal	35% renal

ADVANTAGES

- Wide therapeutic window.
- Predictable pharmacokinetics and pharmacodynamics.
- Rapid onset and offset of action.
- Short half life .
- Low drug-drug and food interactions.
- No dietary restrictions.
- In general no need for laboratory monitoring, although in some cases it is required.

DRAWBACKS

- Do not exist standardised test for laboratory monitoring, when it is necessary for monitoring of these drugs eg : in hepatic and renal disease.
- Sometimes rapid offset and short half life may be considered as disadvantage.

- Currently lack of antidote.
- High cost.
- Not enough experience.

CLINICAL USES

- Stroke prophylaxis in non valvular atrial fibrillation.
- Treatment of stroke and systemic embolism.
- Treatment of deep vein thrombosis or pulmonary embolism.
- Secondary prophylaxis of deep vein thrombosis or pulmonary embolism.
- Deep vein thrombosis prophylaxis following hip or knee replacement surgery.

CONTRAINDICATIONS

- Patients with major bleeding.
- Hepatic disease with coagulopathy.
- Use of other anticoagulants, antiplatelets and non-steroidal anti-inflammatory drugs.
- Hypersensitivity to NOACs.

DRUG INTERACTIONS

- P-glycoprotein inhibitors such as Amiodarone, Quinidine, Verapamil, Dronedarone, Ketoconazole and Macrolide antibiotics may increase the peak plasma concentrations of NOACs and subsequently leads to a increased risk of severe hemorrhage and bleeding.
- Rifampicin ,Hypericum, Antiretroviral protease inhibitors, Tyrosine kinase inhibitors, Dexamethasone, Levetiracetam and Valproic acid also shows drug interactions with NOACs.

FOOD INTERACTIONS

The actions of NOACs are not associated with food .As patients who receive these drugs do not need to avoid any food products because there is no difficulty in balancing anticoagulation therapy

CONCLUSION

A basic understanding on these drugs such as Dabigatran, Rivaroxaban, Apixaban and Edoxaban is highly recommended to provide a better service to the patients . This article aims to provide quick and brief information on the novel oral anticoagulants . It deals with the following areas ,that is :Blood clotting mechanism ,How the drug works ?,pharmacology, pharmacokinetics and pharmacodynamics, advantages ,drawbacks ,clinical uses, Contraindications ,drug interactions and food interactions.

Vitamin K antagonist oral anticoagulation therapy shows some difficulties related to major drug and food interactions as well as other problems such as great individual variability in the effect and the need for continuous monitoring ,additional anticoagulant drugs need to be developed. New oral anticoagulants called novel oral anticoagulants ,direct oral anticoagulants or target specific oral anticoagulants have been introduced. The advantages over vitamin k antagonists are their high efficacy in preventing stroke in non valvular atrial fibrillation, lower incidence of major bleeding ,convenience of use, minor food and drug interactions ,predictable PK and PD ,rapid onset and offset of action ,short half life and lack of the need for laboratory monitoring. However some disadvantages of NOACs should be mentioned , such as their high cost ,the absence of specific antidotes and limited experience with these drugs and also it should not be used in patients with severe renal and hepatic disease, patients with mechanical heart valves ,and individuals younger than 18 years of age.

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