JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

EDOXABAN: A NEW ORAL ANTICOAGULANT

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ABSTRACT: Anticoagulants have a major role in the treatment of arterial and venous thromboembolic disorders. The recently introduced new oral anticoagulants target a single coagulation factor (factor Xa or thrombin) and have various limitations associated with traditional agents. Edoxaban is an oral direct factor Xa inhibitor that inhibits free and clot bound factor Xa and has been investigated in an extensive clinical development program. This article provides a detail note on mechanism of action, pharmacokinetics and pharmacodynamics of edoxaban. Phase III studies have evaluated edoxaban versus conventional therapy to prevent stroke in patients with atrial fibrillation and also in the treatment and prevention of recurrent venous thromboembolism in patients with deep vein thrombosis and/or pulmonary embolism.

KEY WORDS: Direct oral anticoagulant (DOAC), Atrial fibrillation, Edoxaban, Warfarin, Venous thromboembolic, Thromboembolic disorders

INTRODUCTION

Anticoagulation is a critical component in the management of venous thromboembolism (VTE) and atrial fibrillation. Venous thromboembolism, including deep vein thrombosis (DVT) and pulmonary embolism (PE), has an annual incidence rate of approximately 1 per 1000 people in the general population. VTE is the third most common acute cardiovascular disorder after myocardial infarction and stroke, and atrial fibrillation is the most prevalent cardiac arrhythmia, A affecting the people.{1]

Vitamin K antagonists (VKAs) are for the prevention and treatment of VTE, and stroke prevention in atrial fibrillation patients. Prior to 2009, the only oral anticoagulant available was warfarin. Three months of warfarin for idiopathic VTE resulted in a 95% reduction in recurrent thromboembolism. Warfarin has been found to reduce the risk of stroke by 64% compared to placebo in patients with atrial fibrillation. The rate of major bleeding with warfarin in the setting of venous thromboembolism has been estimated. The limitations of VKAs are well documented, including a narrow therapeutic window that requires monitoring, variable therapeutic response, delayed onset and offset of action, dose adjustments, food and drug interactions, and risk for bleeding.

In 2009, the first oral factor IIa (thrombin) inhibitor, dabigatran, was approved by the United States Food and Drug Administration (FDA) for the prevention of stroke in the setting of non-valvular atrial fibrillation (NVAF). Two oral factor Xa inhibitors, rivaroxaban and apixaban, were subsequently FDA-approved for the same indication. Eventually, these agents were all approved for the prevention and treatment of VTE as well. These non-vitamin K oral anticoagulants (NOACs) have challenged the previously accepted realities of therapeutic monitoring, bridging regimens, and dietary modifications. However, these agents are not without their clinical limitations. A number of pharmacokinetic drug interactions still must be considered for appropriate use and dosing. Additionally, apixaban and dabigatran require twice-daily dosing, which may negatively impact patient adherence. The NOACs have resulted in a significant reduction in intracranial haemorrhage compared to VKAs, however several of these agents have been associated with an increase in gastrointestinal bleeding. With these limitations in mind, the search for an optimal oral anticoagulant continues. Edoxaban (Savaysa), a new Xa inhibitor, was FDA-approved in 2015 and appears poised to address some of these practical concerns.

MECHANISM OF ACTION

✓ Edoxaban exerts its therapeutic effects by inhibiting factor Xa (FXa) directly, selectively, and reversibly as part of its mechanism of action.
✓ FXa plays a pivotal role in both the extrinsic and intrinsic pathways of the coagulation cascade. FXa binds with factor Va, creating a complex that facilitates the cleavage of prothrombin into thrombin.
✓ Thrombin subsequently cleaves fibrinogen into fibrin monomers and creates a fibrin meshwork, which adheres to a platelet plug and ultimately forms a clot.[2]
✓ By obstructing the active site of free FXa, thrombin production is inhibited, leading to a reduction in thrombus development.
✓ This inhibition occurs independently of the anticoagulant effects of cofactor antithrombin III. Edoxaban also functions by inhibiting prothrombinase activity, thereby suppressing thrombin-induced platelet aggregation.

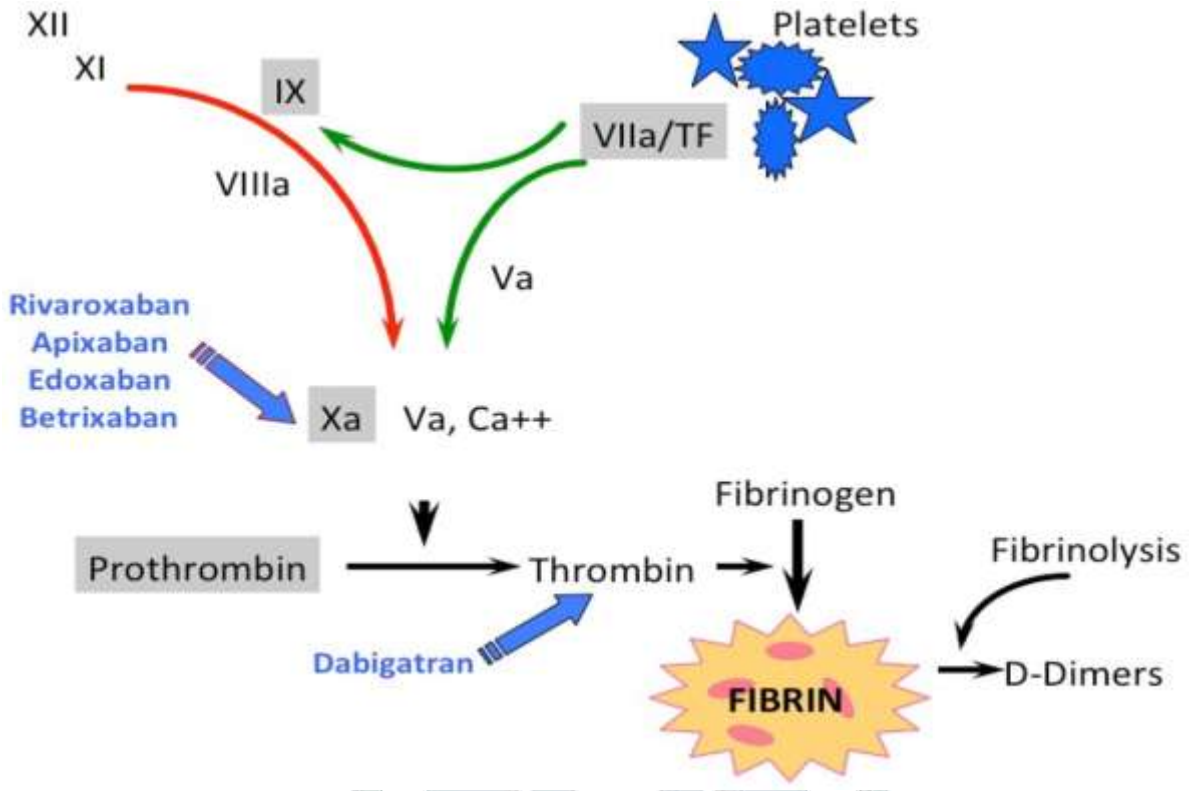
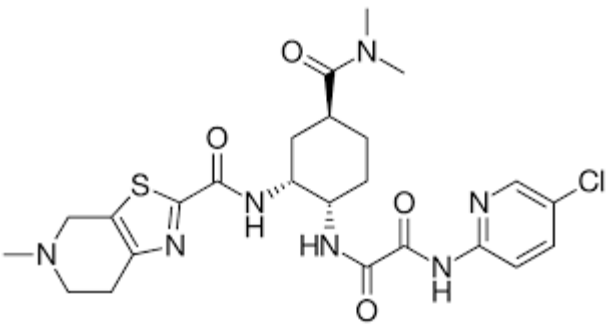
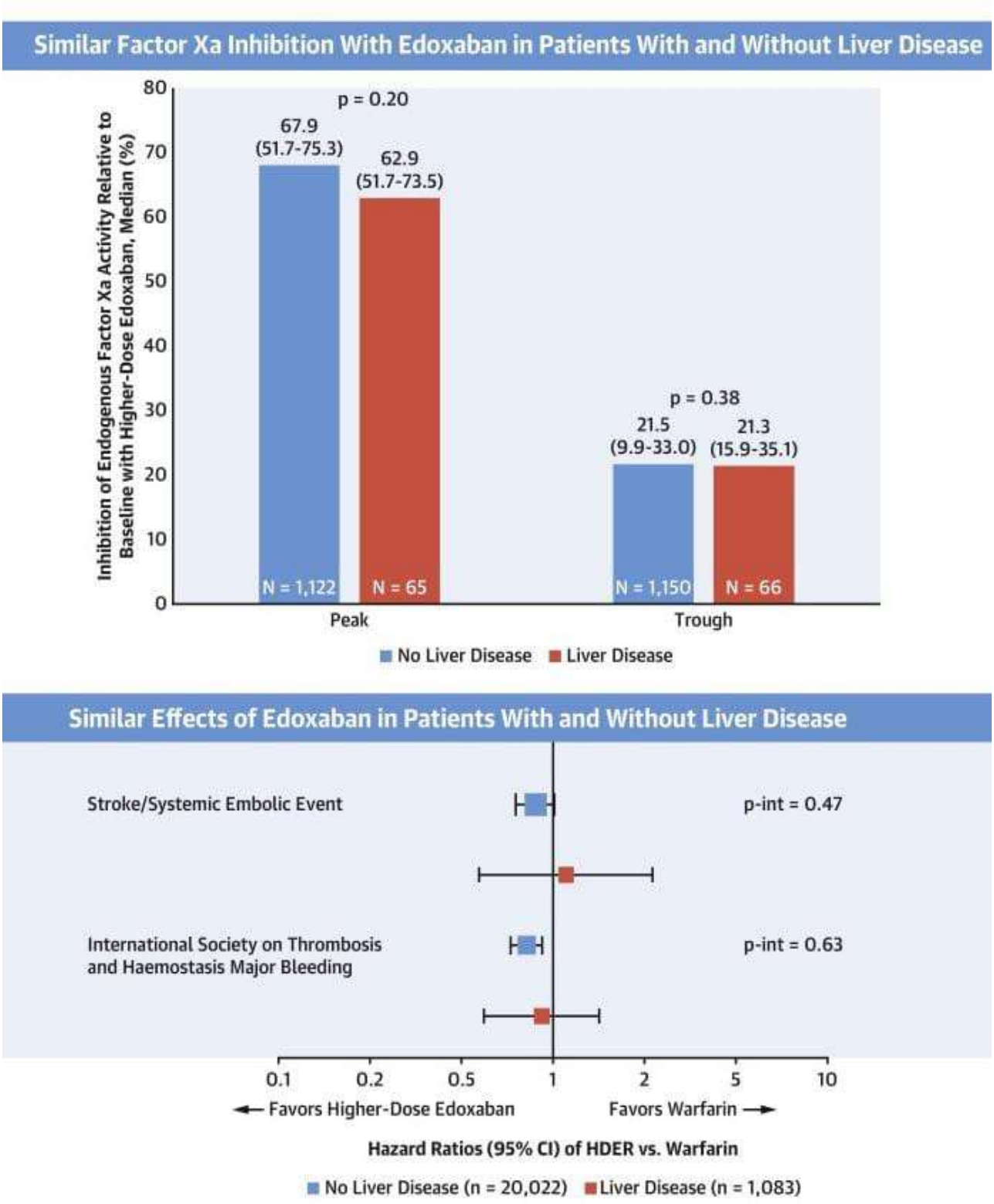


Fig – 1: MOA of new oral anticoagulant



STRUCTURE OF EDOXABAN



PHARMACOKINETICS

- Edoxaban is characterized by rapid absorption and dose proportional increases in plasma concentrations (Fig 2).
- The absolute bioavailability of Edoxaban following a single 60 mg dose is 61.8% [18].
- Mean apparent volume of distribution was generally >300 l due to relatively low protein binding and distribution to extravascular tissues [3]
- Edoxaban has a half-life of 10 to 14 hours and a rapid onset, achieving peak serum concentration levels (Cmax) within 1 to 2 hours.[3]
- Approximately 50% of the drug is eliminated unchanged through the kidneys and excreted in the urine. The remaining portion undergoes elimination via the biliary and intestinal system, ultimately being excreted in the faeces.

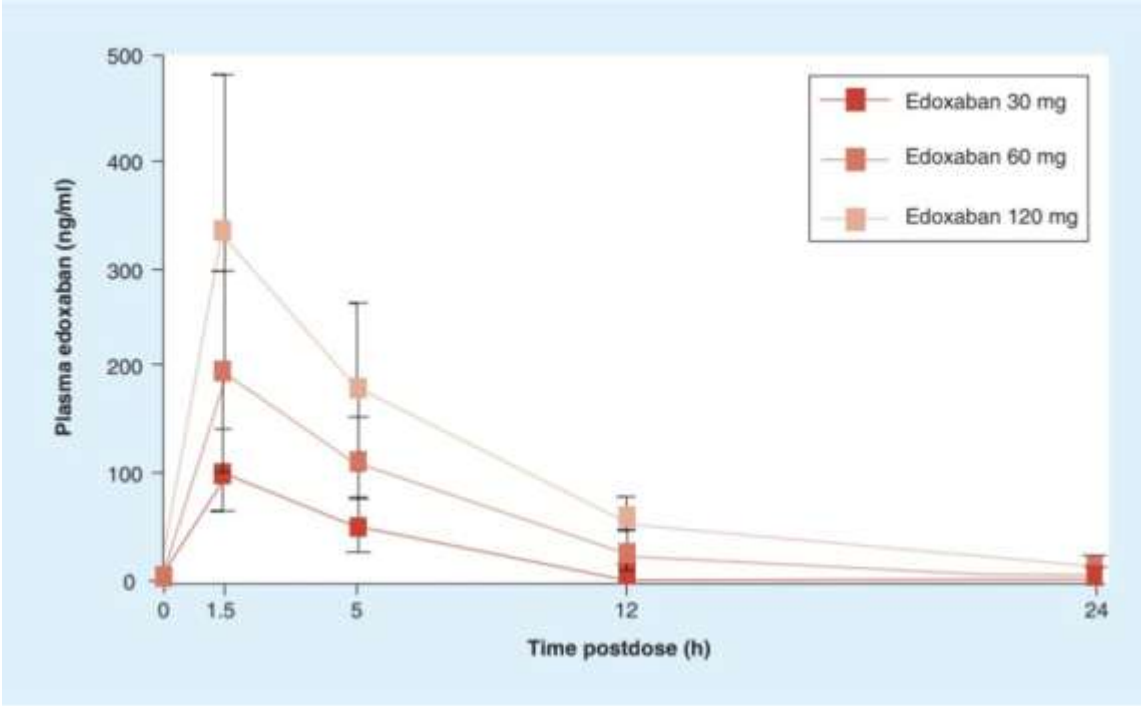


Fig- 2 : Plasma concentration of edoxaban after oral administration

ADMINISTARTION

Dosage Forms and Strengths

Edoxaban is available for oral administration in 15 mg, 30 mg, and 60 mg film-coated tablets. The patient's creatinine clearance (CrCl) should be assessed before initiating the therapy.

Adult Dosage

Dosing regimens based on indications are as follows:

NVAF: The oral dosage of edoxaban for NVAF recommends 60 mg once daily which is administered to patients with a CrCl >50 and ≤ 95 mL/min. The dosage should be adjusted to 30 mg once daily for individuals with a CrCl ranging from 15 to 50 mL/min.

- Edoxaban is not recommended for patients with NVAF and a CrCl >95 mL/min due to the increased risk of ischemic stroke at the highest studied dose.[9]

DVT: Edoxaban is indicated for the treatment of DVT following 5 to 10 days of initial therapy with a parenteral anticoagulant. The recommended oral dosage is 60 mg, administered to patients once daily. The dosage should be adjusted to 30 mg once daily for patients with CrCl ranging from 15 to 50 mL/min and those with a body weight of less than 60 kg.[5]

PE: Edoxaban is indicated for the treatment of PE following 5 to 10 days of initial therapy with a parenteral anticoagulant. The prescribed oral dosage is 60 mg, administered to patients once daily. The dosage should be adjusted to 30 mg once daily for individuals with CrCl ranging from 15 to 50 mL/min and those with a body weight of less than 60 kg.

Although edoxaban is generally not recommended for concurrent use with specific P-glycoprotein (P-gp) inhibitors, recent studies have indicated that this interaction holds limited clinical significance.[10]

Specific Patient Populations

Hepatic impairment: As per clinicians' recommendations, edoxaban should be avoided in patients with Child-Pugh Class B or C hepatic impairment.

Renal impairment: Thromboembolism or stroke prophylaxis: Edoxaban should be avoided in patients with a CrCl >95 mL/min. No dosage adjustment is necessary for patients with impaired renal function and CrCl ranging from 15 to 30 mL/min. Edoxaban should not be utilized in patients with a CrCl <15 mL/min. Furthermore, edoxaban use should be avoided in individuals undergoing peritoneal dialysis or haemodialysis.

DVT/PE treatment: If CrCl ranges from 15 to 30 mL/min, the recommended dosage of edoxaban is 30 mg daily. However, edoxaban should be avoided in patients with a CrCl <15 mL/min. Edoxaban use for these indications in patients undergoing peritoneal dialysis or haemodialysis remains undefined.

Pregnancy considerations: As edoxaban is classified as an FDA pregnancy category C drug, its usage should be avoided during pregnancy due to insufficient data from human studies. However, there is no evidence of teratogenicity with the drug's usage.[5]

Breastfeeding considerations: Clinicians should carefully evaluate the risk-benefit profile when considering breastfeeding patients. Although there is a lack of data from human studies, the drug's pharmaceutical properties may affect its potential to enter breast milk. Research has identified the presence of edoxaban in rat milk. However, no data from human studies are available concerning the drug's effects on milk production.[6][7]

Paediatric patients: Edoxaban is not indicated for use in paediatric patients.

Older patients: For older patients, it is recommended to refer to the renal dosing guidelines.

ADVERSE EFFECTS

Severe Adverse Effects

Include epidural hematoma, spinal hematoma, severe bleeding, thrombocytopenia, angioedema, and thrombosis with premature discontinuation.

Mild-to-Moderate Adverse Effects

Include bleeding, anaemia, rash, and elevated alanine transaminase or aspartate transaminase. Early discontinuation of edoxaban without sufficient alternative anticoagulation can increase the risk of ischemic events.[10]

Drug-Drug Interactions

Edoxaban should not be administered along wth the following agents due to potential drug interactions and an elevated risk of bleeding:

- Anticoagulants
- Antiplatelets
- Thrombolytics
- Selective serotonin reuptake inhibitors
- Serotonin-norepinephrine reuptake inhibitors
- Defibrotide: Using defibrotide in conjunction with edoxaban may lead to additive effects and an increased risk of bleeding.
- Mifepristone: Combining edoxaban with mifepristone may elevate edoxaban levels, thereby increasing the potential for severe bleeding

TOXICITY

Patients with impaired kidney function have a higher risk of toxicity. The efficacy of haemodialysis in enhancing edoxaban clearance has not been established.

Management of Overdose

In cases of overdose or toxicity during bleeding or haemorrhage, general measures can be contemplated, including discontinuing the medication, using mechanical compression, sustaining volume, and replacing hematologic components. Activated charcoal could also be an alternative option if the medication were ingested within the preceding 2 hours. The effects of the agents could potentially endure for up to 24 hours.[8]

Although no approved or licensed reversal therapy exists for edoxaban, prothrombin complex concentrates (PCCs) are commonly used in pathological bleeding cases. The use of PCCs in bleeding individuals has a minimal logical explanation. Although PCCs replenish clotting factors FII, FVII, and FIX, edoxaban operates downstream of the actions of PCCs within the coagulation cascade. Protamine sulphate, vitamin K, and tranexamic acid are not anticipated to counteract the anticoagulant effects of edoxaban.[4]

CONCLUSION

Edoxaban has emerged as an alternative to an ever-growing class of selective oral anticoagulants. It has been shown to be a safe and effective option for the prevention of stroke in the setting of NVAF and the treatment of VTE. Edoxaban has several clinical advantages including a once-daily regimen, the lack of need for bridging or routine therapeutic monitoring, and absence of food-drug interactions. Renal function and P-gp drug interactions will challenge its acceptance as an alternative to traditional and other novel anticoagulants.

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