

Review Article

A Review on Noval Anticoagulants

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ABSTRACT

The long term anticoagulation with warfarin is associated with various bleeding risks which led to the need for newer drugs. With the developments in the anticoagulation therapy the newer agents like dabigatran, rivaroxaba, apixaban and edoxaban have gained popularity with their more predictable pharmacological properties and reduced need for drug monitoring. The United States of America has approved both rivaroxaban and dabigatran to be used in the treatment of VTE (Venous Thrombo Embolism). In Europe and Canada dabigatran is prescribed after elective hip or knee arthroplasty to prevent VTE. For a VTE prophylaxis after an orthopediac surgery and to prevent stroke in AF patient, Rivaroxaban is recommended according to RECORD study. Edoxaban is highly effective in treatment of VTE and acts as a preventive measure of stroke in NVAf (Nonvalvular Atrial Fibrillation). Through this article various pharmacological aspects, dosing regimens, bleeding associated risk will be illustrated.

Keywords: Anticoagulants, venous thromboembolism, Warfarin, Dabigatran, Rivaroxaban, Apixaban and Edoxaban.

INTRODUCTION

The major cause of death in United States and other Western countries includes various Thromboembolic condition, including Acute Myocardial Infarction, Unstable Angina, Deep Vein Thrombosis, Pulmonary Embolism, and Ischemic Stroke¹. Currently, the stroke incidence in India is much higher than Western industrialized countries². Upto recent times for the patients with Atrial Fibrillation, Venous Thromboembolism, Stroke requiring constant anticoagulation, warfarin was considered as the mainstay of treatment for such patients³. The available drugs for these conditions remain only at sub-optimal levels. Moreover, their narrow therapeutic index, unpredictable drug-drug interactions and need for continuous close monitoring also uncontrolled bleeding do mask VKA's (Vitamin K Antagonist) beneficial properties of preventing propagation and re-occurrence of the condition¹.

Initially when LMWH and Fondaparinaux were introduced, were accepted as they require no or less drug monitoring and even gave the choice of subcutaneous administration. Then the limitation was highlighted as the need for frequent administration through the subcutaneous route, thereby it reduced their long term efficiency. To add on the misery, these drugs had lower renal clearance, no known antidotes and at times posed threat in the form of Catheter Thrombosis to the patients receiving Percutaneous Coronary Intervention (PCI). Bivalirudin is the best choice of drug in PCI undergoing patients. Nonetheless, its lack of antidote and shorter half life it is contra-indicated in Renal impaired patients. Even

though these agents are useful, there is a constant call for drug monitoring. This is due to the reason that at sub-therapeutic level clots may be formed, whereas at high level causes bleeding risk. This un-interrupted monitoring does not guarantee the therapeutic levels in the patient sometimes⁴.

These barriers were overcome by introducing Newer Oral Anticoagulant Agents that need lesser monitoring and having more conventional pharmacokinetic profiles¹. Commonly known as Newer Anticoagulant Agents (NOAC), they created a radical change in the oral anticoagulant therapy after its successful phase III trials⁵. The new anticoagulant direct thrombin inhibitor is a step advanced to its predecessor LMWH and heparin. The latter can only destroy the fibrin bound thrombin, the former is efficient in not only removing the fibrin bound thrombin but also can inactivate the free thrombin. Thereby, direct thrombin inhibitors can avert the extensive development of the thrombus⁴.

The region of union for both intrinsic and extrinsic pathway is mediated by factor Xa. Fondaparinaux, its indirect inhibitor stops the unbound factor Xa. The latest advancement in anticoagulant therapy, is the direct thrombin inhibitor which works by inhibiting both bound and unbound thrombin⁴.

Even though they have a slow rate of growth due to their high cost, contra-indication in patients with kidney failure and lack of a successful antidote, but they do have add on advantages like expected pharmacokinetic profile, better therapeutic window and requires a reduced amount or no therapeutic monitoring at all⁵. Due to the lack of any potential drug food interactions, clinicians need not

recommend any dietary restrictions⁴. The three new anticoagulants approved recently by Food and Drug Administration (FDA), the US are dabigatran, rivaroxaban and apixaban. Also, the recently introduced drug edoxaban is an effective anticoagulant belonging to direct factor Xa inhibitor. Conversely, their increased risk of bleeding make it unsuitable for patients in a wider set-up¹.

The intention of this article is to illustrate the pharmacology, advantages of the newer anticoagulants, dosing, bleeding associated risks.

Newer Anticoagulant Agents

Dabigatran

On administering Dabigatran in the form of Dabigatran etixelate, its plasma concentration is recorded as 1.5 hours on oral administration. It not only prevents free thrombin but also clot bound thrombin are also inhibited¹. Dabigatran is a direct thrombin inhibitor which acts straight on the thrombin moiety⁶.

150 mg twice daily (for patients with a creatinine clearance [CrCl] 30 mL/min) and 75 mg twice daily (for those with a CrCl, 15–30 mL/min) are the available commercial and the FDA approved dosing of Dabigatran in the United States of America¹.

In order to prevent Stroke and Ischemic Embolism in patients with any of the risk factors including Hypertension, left ventricular ejection fraction below 40%, NICE has approved Dabigatran¹. It requires two or three times administration only, as its plasma half life ranges from 14–17 hours, of which about 80% is excreted unexchanged by the kidney⁴. There is relatively low chances of drug-drug interaction since CYP450 plays no part in its metabolism⁷. Relatively lower dose of Dabigatran is required when taken along with other P-gp inhibitors (Verampamil and Amiodarone). Drug absorption is reduced when Dabigatran is taken along with proton pump inhibitors (Pantoprazole) by about 20–25 %⁷.

According to RE-LY trial; both doses of Dabigatran (i.e. 110mg and 150mg) showed reduced risk of major bleeding, life threatening bleeding, intracranial bleeding and minor bleeding when compared to Warfarin¹. Predominately due to their dyspeptic side effects, the rate of Dabigatran usage is reduced.

Lesser known side-effects other than gastric irritations include anaphylaxis, allergic edema, anemia are also reported. Even though Dabigatran has incoherent and cannot be used as the efficient clinical marker but it can produce increased coagulation parameters, like activated partial thromboplastin time, ecarin clotting time and thrombin time¹.

In Europe and Canada, Dabigatran is prescribed after elective hip or knee arthroplasty to prevent VTE. The recommended dose in these patients is about 220 mg and for patients taking Amiodarone and those at higher risk of bleeding, such as patients older than 75 years; about 150mg is agreed⁴. Unlike Warfarin, whose bleeding risk can be immediately reversed by giving specific antidotes, Dabigatran does not come with any such antidotes under overdose. So, the bleeding associated with it can be

encountered using activated charcoal claims an invitro study. Soon after the ingestion, activated charcoal must be supplied within one to two hours to avert intestinal absorption⁶. Constant checking for signs and symptoms of active bleeding; obtaining complete blood cell counts, including hemoglobin and hematocrit; and also evaluating markers of renal function, urine output, and CrCl levels must be carried out in patients taking Dabigatran¹.

As far as possible, the patient must be counseled before Dabigatran treatment has been initiated. Any crushing or opening of the Dabigatran capsule may result in 75% increase in its bioavailability putting the patient at serious risk of profuse bleeding, also discard any Dabigatran bottles after four months of its opening even if it hasn't reached its expiry date. Any noticeable symptoms of bleeding must be immediately brought into notice of the health care team¹.

Rivaroxaban

A direct free and bound factor Xa inhibitor, Rivaroxaban inhibits the conversion of prothrombin to thrombin. For a VTE prophylaxis after an orthopedic surgery and to prevent stroke in AF patient, Rivaroxaban is recommended according to RECORD study¹. It has a quick onset and half life of about 7 to 11 hours. Its bioavailability is above 80% when administered orally⁴.

Excretion of Rivaroxaban takes twin pathways, of which 66% is eliminated by kidney and the rest by feces. The drug is contra-indicated in patients with liver dysfunction due to the defective liver enzymes like CYP3A4, CYP2J2 required in its metabolic inactivation⁷. And is also contra-indicated in renal insufficiency as about one third elimination of the drug is through kidney⁵. Due to their reduced fecal and renal excretion, the drugs with CYP3A4 and P-gp inhibitory action like Phenytoin, Ketoconazole and Diltiazem must be cautiously administered as they show blown up anticoagulant action⁷.

According to ROCKET AF, a study has been conducted to analyse Rivaroxaban efficacy over Warfarin. The study showed that Warfarin and Rivaroxaban showed similar effect in preventing stroke or systemic embolism. However, Rivaroxaban showed no superior to Warfarin and had similar side effects like bleeding but had reduced chances of intra-cranial haemorrhage⁵. Unlike Dabigatran, whose crushing of the capsule may result in increased intestinal absorption upto 75% but Rivaroxaban effects are purely based on the location of administration. It shows an increased absorption at the site of stomach rather than the sites such as distal regions of intestines. The FDA approved dosing regimens available in United States are 10, 20 and 30mg¹.

Patients receiving simultaneous lumbar puncture or neuraxial anesthesia are at higher threat of getting spinal/epidural hematoma when administered with Rivaroxaban. It is also contra-indicated in patients with increased risk of bleeding and patients with hypersensitivity reactions¹. Lesser known side-effects such as tachycardia, nausea, syncope pruritis, hypotension and elevated liver enzymes were also highlighted⁸.

Table 1: Pharmacological Characteristics of Newer Oral Anti Coagulants¹⁶.

DRUG	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXYBAN
PATHWAY	Direct thrombin inhibitor	Direct factor Xa Inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
DOSE (mg)	110/50 mg	20mg	2.5/5mg	30 mg
FREQUENCY OF DOSE	BID	OD	BID	BID
BIOAVAILABILITY %	6 %	66%	50%	62%
METABOLISM	P-gp CYP3A4	P-gp	P-gp CYP3A4	CYP3A4
t1/2	12-17h	11-13h (elderly)	12h	10-14 h
RENAL CLEARANCE	80%	35%	25%	50%
PROTEIN BINDING	35%	92-95%	84%	55%

Since Rivaroxaban affects the prothrombin time and the activated partial thromboplastin time, routine monitoring is required in order to evaluate the signs and symptoms of active bleeding; for obtaining the complete blood cell counts (hematocrit and haemoglobin), urine output, and also for identifying the markers for hepatic function such as alanine aminotransferase and bilirubin. Like that of Dabigatran, Rivaroxaban is also not presented with any particular antidote for which activated charcoal comes as a salvage¹. Presently, Rivaroxaban is finding its place in the phase III clinical trials in evaluating its use to treat terminally-ill VTE patients⁴.

According to the study EINSTEIN, Rivaroxaban showed lesser discontinuation when compared to Warfarin when administered, reduced danger of gastrointestinal side effects⁹. The mainstay of VTE treatment including acute pulmonary embolism[PE] and deep vein thrombosis[DVT] are the vitamin K antagonist. One of the major drawback of this treatment is the recurrent need for monitoring the INR and the second having the higher chances of bleeding complications¹⁰. When compared to VKA, Rivaroxaban are significant when compared to other new oral anticoagulants reduced the bleeding risk in VTE patients⁹.

Apixaban

Apixaban shares a similar mechanism of action like Rivaroxaban and is a direct factor Xa inhibitor¹. Apixaban's selectivity and high affinity can be credited to its extremely high attraction for factor Xa and relatively lower association with thrombin and trypsin³.

It reaches a plasma peak level in about 3-4 hours having a bioavailability of 50% when administered orally and is absorbed quickly. Metabolisation is partially done by CYP3A4, a small amount by kidney and also has an independent CYP. Also apixaban does not have any direct effect on the liver enzymes contributing to its low drug-drug interaction profiles^{3,11}.

However, plasma levels of apixaban is reduced when CYP enzyme inducers are administered such as Phenytoin and Carbamazepine¹². About 14day period gap must be observed while administering Ketoconazole to a patient on Apixaban⁸. In order to prevent stroke in patients with AF, the dose recommended is 5 mg twice daily. In May 2012, European national committee agreed to the usage of Apixaban in patients who have undergone knee and hip replacement to prevent VTE¹. The dose recommended for

the same is 2.5mg two times day soon after the operation with or without food.

The ARISTOTLE is a randomized phase III trial which showed that Apixaban had wider actions on overall strokes but had lesser influence on ischemic stroke unlike Warfarin. Also the study showed that the side-effect profile of both Warfarin and Apixaban were not similar, except their gastrointestinal effects are comparable⁵. Lack of available antidotes and simultaneous use of anti-platelet agents result in increased chances of bleeding⁸.

Edoxaban

Edoxaban is a factor Xa inhibitor which promises to have reduced bleeding risk associated with anticoagulation therapy¹³. It is rapidly absorbed within 1-3 hours after the oral administration. About 60mg of Edoxaban has an elimination half life of 10-14 hours¹⁴. In healthy patients about 60% and 35% is eliminated in feces and urine respectively. Major metabolite formed during the biotransformation of Edoxaban by hydrolysis is M4. More than 70% gets excreted unexchanged from the body. Both for AF and Orthopedic surgery VTE with severe renal impairment patients the suggested 15 mg once daily. The clearance effect of Edoxaban is minimal in end stage renal disease (ESRD) patients undergoing hemodialysis. So there is no dosage adjustment required in case of ESRD patients. Meanwhile food does not have any effect on the absorption and mean plasma concentration shows a study conducted on fasted fed and healthy Japanese and Caucasian volunteers.

Observing the venous conditions at time interval like 1.5h and 5h post edoxaban administration, it was found to be 28% at 1.5h and 21% at 5 h. Similarly, the observation on arterial conditions it was found to be 26% at 1.5 h and 17% at 5h¹⁴. Edoxaban 60 mg twice daily has more significant effect on lowering the PT activity than the direct thrombin inhibitor Ximelagatran. If administered with potent P-gp inhibitors like azithromycin, ketoconazole and omeprazole, there is an increase in the bioavailability of Edoxaban, hence require a 50% dose reduction. While on Edoxaban the patient must avoid consumption of food containing Warfarin derivatives like chamomile, horseradish etc¹⁵.

Edoxaban is highly effective in treatment of VTE and acts as a preventive measure of stroke in NVAF (Nonvalvular Atrial Fibrillation). In a VTE trial Edoxaban was compared to Warfarin for analysing their bleeding risk, it

was found 1.4 % for Edoxaban and 1.6 % for warfarin. In case of an acute Edoxaban overdose activated charcoal (50-100 mg) can be administered within three hours of consumption. Even though there is no specific antidote for OFXaIS, two investigational drugs like Andexanet alfa and Aripazine binds to OFXaIS and neutralizes the effect¹⁵.

DISCUSSION

The new oral anticoagulants have led to a revolutionary outbreak by channelling a streamline of out-of-hospital thromboprophylaxis. The need for less drug monitoring and fewer drug-drug interactions, they are getting a broader acceptance. By maintaining a balance between both safety and efficacy when judged against VKA, they are being recommended to prevent stroke in vulvular AF and VTE. They also have the ability to probably eliminate any pre-operative therapy with an intravenous agent. The most important advantage is their reduced risk of bleeding when compared to Warfarin or Heparin. Another important factor in determining its therapy will be patients age, hepatic and renal function. The lack of available antidote for its overdose is one of the major drawback. The wider expansion of NOAC may take time according to the clinician considerations and patients tolerability.

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