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RIVAROXABAN, A DIRECT FACTOR XA INHIBITOR: A DRUG UPDATE

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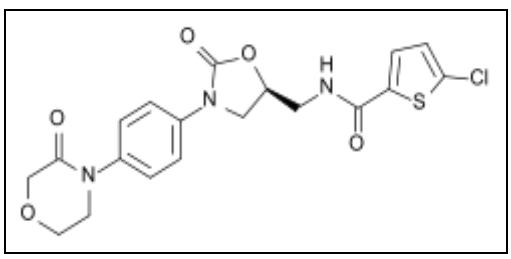
ABSTRACT: Warfarin, a vitamin K antagonist has been the leading oral anticoagulant since early 1940s despite limitations like slow onset and offset of action, variations in metabolism, multiple food and drug interactions, narrow therapeutic index and need for routine laboratory monitoring. Rivaroxaban, a direct factor Xa inhibitor is a recently introduced orally effective novel anticoagulant offering improvement over current standard of care such as good bioavailability, low propensity for food and drug interactions, rapid onset of action, ease of administration, wide therapeutic index, predictable anticoagulant response and fixed oral dosage, limited side effects and no inter subject variability. Over and above, the drug doesn't require coagulation monitoring. Thus rivaroxaban has the potential to be an attractive alternative to current anticoagulants, providing effective and well tolerated anticoagulation in a convenient manner in patients with stroke and systemic embolism with non-valvular atrial fibrillation (AF), treatment and prevention of deep vein thrombosis (DVT), pulmonary embolism (PE) etc. Moreover, specific antidotes (Aripazine-PER 977; Ciraparantag) and Andexanet (PR TO64445) antagonising the pharmacodynamic effect of rivaroxaban are under trial.

INTRODUCTION: Warfarin, a Vitamin K antagonist has been the leading oral anticoagulant since early 1940s despite limitations like slow onset and offset of action, variations in metabolism, multiple food and drug interactions, narrow therapeutic index and need for routine laboratory monitoring [1]. So there is a need for novel anticoagulant offering improvement over current standard of care such as fixed oral dosing and no need for routine monitoring.

Rivaroxaban is a recently introduced orally effective novel anticoagulant having wide therapeutic index[2], which directly inhibits factor Xa that may provide more consistent and predictable anticoagulant action than warfarin, unfractionated heparin, LMWH, fondaparinux[3, 4, 5]. Chemically Rivaroxaban is (S)-5-chloro-N-{[2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]oxazolidin-5-yl]methyl }thiophene-2-carboxamide.

(Chemical formula=$C_{19}H_{18}Cl\ N_3\ O_5\ S$) [3] (**Fig. 1**)



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Pharmacokinetics:

After oral administration, rivaroxaban is well absorbed from the gut. The bioavailability following administration of oral rivaroxaban is 80%-100%. In a fasted state, rivaroxaban pharmacokinetics are approximately linear upto about 10mg once daily and oral bioavailability is reduced to 66% after a 20mg tablet as a result of poor solubility.[1] Maximum plasma concentration (C_{max}) is attained four hours after a 10mg dose and the plasma concentration declines with a half life of 8-12 hours but factor Xa activity does not return to normal within 24hours. Hence, once daily dosing is possible [6]. 90-95% are bound to serum albumin with volume of distribution of approximately 50litres.

Two third of the orally administered drug are metabolised in the liver by CYP3A4, CYP2J2 and CYP independent mechanism. The rest are excreted unchanged in urine[7].The pharmacokinetic profile is unaffected by body weight, sex, ethnicity. Safety and efficacy have not been established for children and adolescents upto 18 years[8]. The terminal half life of rivaroxaban is prolonged in subjects over 75 years compared with younger subjects but the effects were minor and within expectations[2]. Food does not affect C_{max} of the 10mg dose and dietary restrictions are not necessary in patients receiving rivaroxaban[1].No dose adjustment is necessary in patients with mild renal impairment (CrCl 50-80ml/min)[6].

Mechanism of Action:

Rivaroxaban specifically inhibits both free Factor Xa and Factor Xa bound in the prothrombinase complex[3]. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II), and no effects on platelets have been demonstrated[6].

Adverse effects:

Use of rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia [2]. In a clinical studies non major bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen to be almost similar during long term rivaroxaban treatment compared with vitamin K antagonists treatment. But risk of major bleeding i.e intracranial bleeds were lower with rivaroxaban[9, 10]. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate[1].There may be transient elevation in liver enzymes[11].

Drug Interaction:

Rivaroxaban demonstrated a low propensity for drug-drug interaction. Results of interaction studies have shown no clinically relevant interaction between rivaroxaban and potential concomitant medications in patients receiving anticoagulants like warfarin, low molecular weight heparin, fondaparinux, NSAIDs like naproxen[12] and acetylsalicylic acid[13], clopidogrel[14]. After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT)[6].

The use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp like azole-antimycotics, HIV protease inhibitors, erythromycin, clarithromycin which may lead to an increased bleeding risk[2].

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban plasma concentrations with parallel decrease in its pharmacodynamic effects. Strong CYP3A4 inducers like phenytoin, carbamazepine, Phenobarbital, St. John's Wort should be co-administered with caution[6].

Dosing Schedule: [6, 15]

- Optimal dose range is 5-20mg daily.
- It is recommended in a fixed dose of 10mg once daily starting 6-10 hours after surgery for prophylaxis of venous

thromboembolism following total knee/hip replacement.

- The recommended dose is 20 mg once daily for prevention of stroke and systemic embolism.

- The recommended dose for the initial treatment of acute deep vein thrombosis(DVT) and pulmonary embolism (PE) is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

Contraindication and precaution:

Rivaroxaban is contraindicated in any type of severe, active bleeding[5]. Precaution should be taken in the following conditions: [2]

- Hypersensitivity to the active substance or to any of the excipients.

- Patients with risk of bleeding like uncontrolled hypertension, thrombocytopenia, current or recent gastrointestinal ulceration, recent intracranial haemorrhage, malignancy etc.

- Concomittant use with anticoagulants

- Renal insufficiency

- Hepatic disease associated with risk of clinically relevant bleeding and coagulopathy.

- Pregnancy and breast feeding

Clinical efficacy and safety:

The safety of rivaroxaban has been evaluated and established in several studies. In four RECORD studies, with a total enrollment of over 12,000 patients have shown that 10mg per day oral rivaroxaban has non-inferior and possibly superior efficacy compared to 40mg per day of the subcutaneous low molecular weight heparin (LMWH) enoxaparin in preventing venous thromboembolism in adult patients undergoing total hip or knee replacement surgery. However, the risk of bleeding were same in both groups[16].

In pivotal double-blind ROCKET AF study, 6229 patients aged ≥75 years with atrial fibrillation and stroke risk factors randomized to warfarin or rivaroxaban (20 mg daily; 15 mg if creatinine clearance <50 mL/min) shows that rates of major bleeding which was restricted to extracranial bleeding were higher in older than in younger patients, but not significantly different between treatment groups. Thus, factor Xa inhibitor, rivaroxaban is as effective as adjusted-dose warfarin to anticoagulate elderly patients with nonvalvular AF[17].

In Einstein DVT, Einstein PE and Einstein Extension studies in patients with active cancer and venous thromboembolism, rivaroxaban had similar efficacy to prevent recurrence of venous thromboembolism and reduced major bleeding events compared with treatment with enoxaparin and a vitamin K antagonist, although there was no difference between groups for clinically relevant bleeding[9].

Uninterrupted rivaroxaban therapy appears to be as safe and efficacious in preventing bleeding and thromboembolic events in patients undergoing AF ablation as uninterrupted warfarin therapy[18].

In a matched sample study including 3654 rivaroxaban and 14,616 warfarin patients where matching was adequate, with all standardized differences in patient characteristics <10%, no significant differences were observed for bleeding and composite stroke and systemic embolism outcomes, although rivaroxaban users were associated with significantly fewer VTE events[19].

According to a randomized trial of 1504 patients, the oral anticoagulant rivaroxaban appears to safely and effectively prevent the risk of stroke associated with cardioversion in patients with atrial fibrillation. Patients scheduled for elective cardioversion were assigned to receive rivaroxaban or dose-adjusted Vitamin K antagonists. Researchers chose either an early (target period of

1-5 days after randomization) or delayed (3-8 weeks) cardioversion strategy. Patients taking rivaroxaban in the early and delayed cardioversion groups had low thromboembolic and bleeding risks that were reported similar with Vitamin K antagonists treatment in earlier studies. Rivaroxaban's action in 2 to 4 hours also allowed for more rapid cardioversion than Vitamin K antagonists[10].

A randomized, open-label, blinded endpoint evaluation trial to evaluate the feasibility of early anticoagulation with rivaroxaban in acute ischemic stroke or TIA patients with nonvalvular AF is underway.Inclusion criteria are nonvalvular AF, presumed cardioembolic stroke or transient ischemic attack (TIA) confirmed by MRI within five-days from onset, and mild to moderate stroke severity. 196 patients were randomized to either rivaroxaban (10 mg once daily for five-days followed by 15 mg or 20 mg once daily) or dose-adjusted warfarin (coadministration of aspirin 100 mg per day until achieving international normalized ratio of 1·7). The study is registered in ClinicalTrials.gov (NCT02042534)[20].

Of 27,467 patients receiving rivaroxaban, 496 major bleeding events occurred in 478 patients, an incidence of 2.86 per 100 person-years. Major bleeding were common in elderly patients above 75 years of with hypertension, coronary artery disease, heart failure and renal disease Major bleeding was most commonly gastrointestinal (88.5%) or intracranial (7.5%). Although 46.7% of major bleeding patients received a transfusion, none had sufficient evidence of receiving any type of clotting factor. Thus in this large observational study,fatal bleeds were rare[21].

Specific antidotes (Aripazine-PER 977; Ciraparantag), a synthetic D-Arginine compound and Andexanet (PR TO64445), a recombinant modified factor Xa molecule antagonising the pharmacodynamic effect of rivaroxaban are under trial[22, 23]. But should a bleeding complication arise, it should be manage symptomatically. If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Regulatory approval and indication: [6]

- In September 2008, Health Canada and the European Commission granted marketing authorization for rivaroxaban as 10 mg tablet taken once daily for the prevention of venous thromboembolism (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery.

- In December 2011 rivaroxaban has been approved by the European Commission for use in two new indications: prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors and treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

- On July 1, 2011, the U.S. Food and Drug Administration (FDA) approved rivaroxaban for prophylaxis of deep vein thrombosis(DVT), which may lead to pulmonary embolism (PE), in adults undergoing hip and knee replacement surgery.

- On November 4, 2011, the U.S. FDA approved rivaroxaban for stroke prophylaxis in patients with non-valvularatrial fibrillation.

- On November 2, 2012, the U.S. Food and Drug Administration (FDA) approved rivaroxaban for the treatment of patients with deep vein thrombosis (DVT) and pulmonary embolism (PE) and for long-term treatment to prevent recurrence.

CONCLUSION: The efficacy and safety profiles of rivaroxaban have been demonstrated in preclinical and clinical studies. The drug offers advantages over vitamin K antagonists in terms of good bioavailability, low propensity for food and drug interactions, rapid onset of action, ease of administration, wide therapeutic index, predictable anticoagulant response, fixed oral dosage, limited side effects and no inter subject variability. Over and above, the drug doesn't require coagulation monitoring. Because of these therapeutic potentials, rivaroxaban has the potential to be an attractive alternative to current anticoagulants, providing effective and well tolerated anticoagulation in a convenient manner, from hospital to home. However the bleeding potential of rivaroxaban has prompted the FDA advisory Committee against approval of its use to reduce the risk of thrombotic cardiovascular events in patients with Acute Coronary Syndrome[24]. With further information from several ongoing studies, it remains to be seen that rivaroxaban replaces warfarin as the mainstay in oral anticoagulant therapy.

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