Dabigatran : A Novel Oral Anticoagulant

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ABSTRACT

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In this issue we shall discuss about the Anti IIa (antithrombin) agent that has become available in India recently- Dabigatran (Pradaxa, Boehringer Ingelheim). Dabigatran is recommended by most cardiology societies as a useful alternative to warfarin to prevent stroke and blood clots in patients with either paroxysmal or permanent atrial fibrillation, who do not have a prosthetic heart valve, significant heart valve disease, severe renal failure or advanced liver disease. Dabigatran has also been shown to be useful in the prophylaxis of venous thromboembolism after orthopaedic surgery and is non-inferior to warfarin in the extended treatment of deep vein thrombosis.

Keywords: Oral anticoagulants, Thrombotic disorders

*See End Note for complete author details

Traditionally, the treatment of thrombotic disorders has involved aspirin, oral anticoagulants (OAC) and heparin. Despite remarkable progress in life sciences, these drugs still remain a challenge and mystery to us, and their use is far from optimized. Newer agents like low molecular weight heparin, Fondaparinux (Factor Xa inhibitor), Clopidogrel, Prasugrel and glycoprotein IIb/IIIa inhibitors have helped us deal with the thrombotic milieu better. Although Warfarin and similar orally active anticoagulants provide a convenient and affordable approach in the long-term outpatient management of thrombotic disorders; OAC therapies still remain a challenge. The clinician has to tread a narrow lane between the risk of thrombosis on one end and the peril of bleeding on the other. Moreover OAC therapy involves frequent, and often, lifelong monitoring of anticoagulation levels, food-drug and drug-drug interactions and the risk of bleeding in an effort to minimize the risk of thrombosis. Anti-factor Xa agents, Rivaroxaban and Apixaban, and antithrombin agent Dabigatran have been developed as alternative agents for oral use and have provided impressive clinical outcomes in preliminary trials. In this issue we shall discuss about the Anti IIa (antithrombin) agent that has become available in India recently- Dabigatran (Pradaxa, Boehringer Ingelheim).

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, Dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Both free and clot-bound thrombin and thrombin-induced platelet aggregation are inhibited by the active moieties.

Pharmacokinetics

After oral administration, Dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. Peak plasma concentrations are attained within 0.5 - 2.0 hours post administration, and mean terminal half-life is approximately 12–14 hours in elderly healthy volunteers. Dabigatran is eliminated primarily unchanged in the urine. Dose modification in hepatic insufficiency is not recommended. Safety of Dabigatran in pregnancy, labor, delivery, lactating mothers and in pediatric population has not been established.

Indications & Dosage

Dabigatran is recommended by most cardiology societies as a useful alternative to warfarin to prevent stroke and blood clots in patients with either paroxysmal or permanent atrial fibrillation, who do not have a prosthetic heart valve, significant heart valve disease, severe renal failure or advanced liver disease. Dabigatran has also been shown to be useful in the prophylaxis of venous thromboembolism after orthopaedic surgery and is non-inferior to warfarin in

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the extended treatment of deep vein thrombosis.[1,2]

Recommended Dose

For patients with creatinine clearance (CrCl) >30 mL/ min, the recommended dose is 150 mg taken orally, twice daily, with or without food. For patients with severe renal impairment (CrCl 15-30 mL/min), the recommended dose is 75 mg twice daily. Dosing recommendations for patients with a CrCl<15 mL/ min or on dialysis has not been provided. Renal function has to be assessed prior to initiation of treatment with Dabigatran. Periodical assessment of renal function as clinically indicated and appropriate adjustment of therapy is recommended. Dabigatran should be discontinued in patients who develop acute renal failure while on Dabigatran and alternative anticoagulant therapy must be considered.

Converting from or to Warfarin

When converting patients from warfarin therapy to Dabigatran, discontinue warfarin and start Dabigatran when the INR is below 2.0.

When converting from Dabigatran to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCl e"50 mL/min, start warfarin 3 days before discontinuing Dabigatran.
- For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing Dabigatran.
- For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing Dabigatran.
- For CrCl<15 mL/min, no recommendations are made.

Because Dabigatran can increase INR, the INR will better reflect warfarin's effect only after Dabigatran has been stopped for at least 2 days.

Converting to and from parenteral anticoagulants

For patients currently receiving a parenteral anticoagulant, Dabigatran may be started 0 to 2 hours before the time the next dose of the parenteral drug would have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin). For patients currently taking Dabigatran, it is better to wait 12 hours (CrCl e"30 mL/min) or 24 hours (CrCl<30 mL/ min) after the last dose of Dabigatran before initiating treatment with a parenteral anticoagulant.

Dabigatran in patients planned for surgery

If possible, Dabigatran should be discontinued 1 to 2 days (CrCl e"50 mL/min) or 3 to 5 days (CrCl<50 mL/ min) before invasive or surgical procedures because of the increased risk of bleeding. Longer periods may be considered for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required.

Monitoring for the anticoagulant action of Dabigatran

Generally, the extent of anticoagulation need not be assessed regularly. Prothrombin time (PT) is too insensitive to reliably detect anticoagulant activity of Dabigatran and is therefore not recommended. Ecarin Clotting Time (ECT) and Thrombin Time (TT) are sensitive assays that increase in direct proportion to Dabigatran plasma concentration without any deviation from linearity at high plasma concentrations. However, ECT is not readily available in clinical practice. Activated Partial Thromboplastin Time (aPTT) increases in a non-linear manner to dabigatran concentration and is less proportional at higher Dabigatran concentrations. ECT, TT and aPTT are not standardized or validated with Dabigatran for commercial use. In cases of emergency, TT and aPTT are the most accessible qualitative methods for determining the presence or absence of the anticoagulant effect of Dabigatran.

Antidote

A specific reversal agent for Dabigatran is not available. Dabigatran can be dialyzed (protein binding is low, with the removal of about 60% of drug over 2-3 hours); however the amount of data supporting this approach is limited. Activated Prothrombin Complex Concentrates (aPCCs, e.g., FEIBA), or recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X may be considered but their use has not been evaluated in clinical trials. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of Dabigatran.

Adverse Events

In the pivotal trial comparing Dabigatran to warfarin, the most frequent adverse reactions leading to discontinuation of Dabigatran were bleeding and gastrointestinal (GI) events. Dabigatran 150 mg resulted in a higher rate of major GI bleeds and any GI bleeds compared to warfarin. The risk of bleeding increases with age, but the risk-benefit profile is favourable in all age groups. Patients on Dabigatran150 mg had an increased incidence of GI adverse reactions. These

were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis- like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and GI ulcer). Drug hypersensitivity reactions were reported in <0.1% of patients receiving Dabigatran. The concomitant use of Dabigatran with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. No other significant drug interactions have been reported.

END NOTE

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