Dabigatran : A Novel Oral Anticoagulant

*Jayant Kelwade** M S Pandharipande ***P P Joshi

Oral anticoagulants are widely used in clinical practice since 1940's .Vitamin K antagonists are the only group of approved drugs for long term use. Although the available vitamin K antagonists are highly effective for the prevention and/or treatment of most thrombotic disease, the significant interpatient and intrapatient variability in dose-response, the narrow therapeutic index, and the numerous drug and dietary interactions associated with these agents have led clinicians, patients, and investigators to search for alternative agents. Three new orally administered anticoagulants (apixaban, dabigatran, and rivaroxaban) are in the late stages of development and several others are in the earlier phases of investigation. These newer anticoagulants target factor Xa or thrombin, have rapid inset of action and longer half lives that permit once or twice daily administration . Designated to produce a predictable level of anticoagulation, these drugs are given in fixed doses without routine coagulation monitoring. .These novel anticoagulant medications are being studied for the prevention and treatment of venous thromboembolism, the treatment of acute coronary syndromes and the prevention of stroke in patients with atrial fibrillation. Dabigatran etixilate, a thrombin inhibitor and Rivaroxaban, an oral factor Xa inhibitor, are licensed in Europe and Canada for short term prophylaxis after elective hip or knee replacement .USFDA has approved the first new anticoagulant in 50 years, Dabigatran (marketed by Boehringer Ingelheim Pharmaceuticals under the trade name Pradaxa) for stroke prevention in patients with non-valvular atrial fibrillation.

Background

Warfarin, a vitamin K antagonist, has been the essential key in deep venous thromboembolism treatment for more than 60 years. Warfarin is a coumarin derivative and acts as a vitamin K antagonist to antagonize the effect of vitamin K required for the synthesis of active clotting factors II, VII, IX, and anticoagulant proteins C and S. Antagonism of vitamin K reduces the amount of these clotting factors, thereby producing anticoagulation. However, warfarin is a relatively dangerous drug, with serious and significant limitations in relation to titrating a safe and therapeutic anticoagulation level. It requires adjusted and variable doses dependent upon the prothrombin time, reported as the International Normalized Ratio. It Has s narrow therapeutic dose range (INR 2.0-2.5.) To achieve the desired therapeutic level, warfarin requires frequent monitoring and takes about 5 days for a stable antithrombotic effect to be achieved. Warfarin is influenced by several factors such as age, genetic status, medications, diet, and some medical conditions that contribute to variability of patient response. Resistance to warfarin has also been reported in literature, defined as requirement more than 20 mg/day to maintain INR in the therapeutic range.On the contrary,approximately,10% of the patients require less than 1.5 mg/day of warfarin to achieve an INR of 2 to 3, labelled as warfarin sensitivity. These patients are more likely to represent one or two variant alleles CYP2C9. It should also be kept in mind that total direct and indirect costs for management of anticoagulation with warfarin far exceed the actual cost of the drug.

Although the safe use of warfarin is a challenge, there has not been a market competitor for oral long-term anticoagulation in the management of venous thromboembolism (VTE) until recently, with the development of two new oral anticoagulants: Dabigatran, a direct thrombin inhibitor and Rivaroxaban, a direct factor Xa inhibitor.

Dabigatran directly inhibits both free and clot-bound thrombin. Dabigatran etexilate (a pro-drug) is rapidly converted (after oral administration and hepatic processing) to dabigatran, with peak plasma dabigatran concentrations recorded approximately 1.5 hours after oral ingestion. Once at steady state, dabigatran has a half-life of 14 to 17 hours. With oral treatment, bioavailability is 7.2%, and dabigatran is predominantly excreted in the feces.4 Although part of

Address for correspondence

*resident **lecturer***HOD Medicine
Department IGGMC Nagpur

the bioconversion from pro-drug to active metabolite occurs in the liver, the cytochrome p450 system is not involved. Potentially important drug interactions with quinine/quinidine and verapamil have been described. Elimination of dabigatran after hepatic activation occurs predominantly (up to 80%) in the kidneys; thus, patients with significant renal impairment have been excluded from most clinical trials involving dabigatran. Approved labels in Canada and elsewhere recommend an arbitrary dose reduction in the setting of moderate renal dysfunction, and recommend against use with severe renal dysfunction.

Patients at high risk of thromboembolism from non-valvular atrial fibrillation are candidates for the drug including patients with previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening for the medication, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease.

Patients who should NOT receive the drug include those with a severe heart-valve disorder, stroke within 14 days or severe stroke within the last 6 months, a condition that increases the risk of hemorrhage, a creatinine clearance of less than 30 ml per minute, active liver disease, or pregnancy. Patients taking quinidine should also not take the medication because of a significant drug interaction.

The drug does not typically require measurement of blood thinning levels (prothrombin times expressed as and international normalized ratio (INR) of clotting time to a standard clotting control.

The USFDA approval was based on the prospective, randomized RE-LY trial recently published in the New England Journal of Medicine that compared the safety and efficancy of two doses of dabigatran (110 mg and 150 mg twice daily) to conventional warfarin (Coumadin) therapy in 18,113 patients:

Rates of the primary outcome (stroke and systemic embolization) were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI], 0.74 to 1.11; P < 0.001 for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82; P < 0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran (P=0.003) and 3.11% per year in the group receiving 150 mg of dabigatran (P=0.31). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (P < 0.001) and 0.10% per year with 150 mg of dabigatran (P < 0.001). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051).

It should be noted that the FDA did not approve the lower 110 mg dose of the medication. The drug's most common side effect was dyspepsia (GI upsetelevations were not any different than that seen with warfarin.

The RE-NOVATE trial was conducted to demonstrate utility of Dabigatran for the prevention of venous thromboembolism in which patients were randomized to either dabigatran 220 mg daily or 150 mg daily or enoxaparin 40 mg subcutaneously daily, with the first dose administered preoperatively.[5] The primary endpoint was a composite of total VTE and death from all causes. Both doses of dabigatran were noninferior to enoxaparin; major bleeding was similar between dabigatran 220 mg, 2.0% (P = .44); dabigatran 150 mg, 1.3% (P = .6); and enoxaparin, 1.6%. Patients undergoing total knee replacement were studied in the RE-MODEL study.[6] The primary outcome, the composite of total VTE and mortality, occurred in 36.4% of patients in the dabigatran 220 mg group and 40.5% of patients in the dabigatran 150 mg group and 37.7% of patients in the enoxaparin 40 mg group. Both trials demonstrated noninferiority for dabigatran compared with enoxaparin. The RE-MOBILIZE study compared dabigatran with enoxaparin administered at a dose of 30 mg twice daily, started postoperatively. The primary outcome of total VTE and death occurred in 31.1% of patients in the dabigatran 220 mg group, 33.7% of patients in the dabigatran 150 mg group, and 25.3% of those in the enoxaparin group. Dabigatran, as administered in the RE-MOBILIZE study, was thus inferior to enoxaparin administered at standard North American doses after knee replacement surgery.[7] Large phase 3 studies of dabigatran versus warfarin for the secondary prevention of acute VTE are ongoing: patients in both arms will receive short-term "overlap" treatment with LMWH.

More than 18 000 patients with nonvalvular AF were enrolled in RELY, an open-label study of stroke prevention where 2 doses of dabigatran (110 mg or 150 mg twice daily) were compared with warfarin (target INR = 2-3); median follow-up was 2 years. Designed as a noninferiority trial with a primary outcome of stroke or systemic embolism, RELY demonstrated that dabigatran 110 mg twice daily not only provided antithrombotic protection similar to well-managed warfarin but also was associated with a lower annual rate of major bleeding (3.36% vs 2.71%, P = .003). The twice daily 150-mg dose of dabigatran resulted in a lower rate of stroke/systemic embolism, 1.11% vs 1.69%; (relative risk = 0.66; 95% confidence interval, 0.53-0.82; P < .001 for superiority), and was associated with a similar risk of major bleeding Dyspepsia was reported by approximately 12% of patients taking both doses of dabigatran, compared with only 5.8% of patients taking warfarin. Transaminase levels were monitored closely in this trial, and no evidence of hepatoxicity was reported.[8]The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051).It should be noted that the FDA did not approve the lower 110 mg dose of the medication

References

1. Venous thromboembolism - rivaroxaban, NICE Technology Appraisal Guidance (April 2009);Rivaroxaban for the prevention of venous thromboembolism
2. Venous thromboembolism - dabigatran, NICE Technology Appraisal Guideline (September 2008);Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults
3. Antithrombotic Therapy, Scottish Intercollegiate Guidelines Newwork - SIGN (1999)
4. McCahon D, Murray ET, Jowett S, et al ; Patient self management of oral anticoagulation in routine care in the UK. J Clin Pathol. 2007 Nov;60(11):1263-7. Epub 2007 Jan 26. [abstract]
5. Blann AD, Fitzmaurice DA, Lip GY; Anticoagulation in hospitals and general practice.; BMJ. 2003 Jan 18;326(7381):153-6.
6. Shalansky S, Lynd L, Richardson K, et al; Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis. Pharmacotherapy. 2007 Sep;27(9):1237-47. [abstract]
7. Mackenzie AR, Laing RB, Douglas JG, et al; High prevalence of iliofemoral venous thrombosis with severe groin infection among injecting drug users in North East Scotland: successful use of low molecular weight heparin with antibiotics. Postgrad Med J. 2000 Sep;76(899):561-5. [abstract]
8. Meyer G, Marjanovic Z, Valcke J, et al ; Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med. 2002 Aug 12-26;162(15):1729-35. [abstract]