Advances in Anticoagulation: Focus on Dabigatran, an Oral Direct Thrombin Inhibitor

John G.T. Augoustides, MD, FASE, FAHA

Dabigatran is an oral direct thrombin inhibitor with a rapid onset. Patients on dabigatran do not require coagulation monitoring. Recent prospective randomized trials have shown the efficacy of dabigatran for the prevention of venous thromboembolism after knee or hip arthroplasty and for the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. Because dabigatran is cleared principally by the kidneys, dosage adjustments are required in the setting of renal dysfunction. There currently is no reversal agent for dabigatran although hemodialysis can facilitate its rapid removal in life-threatening circumstances. The management of severe bleeding associated with dabigatran also may include the administration of a procoagulant, such as recombinant activated factor VII. Based on recent guidelines, regional anesthesia should be used cautiously in patients taking this novel oral thrombin inhibitor.

KEY WORDS: dabigatran, thrombin, atrial fibrillation, venous thromboembolism, hip arthroplasty, knee arthroplasty, hemodialysis, reversal agent, glycoprotein transporter, renal dysfunction, mechanical heart valve, anticoagulation

UNTIL RECENTLY, the only oral clinical anticoagulants have been the vitamin K antagonists, such as warfarin. Because of the multiple limitations of this drug class, oral anticoagulant alternatives recently have been developed. The two recent alternatives to warfarin are the oral thrombin inhibitors (dabigatran) and the oral factor Xa inhibitors (rivaroxiban and apixaban). Based on recent large prospective, randomized trials, these drugs are poised to transform the clinical practice of anticoagulation worldwide. The focus of this review is dabigatran, the novel oral direct thrombin inhibitor. A subsequent expert review will cover the oral factor Xa inhibitors in detail.

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From the Cardiovascular and Thoracic Anesthesiology and Critical Care Section, Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

Address reprint requests to John G.T. Augoustides, MD, FASE, FAHA, Cardiothoracic Section, Anesthesiology and Critical Care, Dulles 680, HUP, 3400 Spruce Street, Philadelphia, PA, 19104-4283. E-mail: yiandoc@hotmail.com

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LIMITATIONS OF STANDARD ANTICOAGULANTS

The advent of low-molecular-weight heparin and fondaparinux streamlined anticoagulation for vascular thrombosis because their administration was subcutaneous, with greater freedom from coagulation monitoring and from the risk of heparin-induced thrombocytopenia.[1] The requirement for daily subcutaneous injection of these agents has limited their long-term application. Oral vitamin K antagonsists such as warfarin have been the traditional long-term solution for anticoagulation despite multiple disadvantages.[1,2] Because their anticoagulant effect has a slow onset and offset, their clinical application requires bridging with parenteral anticoagulation. Significant interindividual sensitivity, multiple food and drug interactions, and a narrow therapeutic index all have necessitated an individualized approach to therapy with obligatory coagulation monitoring.

Because of these multiple limitations, the quality of anticoagulation with oral vitamin-K antagonists frequently is suboptimal. As an example, 30% to 50% of patients with atrial fibrillation who require long-term anticoagulation for stroke prevention are not managed with an oral vitamin-K antagonist.[3,4] This significant clinical gap has prompted the development of alternative oral anticoagulants.[1,2] The first promising oral thrombin inhibitor was ximelagatran.[5] This agent was evaluated extensively in phase III clinical trials in the management of vascular embolism, atrial fibrillation, and myocardial

infarction. Its further clinical development was blocked by the risk of hepatotoxicity.[6]

PHARMACOLOGY OF DABIGATRAN

Dabigatran etexilate is available as a capsule formulated with tartaric acid to minimize variability in intestinal absorption. Although it requires an acidic environment for absorption, it is not affected significantly by the concomitant administration of a proton pump inhibitor.[7] This prodrug is activated after oral administration by nonspecific esterases to dabigatran, which is a competitive thrombin antagonsist.[8] Dabigatran binds to the active site of thrombin and so can inhibit thrombin whether it is bound to fibrin or not. The antagonism of fibrin-bound thrombin is an important advantage of dabigatran over heparin because bound thrombin still is able to trigger the formation of thrombus.[9] The anticoagulant effect of dabigatran peaks on average about 1.5 hours after oral administration.[7]

Hepatic metabolism of dabigatran does not involve the cytochrome P450 enzyme system, and so dabigatran is not subject to drug and food interactions at this level. Hepatic conjugation of dabigatran with glucoronic acid accounts for about 20% of dabigtran excretion via the biliary system.[10] The half-life of dabigatran ranges from 12 to 14 hours. The major elimination pathway is via the kidney. Consequently, renal dysfunction raises dabigatran plasma levels and prolongs its half-life substantially.[11] Drug interactions are possible at the level of the efflux permeability glycoprotein transporter, which affects reabsorption of dabigatran etelixate into the gastrointestinal tract. Potent inhibitors of the glycoprotein transporter, such as quinidine, ketoconazole, amiodarone, and verapramil, may increase plasma levels of dabigatran because of reduced intestinal reabsorption.[8] Furthermore, inducers of the glycoprotein transporter, such as rifampicin, can decrease dabigatran plasma levels because of increased intestinal reabsorption.[8]

Dabigatran prolongs the thrombin time, the ecarin coagulation time, and the activated partial thromboplastin time.[12,13] The thrombin time is the most sensitive test of dabigatran. There already is thrombin time assay that is certified in Europe for the determination of dabigatran plasma levels (Hemoclot Test; Hyphen Biomed, Neuville-Sur-Oise, France).[12] Although dabigatran typically has a minimal effect on the prothrombin time at clinical concentrations, it can prolong the prothrombin time in a linear fashion at high plasma concentrations. In contrast, the effect of dabigatran on the partial thromboplastin time is curvilinear, with flattening of this response curve at higher concentrations.[13]

Because of its unique pharmacology, dabigatran offers solutions to the traditional limitations of the oral vitamin K antagonists.[12] Its rapid onset of action renders bridging with heparin obsolete. Routine coagulation testing is not required because dabigatran has a predictable and reliable anticoagulation profile. Its low potential for food and drug interactions frees patients from dietary and drug restrictions.

Unlike ximelagatran, dabigatran appears to be free from hepatic toxicity. This clinical observation is based on extensive liver function monitoring in nearly 40,000 patients enrolled in recent clinical trials.[12] A possible explanation for this phenomenon is that the prodrug dabigatran etexilate is converted to dabigatran throughout the body by nonspecific esterases in the gastrointestinal tract, plasma, and liver. This widespread conversion of the prodrug results in barely detectable levels of dabigatran etexilate in the plasma. In contrast, the activation of the prodrug ximelagatran to the active metabolite melagatran occurs primarily in the liver, resulting in temporary high hepatic concentrations of ximelagatran, which is hepatotoxic.[14]

DABIGATRAN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM

There have been four major randomized, controlled trials evaluating dabigatran for the prevention of venous thromboembolism (VTE) after major elective orthopedic surgery. The first European trial (n = 2,101) randomized patients undergoing knee arthroplasty to enoxaparin, 40 mg once daily, or dabigatran, either 150 mg or 220 mg once daily, for up to 10 days postoperatively.[15] The rates of VTE, death, and bleeding were similar in all study groups. The second European trial (n = 3,494) randomized patients undergoing total hip arthroplasty to enoxaparin, 40 mg once daily, or dabigatran, 150 mg or 220 mg once daily, for up to 35 days postoperatively.[16] The rates of VTE, death, and bleeding were equivalent across all study groups. The North American trial (n = 1,896) randomized patients undergoing knee arthroplasty to enoxaparin, 30 mg twice daily, or dabigatran, 150 mg or 220 mg once daily, for up to 15 days postoperatively.[17] Dabigatran at both doses was significantly inferior to enoxaparin for the prevention of VTE (dabigatran, 220 mg 31% [$p = 0.02$ *v* enoxaprin]; dabigatran, 150 mg 34% [$p < 0.001$ *v* enoxaparin]; enoxaparin, 24%).[17] Bleeding rates were similar across all study groups. The authors concluded that dabigatran was inferior to enoxaparin in this trial because of the more intensive enxoaparin therapy as compared with the European approach. The third European trial (n = 2,055) randomized patients undergoing total hip arthroplasty to enoxaparin, 40 mg once daily, or dabigatran, 220 mg once daily, for up to 35 days postoperatively.[18] The main finding was that high-dose dabigatran was equivalent to enoxaparin for reducing the combined incidence of VTE and related mortality but was superior to enoxaparin for reducing the risk of major VTE, defined as proximal deep vein thrombosis or nonfatal pulmonary embolism (risk difference, −1.9%; 95% confidence interval, −3.8% to −0.2%; $p = 0.03$).[18] Bleeding rates were similar across all study groups. A recent meta-analysis of these four trials showed that dabigatran (220 mg daily) as compared with enoxaparin (40 mg daily or 30 mg twice daily) was equivalent for the prevention of total VTE and all-cause mortality (risk ratio, 1.03; 95% confidence interval, 0.93-1.15) with no increased risk of major bleeding (risk ratio, 1.09; 95% confidence interval, 0.74-1.61).[19]

As a result, dabigatran currently is approved in more than 75 countries worldwide for the prevention of VTE after knee and hip arthroplasty.[12] It is not yet approved for this indication in the United States. The approved dabigatran dose for most patients is 220 mg once daily. The lower dose of dabigatran (150 mg daily) has been approved for patients at higher risk of bleeding, such as those aged > 75 years, those with moderate renal dysfunction (creatinine clearance 30-50 mL per minute) or those taking permeability glycoprotein inhibitors, such as amiodarone or verapamil. Dabigatran currently is contraindi-