Dabigatran in Clinical Practice

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ABSTRACT

Background: Stroke and systemic thromboembolism remain critical causes of mortality and morbidity in patients with paroxysmal or persistent atrial fibrillation. Dabigatran etexilate is a novel oral direct thrombin inhibitor, which provides stroke risk reduction for patients with nonvalvular atrial fibrillation. Randomized clinical data demonstrate dabigatran to be an alternative oral anticoagulant with an improved efficacy profile compared with oral warfarin dose adjusted to an INR (international normalized ratio) target of 2.0 to 3.0.

Objectives: Our aim was to review the pharmacology, mechanism of action, drug metabolism, and clinical trial data supporting dabigatran use.

Methods: We reviewed all the major published clinical studies of dabigatran and analyzed data regarding practical applications in selected clinical scenarios.

Results: This review provides recommendations for clinicians regarding dosing during invasive surgical procedures, transitioning off alternative anticoagulants, and a discussion of storage and handling of the drug.

Conclusions: Our effort should facilitate the safe and effective use of dabigatran in atrial fibrillation. (*Clin Ther*. 2012;34:2051–2060)

Key words: anticoagulant, atrial fibrillation, dabigatran etexilate, stroke, thrombin inhibitor.

INTRODUCTION

Stroke and systemic thromboembolic events remain the major source of mortality risk from atrial fibrillation and are responsible for considerable patient morbidity.[1] The prevalence of atrial fibrillation currently exceeds 2.5 million patients in the United States and is expected to double by the year 2040 to >5 million.[2] Anticoagulation for the reduction of stroke and systemic thromboembolism in nonvalvular atrial fibrillation (NVAF) has been largely accomplished with oral vitamin K antagonists for 5 decades. Antiplatelet therapies consistently prove inferior to warfarin in randomized clinical trials using either aspirin alone, aspirin with low-dose warfarin, or aspirin combined with clopidogrel.[3,4] Although traditional oral anticoagulants are effective (average relative risk reduction ~60% for stroke), treatment[5] with vitamin K antagonists is complicated in practice because of a narrow therapeutic window, genetic heterogeneity in pharmacokinetic response, numerous food and drug interactions, and the need for regular international normalized ratio (INR) monitoring.[6,7] As a result, novel anticoagulants have been developed targeting direct inhibition of clotting cascade factors rather than indirect reduction of hepatic synthesis of circulating procoagulant proteins. These agents selectively block key factors (eg, thrombin or factor Xa) in the anticoagulation cascade and hence block conversion of fibrinogen to fibrin (**Figure 1**).[8]

Dabigatran etexilate is an oral, low molecular weight, reversible direct thrombin inhibitor and is the first direct thrombin inhibitor to be approved by the US Food and Drug Administration (FDA) for stroke and systemic embolism risk reduction in NVAF.[9,10] In this review, we discuss dabigatran's mechanism of action, clinical trial evidence, and practical information useful to prescribing physicians.

MECHANISM OF ACTION AND PHARMACOLOGY

Dabigatran is an univalent, low molecular weight, novel oral anticoagulant in the direct thrombin inhibitor class. Dabigatran binds to the active site (exosite 1) of human thrombin. It competitively and reversibly inhibits thrombin in a dose- and concentration-dependent fashion. Dabigatran has potent anticoagulant activity prolonging the thrombin time (TT) and activated partial thromboplastin time (aPTT), with elevation in ecarin clotting time (ECT) most tightly correlated with dabigatran plasma concentration at steady state (**Figure 2**).[11,12] Dabigatran acts independently of antithrombin (AT) and inhibits fibrin-bound thrombin.[13]

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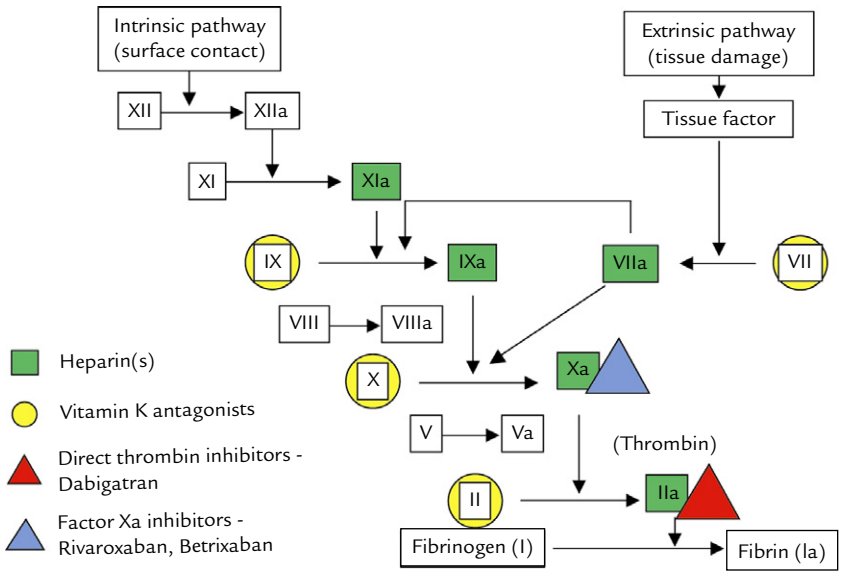

Figure 1. Detailed visual description of the coagulation cascade and the sites blocked either directly or indirectly by old and newer systemic anticoagulants.

Dabigatran is absorbed as a prodrug, dabigatran etexilate. Peak absorption is delayed up to 2 hours with food intake (peak drug effect at ~1 hour after ingestion on an empty stomach, ~2–3 hours when taken with food).[12] The drug is subsequently converted into its active form, dabigatran, by esterase–mediated hydrolysis. The bioavailability of dabigatran etexilate is ~3% to 7%. Its half-life is 12-17 hours in healthy individuals. Administration is twice daily, yielding a peak-to-trough plasma concentration ratio of 2:1.[9,12] Approximately 80% of dabigatran is cleared unchanged by the kidneys, which needs to be carefully considered in patients with impaired renal function.[14]

Because dabigatran is predominantly metabolized by esterases, the genetic variations affecting cytochrome P450 enzyme–mediated drug–drug interactions are not seen[15] Drug availability is, however, affected in patients taking some P-glycoprotein (P-gp) inhibitors (eg, dronedarone, systemic ketoconazole) or inducers (eg, rifampin).

CLINICAL TRIAL EVIDENCE

Dabigatran etexilate for patients with NVAF was initially evaluated in a 12-week, multicenter 502-patient phase II PETRO (Prevention of Embolic and Thrombotic Events With Persistent AF) study that assessed bleeding events and pharmacodynamics (D-dimer suppression) for dose determination. The dose of 150 mg BID demonstrated the best balance of efficacy and safety.[16]

The 150-mg dose and an ~30% lower dose (110 mg BID) were tested in the phase III RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate) trial. In RE-LY, 18,113 patients with NVAF and ≥1 additional risk factor for stroke were randomized to dabigatran 110 mg BID, dabigatran 150 mg BID, or adjusted dose warfarin (INR: 2.0–3.0).[17] This was designed to compare of 2 blinded doses of dabigatran and open-label warfarin. After mean follow-up of 2 years, 110 mg dabigatran proved noninferior to warfarin, and 150 mg dabigatran superior to warfarin for the primary end point. Stroke or systemic embolism occurred at 1.71%/year with warfarin compared with 1.54%/year with dabigatran 110 mg BID (relative risk [RR] = 0.90; 95% CI: 0.74–1.10) and 1.11%/year with dabigatran 150 mg BID (RR = 0.65; 95% CI: 0.52–0.81) (**Figures 3** and **4**).[18–20] Major bleeding rates were similar among patients on warfarin (3.57%/year) and dabigatran 150 mg BID (3.32%/year, $P = 0.32$), whereas major bleeding was less frequent in patients on the lower dose dabigatran (2.87%/year, $P = 0.003$ for dabigatran 110 mg BID). Hemorrhagic strokes were less frequent with