

Dabigatran etexilate - A novel oral anticoagulant for bleeding complications**Himabindu Reddy, Chakka Gopinath, Mohamed Saleem, Thattakudian Sheikuduman***

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*Received: Sep 12, 2015, Revised: Oct 10, 2015, Accepted: Nov 20, 2015***Abstract**

Thromboembolic disease is a common cause of morbidity and mortality. Thrombin plays a key role in thrombotic events and thrombin inhibition represents a therapeutic event for thromboembolic events and has been identified as a target of therapy of its pivotal role in coagulation process. Anticoagulation is a major intervention for the management of arterial and venous thromboembolic events. Dabigatran etexilate is an orally effective anti-thrombin drug, several animal and human trials were conformed the efficacy of this drug in reduction of major bleeding in related to acute coronary syndrome, knee replacement surgery and venous thromboembolism conditions. The therapeutic use of this drug also shows limited side effects to select the dabigatran as promising therapeutic agent in bleeding complications.

Keywords: Anticoagulation, dabigatran, thromboembolic disease, thrombin inhibition

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Introduction

Anticoagulation is a major intervention for the management of arterial and venous thromboembolic events (1). Thrombin plays a key role in thrombotic events and thrombin inhibition represents a therapeutic event for thromboembolic events and has been identified as a target of therapy of its pivotal role in coagulation process (2). Thrombin plays major role in and responsible for conversion of soluble fibrinogen to fibrin and clot stabilization by factor XIII, V, VIII, XI activation and the formation of cross linkage of fibrin molecules (3).

Thromboembolic (TE) disease is a common cause of morbidity and

mortality. Vitamin K antagonists (VKAs) such as warfarin are traditionally used for the prolonged management and secondary prevention of venous thromboembolism (VTE) for many years, and are recognized by international guidelines as the current standard of care (4). VKA's establish anticoagulant effect within 2-3 days, monitoring is required to ensure that the International Normalized Ratio (INR) is maintained within the target therapeutic range (INR 2.0-3.0) (5). Slow onset of action of these oral medications, a bridging therapy with either unfractionated or low molecular weight heparin (LMWH) is routinely used (4).

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Oral factor Xa and IIa (thrombin) inhibitors, direct oral anticoagulants (DOACs), have proven to be an effective and safe alternative treatment in thromboembolism. DOACs offer significant simplification of long-term anticoagulation because these drugs, unlike VKAs, do not require frequent laboratory monitoring and subsequent, INR ratios, and dose adjustments (6).

The limitations of VKAs and Direct oral anticoagulants include bleeding complications, narrow therapeutic index, inter-individual patient variability, multiple drug and food interactions, longer half-life, lower patient compliance and need for regular anticoagulation laboratory monitoring which limits the VKA's and DOACs clinical effectiveness and safety of conventional anticoagulant (7). These limitations have been modified with the introduction of the novel oral anticoagulants (NOACs)–dabigatran (a reversible direct thrombin inhibitor), factor IIa (thrombin) inhibitor, and the factor Xa inhibitors rivaroxaban and apixaban (8).

Dabigatran etexilate is a novel oral anticoagulant, which directly targets and inhibits thrombin which is the recent focus of research in the treatment and prevention of thromboembolic diseases. Dabigatran has overcome all the limitations of existing anti-coagulants and having several advantages, which includes target specific action, better pharmacokinetic profile and predictable anticoagulant response, without the need for

therapeutic monitoring (7). The present review is mainly focussed on the complete pharmacology profile of Dabigatran etexilate.

Dabigatran etexilate

Chemistry

Dabigatran (alanine, N-[[[2-[[[4-(aminoiminomethyl)phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl) (Fig. 1)

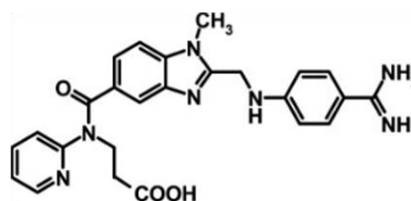


Figure 1 Chemical structure of Dabigatran etexilate

is an orally active prodrug belongs to class of non-peptidic inhibitors with trisubstituted benzimidazole as the central scaffold and 4-amidinophenylalanine as a mimetic of arginine which exhibits a specific, competitive, and reversible inhibition of thrombin. Dabigatran directly and reversibly inhibits both free and fibrin-bound thrombin, thereby interrupting the coagulation cascade (7). The molecular weight of dabigatran etexilate is 628, whereas dabigatran has a molecular weight of 471 (9).

The active moiety, dabigatran selectively inhibits thrombin with a K_i of 4.5 nM and has been shown to exhibit potent anticoagulant and antithrombotic activities in a number of

animal models of thrombosis (10). Like melagatran, dabigatran is a small molecule mainly act through by reversibly inhibition of both free and clot-bound thrombin by binding to exosite 1 and/or the active site of thrombin (11). Dabigatran etexilate the prodrug differs from dabigatran by an ethyl group at the carboxylic acid and a hexyloxycarbonyl side chain at the amidine (12).

Regulatory status

US food and drug administration (FDA) approved dabigatran etexilate on october 19, 2010 for prevention of stroke in patients with atrial fibrillation (AF), on April 17, 2014 approved for DVT and pulmonary embolism (13). On December 2011, Drug controller general of india given the approval for dabigatran for the prevention of stroke in patients with AF, and on 11th February 2013, given the approval for primary prevention of VTE after major orthopedic surgery (14).

Pharmacokinetics

Dabigatran etexilate is an oral prodrug that rapidly convert in to dabigatran (active moiety) and it is conjugated with activated glucuronic acid, yielding pharmacologically active glucuronide conjugates that comprise about 20% of total drug in plasma and not metabolized by hepatic cytochrome P450 isoenzymes and does not affect other drugs utilizing this system (15). Several types of dabigatran metabolites M324, M325, M355, M396, M400, and

M600 were identified (16). Dabigatran is a very polar, permanently charged molecule with a logP of 2.4 (n-octanol/buffer, pH 7.4) and therefore has no bioavailability after oral administration. Thus, a double prodrug dabigatran etexilate was generated by masking the amidinium moiety as a carbamate ester and by turning the carboxylate into an ester group (17). Bioavailabilty approximately 6%, so to ensure the therapeutic plasma levels high doses must be given. Absorbtion of dabigatran in the stomach and small intestine is dependent on an acid environment, drug absorbtion reduced with proton pump inhibitors combination at rate of 20-15%, peak concentration in plasma seen after 2 h of administration. Half-life is 8 h of single dose and up to 14 to 17 of multiple dose administration (18). Binding to plasma proteins of about 35%. Steady state is achieved on the third day of twice-daily (bid) treatment (10). Dabigatran clearance is predominantly renal, with 80% excreted unchanged in the urine and for this reason needs a dose adjustment when administered to subjects with a creatinine clearance <50 mL/min (19). The recommended dose of dabigatran etexilate is 220 mg daily, taken orally as 2 capsules of 110 mg once daily and patients with intact kidney function started between 1 and 4 hours after surgery was found to be effective as enoxaparin 40 mg once daily prior to surgery to prevent VTE (20-22).

Mechanism of action

Thrombin plays pivotal role in blood coagulation cascade, targeted inhibition of thrombin within coagulation cascade attenuates not only thrombin formation, but also reduces thrombin activation and limits platelet activation (7). Dabigatran is a novel, potent, non-peptide, competitive, reversible, thrombin inhibitor that strongly binds as well as high selectivity towards the active binding site of fibrin bound or free thrombin (IIa) in a concentration dependent manner (23). Dabigatran prevents the conversion of fibrinogen into fibrin, crosslinking of fibrin polymers, platelet activation, positive feedback of amplification of coagulation activation, and inhibition of fibrinolysis (24). Figure 2 shows

schematic representation of mechanism of action of dabigatran.

Evidence from research*Animal research*

6-8 week old female C57BL/6 mice were induced with lung injury by a single intratracheal instillation of bleomycin. The animal was treated with Dabigatran etexilate pre and post administration of bleomycin. It is observed that dabigatran significantly attenuated development of bleomycin induced lung fibrosis by reducing thrombin activity and levels of transforming growth factor (TGF) - β 1 and PDGF-AA and simultaneously decreasing inflammatory cells and protein concentrations. The fibrosis was significantly decreased in dabigatran

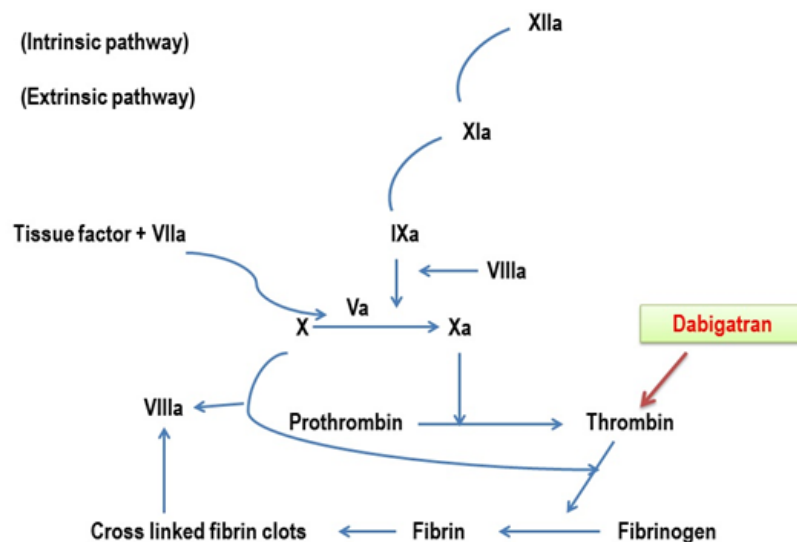


Figure 2 Mechanism of action of Dabigatran etexilate

treated mice (25).

Thirty swine underwent implantation of modified bi-leaflet mechanical valved conduit bypassing the ligated, native descending thoracic aorta and treated with no anticoagulation (n ¼ 10), enoxaparin 2 mg/kg subcutaneously twice daily (n ¼ 10), or dabigatran etexilate 20 mg/kg orally twice daily randomly. By thromboelastographic analysis, dabigatran etexilate produced less prolongation of K value (P ¼ 0.01) and less decreases in angle (P ¼ 0.01) and maximum amplitude (P ¼ 0.001) than enoxaparin and proves that dabigatran shows better thrombo prophylaxis of mechanical valves than enoxaparin (26).

Dabigatran when tested in rats it shows dose depended thrombin inhibition with an ED₅₀ of 0.066 mg/kg compared with other anticoagulants and shows values of melagatran (ED₅₀ of 0.058 mg/kg), unfractionated heparin (ED₅₀ of 9.84 U/kg), and hirudin (ED₅₀ of 0.016 mg/kg). Similarly, in rabbits, a dose-dependent increase in aPTT was observed in these studies (27).

Human research

Several phase 2 studies have been completed successfully with encouraging results and recruitment is being conducted for several phase 3 studies (2). The outcome of dabigatran trials was represented in Table 1.

RE-LY study

The RE-LY study compared warfarin with dabigatran in patients with AF at risk for stroke from 967 centres in 44 countries and showed 110 mg of dabigatran twice daily was as effective as conventional adjusted-dose warfarin and with low rates of major haemorrhage (28). In another study (phase III trial) it is conformed that patients with nonvalvular atrial fibrillation who received a twice daily dose of 150 mg of dabigatran for prevention of stroke resulted in a lower rate of stroke/systemic embolism compared with warfarin (1.11% vs. 1.69%; P < 0.003), with a similar risk of major bleeding (29).

BISTRO study

The phase II Boehringer Ingelheim study (BISTRO) trails reported that the twice daily oral administration of dabigatran etexilate (150 mg) was effective for the prevention of VTE (30).

RE_MOBILIZE trial

Total 2615 patients were treated with dabigatran during post total knee replacement and the dabigatran effect was compared with enoxaparin for the prevention of VTE. The efficacy of dabigatran was significantly increased with reduction in the bleeding when compared to enoxaparin (31,32).

RE-NOVATE trial

3949 patients who underwent hip arthroplasty received dabigatran for 28-35 days in two different doses (150 and

Table 1 Outcome of Dabigatran trials

Trial name/Year	Type of study method and number of patient	Outcome	References
RE-COVER II study, 2011	patients with acute VTE Randomized double blind double-dummy trial 2589 patients	Dabigatran has similar effects on VTE recurrence and a lower risk of bleeding compared with warfarin for the treatment of acute VTE.	28
RE-LY Study/2009	Randomized noninferiority trial Patients with risk of stroke has been included 18,113 patients	Dabigatran given at a dose of 150 mg was associated with lower rate of stroke and systemic embolism when compare to warfarin	29, 30
REDEEM study/2009	A phase II double blind, placebo-controlled, dose-escalation study patients with recent acute coronary syndromes (ST- or non-ST-elevation myocardial infarction) 1874 patients	Orally administered dabigatran etexilate is as effective as other drugs in preventing thrombus formation on mechanical heart valve	36, 37
RE_MOBILIZE trial/2008	Randomized double blind multicentre study 2615 patients patients undergoing total knee replacement	The efficacy of dabigatran was significantly increased with reduction in the bleeding when compared to enoxaparin	32, 33
RE-NOVATE trial/2007	Randomized double blind multicentre study 3949 patients patients undergoing total hip replacement	Dabigatran significantly reduced the bleeding of these patients at a rate of 0.9% when compared to enoxaparin which is shows 1.4%	24, 34, 35
BISTRO study/2005	Randomized double blind multicentre study 393 patients patients undergoing total hip or knee replacement	The twice daily oral administration of dabigatran etexilate (150 mg) was effective for the prevention of VTE	31

220 mg) and the efficacy was compared with enoxaparin. Both the drugs does not show any variation in reduction of bleeding (1.6%, 1.3%, and 2.0%, respectively). Second time (RE-NOVATE II) two groups of total 2055 patients were administered dabigatran (220 mg) and enoxaparin (40 mg) oral and subcutaneous route respectively for 28-35 days. Over all death rate in the treatment groups were 7.7% and 8.8% respectively and dabigatran significantly reduced the bleeding of these patients at a rate of 0.9% when compared to enoxaparin which is shows 1.4% (24,30,33).

In one study it is found that the lower doses of dabigatran non-inferior to warfarin in reducing the risk of systemic embolism and the higher dose of dabigatran etexilate 220 mg OD was found to be superior to warfarin (34).

RE-DEEM study

A phase II double blind, placebo-controlled, dose-escalation study was conducted in patients with acute coronary syndrome (ACS). Patients received dabigatran along with either aspirin or clopidogrel; this dual anti-coagulant therapy reduces coagulation activity in patients with recent myocardial infarction with a dose dependent increase in bleeding events (35).

Thromboembolism and anticoagulant-related bleeding accounts for approximately 75% of all complications experienced by heart valve recipients, however anticoagulants are associated

with limitations of relatively low bioavailability, short half-life, platelet activation and inter individual variability's and represented with an additional bridging therapy, this new anticoagulant dabigatran etexilate could improve in this patients and without this limitations. Orally administered dabigatran etexilate is as effective as other drugs in preventing thrombus formation on mechanical heart valve (36).

Drug interactions

Dabigatran etexilate is a substrate of the efflux permeability glycoprotein transporter, which is highly expressed in the intestine and kidneys. Co-administration of potent permeability drugs such as ketoconazole, quinidine, amiodarone, verapamil can increase dabigatran plasma levels. Rifampicin potent inducer of microsomal enzyme can reduce dabigatran concentration by increasing its reabsorption via permeability glycoprotein into the gut. Co-administration with other anticoagulants caution due to risk of bleeding (24).

Adverse effects

The common adverse effects documented in clinical trials are epistaxis, anaemia, urogenital haemorrhage, dyspepsia, nausea, gastrointestinal haemorrhage, diarrhoea, hepatic abnormalities particularly with elevated aminotransferases (37).

Advantages and disadvantage of dabigatran

Advantages of dabigatran

It has rapid onset of action, easy to predict the anticoagulant effect, it has lower rate of adverse drug reaction, and it has low potential for food and drug interaction.

Disadvantage of dabigatran

Dabigatran is newly released drug, so it has low familiarity for therapeutic application. The monitoring of dabigatran is uncertain for thrombin time, ecarin clotting time, and activated partial thromboplastin time. It has 80% renal clearance, so contraindicated for renal disease patients. In case of major bleeding there is no antidote available for treatment (38,39).

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Conclusion

Dabigatran etexilate is an orally effective anti-thrombin drug, several animal and human trials were conformed the efficacy of this drug in reduction of major bleeding in related to acute coronary syndrome knee replacement surgery and venous thromboembolism conditions. The therapeutic use of this drug also shows limited side effects to select the dabigatran as promising therapeutic agent in bleeding complications.

Conflict of interests

The authors declared that there is no conflict of interests.

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