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Review Article

DABIGATRAN ETEXILATE: NEW DIRECT THROMBIN INHIBITORS ANTICOAGULANTS

Mehta Hiren R[1]*, Patel Paresh B[2], Galani Varsha J[2], Patel Kinjal B[3]
[1]Torrent Research Centre, Near Bhat village, Gandhinagar, Gujarat, India
[2]A R Collage of Pharmacy, Vallabh Vidhyanagar, Anand, Gujarat, India
[3]K. B. Institute of Pharmaceutical Education and Research Centre, Gandhinagar, Gujarat, India

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*Hiren Mehta, Torrent Research Centre, Near Bhat village, Gandhinagar-382424, Gujarat, India
E-mail: hirenpharm@rediffmail.com

ABSTRACT
Thrombin plays a key role in thrombotic events, and therefore thrombin inhibition represents a therapeutic target for numerous thromboembolic diseases. Thrombin is responsible for the conversion of soluble fibrinogen to fibrin; clot stabilization through activation of factor XIII and the formation of cross-linkage among fibrin molecules; and the generation of additional thrombin through activation of factors V, VIII, and XI. Direct thrombin inhibitors are an innovative class of anticoagulants that bind directly to thrombin to inhibit its actions and impede the clotting process. Dabigatran is the first direct thrombin inhibitor, orally available first approval by US Food and Drugs Administration in 2010. Specifically and reversibly inhibits thrombin, so the duration of action is predictable. The anticoagulant effect correlates well with plasma drug concentrations, which implies an effective anticoagulation with low bleeding risk without major problems of interactions with other drugs. The predictable pharmacokinetics and pharmacodynamics characteristics of dabigatran may facilitate dental management of patients who until now have been in treatment with traditional anticoagulants, given that it doesn't require routine laboratory monitoring in the vast majority of patients treated. They also present a profile of drug interactions very favorable.
KEY WORDS: Thromboembolism, Anticoagulants, Direct thrombin inhibitors, Dabigatran.

INTRODUCTION

Thrombin plays a key role in thrombotic events, and therefore thrombin inhibition represents a therapeutic target for numerous thromboembolic diseases.[1] Thrombin has been identified as an essential target of therapy because of its pivotal role in the coagulation process. Thrombin is responsible for the conversion of soluble fibrinogen to fibrin; clot stabilization through activation of factor XIII and the formation of cross-linkage among fibrin molecules; and the generation of additional thrombin through activation of factors V, VIII, and XI.[2] Direct thrombin inhibitors (DTIs) are an innovative class of anticoagulants that bind directly to thrombin to inhibit its actions and impede the clotting process. Although clinically available DTIs are parenteral agents, efforts are being concentrated in the development of an oral DTI.[2]

Current anticoagulant therapy includes unfractionated and fractionated heparins and, for oral treatment, warfarin, vitamin K antagonist. However, the clinical use of these agents has several drawbacks.[1] Heparins need to be administered parenterally, whereas the use of warfarin requires frequent monitoring, with drug and food interactions being common.[1]

Warfarin (Coumadin, Bristol-Myers Squibb), an oral vitamin K antagonist, has been the primary agent utilized in long-term anticoagulation therapy. Despite its ability to reduce and treat thromboembolic events, warfarin therapy has several limitations, including a slow onset of action; a narrow therapeutic range; variable patient responses; and numerous interactions with drugs, herbal medications, and foods containing vitamin K.[1] As a result of this agent's pharmacokinetic (PK) and pharmacodynamic (PD) limitations, patients receiving warfarin often require frequent monitoring to ensure optimal efficacy and safety. In recent years, efforts have been focused on the development of new oral anticoagulants with further predictable PK and PD profiles, which may reduce the need for vigilant monitoring.[3]

Introduction of Dabigatran

Research has therefore focused on the identification of synthetic, low-molecular-weight, oral, active direct thrombin inhibitors.[1] Dabigatran etexilate (Rendix, Boehringer Ingelheim) is a new oral DTI that is currently being studied in clinical trials. Several phase 2 studies have been completed with encouraging results, and recruitment is being conducted for several phase 3

studies. This article presents a review of the currently available information on this investigational product.[3] Dabigatran etexilate was first approved by US Food and Drugs Administration (FDA) in 2010 to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[4]

The chemical name for dabigatran etexilate mesylate, a direct thrombin inhibitor, is β-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate. The empirical formula is $C_{34}H_{41}N_7O_5.CH_4O_3S$ and the molecular weight is 723.86 (mesylate salt), 627.75 (free base).[3, 4, 5] The structural formula is shown in figure 1.

Pharmacology / Mechanism of action

Dabigatran is a non-peptidic, synthetic, small molecule that is a potent, specific, competitive and reversible DTI.[1,3-8,9] It binds directly to clot-bound and free thrombin with high affinity and specificity, and can be administered orally as the prodrug dabigatran etexilate. It specifically and reversibly inhibits thrombin, which is the key enzyme of the cascade of the coagulation (Figure 2).[10] In preclinical studies, dabigatran has shown promise as an anticoagulant and antithrombotic agent, with a good safety profile. In studies conducted in healthy male subjects, dabigatran has demonstrated predictable pharmacokinetic and pharmacodynamic characteristics, with good safety and tolerability profiles.[1,3-8]

Pharmacokinetics

Dabigatran etexilate is rapidly converted to its active form, dabigatran, after oral administration.[4-6,9,10] In healthy volunteers, the PK profile is characterized by a time to peak plasma (T_{max}) concentration within two hours, an absolute bioavailability of 3.5% to 5%, a bi-exponential distribution phase, and a terminal half-life of 14 to 17 hours after multiple dose administration.[3,10] A low (34-35%) concentration-independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigatran is 60 – 70 L which exceeds the volume of total body water indicating moderate tissue distribution of dabigatran.[5,9,10]

As with other agents in this class of drugs dabigatran is not metabolized by, and does not affect, cytochrome P450 (CYP) isoenzymes, and is therefore unlikely to alter the metabolism of drugs metabolized by the CYP family of enzymes, reducing the potential for drug-drug interactions. A phase 1 PK study has also indicated that food does not affect the bioavailability of dabigatran. Renal excretion of unchanged dabigatran is the predominant pathway for the elimination of dabigatran; about 85% of an intravenous dose of dabigatran is recovered in the urine, as has been demonstrated with other DTIs. In addition, a metabolic pathway involves conjugation with glucuronic acid, resulting in the formation of pharmacodynamically active glucuronides.[3,6]

Pharmacokinetic and Pharmacodynamic study

To investigate the PK and PD profile of dabigatran study in healthy elderly subjects was carried out to assess the intra- and inter-individual variability of dabigatran PK in order to assess possible gender differences, and to assess the effect of pantoprazole co-administration on the bioavailability of dabigatran. Due to this, study was conducted as open-label, parallel-group, single-centre, consisting of a baseline screening visit, 7-day treatment period and post-study examination visit.[6]

A total of 36 healthy elderly subjects (aged ≥65 years) with a body mass index of 18.5–29.9 kg/m^2 were randomized to receive dabigatran etexilate either with or without co-administration of pantoprazole. Dabigatran etexilate was administered as capsules of 150 mg twice daily over 6 days and once on the morning of day 7. Pantoprazole was administered at 40 mg twice daily, starting 2 days prior to dabigatran etexilate administration and ending on the morning of day 7. The primary pharmacokinetic measurements included the area under the plasma concentration-time curve at steady state (AUC_{ss}), maximum ($C_{max,ss}$) and minimum ($C_{min,ss}$) plasma concentrations at steady state, terminal half-life ($t_{1/2}$), time to reach $C_{max,ss}$ and renal clearance of dabigatran and the secondary pharmacokinetic parameters included the mean residence time, total oral clearance and volume of distribution.[6]

The PD parameters measured were the blood coagulation parameters ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT). Final outcomes observed like, after twice-daily administration of dabigatran etexilate, plasma concentrations of dabigatran reached steady state within 2–3 days, which is consistent with a $t_{1/2}$ of 12–14 hours. The mean ± SD peak plasma concentrations on day 4 of treatment in male and female elderly subjects were 256 ± 21.8 ng/mL and 255 ± 84.0 ng/mL respectively. The peak plasma concentrations were reached after a median of 3 hours (range 2.0–4.0 hours). Co-administration with pantoprazole decreased the average bioavailability of dabigatran (the AUC_{ss}) by 24% (day 4; 90% CI 7.4, 37.8) and 20% (day 7; 90% CI 5.2, 33.3). Intra- and inter-individual pharmacokinetic variability in the overall population was low (<30% coefficient of variation), indicating that dabigatran has a predictable PK profile.[6]

Prolongation of the ECT and aPTT correlated with, and paralleled, the plasma concentration-time profile of dabigatran, which demonstrates a rapid onset of action without a time delay, and also illustrates the direct mode of action of the drug on thrombin in plasma. The ECT increased in direct proportion to the plasma concentration, and the aPTT displayed a linear relationship with the square root of the plasma concentration. The mean AUC_{ss} was 3–19% higher in female subjects than in male subjects, which was likely due to gender differences in creatinine clearance.[6]

The safety profile of dabigatran was acceptable, with and without pantoprazole co-administration. Finally author concluded that the dabigatran demonstrated reproducible and predictable pharmacokinetic and pharmacodynamic characteristics, together with a good safety profile, when administered to healthy elderly subjects. Minor gender differences were not considered clinically relevant. The effects of pantoprazole co-administration on the bioavailability of dabigatran were considered acceptable, and dose adjustment is not considered necessary.[6]

CLINICAL TRIALS

An open label, multicenter, sequential, dose escalating trial, was conducted in 314 patients undergoing total hip replacement in Sweden and Norway (BISTRO I). The primary objective of this study was to investigate the therapeutic range of dabigatran etexilate to determine optimal dosing for future studies.

The primary safety outcome was the rate of major bleeding events during the treatment phase. In this multicenter, open-label, dose-escalating study, 314 patients received oral doses of dabigatran etexilate (12.5, 25, 50, 100, 150, 200 and 300 mg twice daily or 150 and 300 mg once daily) administered 4–8 hour after surgery, for 6–10 days.[11]

Dose escalation was based on clinical and PK data. The primary efficacy outcome included venographic deep vein thrombosis (DVT), symptomatic DVT and pulmonary embolism, during the treatment period.

Results of this multicentre trial explored that no major bleeding event was observed in any group, but 2 patients at the highest dose (300 mg twice daily) suffered bleeding from multiple sites associated with reduced renal clearance and prolonged PD parameters. A dose response was demonstrated for minor bleeding events. Of the 289 treated patients, 225 patients had evaluable venograms. The overall incidence of DVT was only 12.4%. There were no consistent relationship between the dose and incidence of DVT, the highest incidence in any group being 20.8%. The lowest dose (12.5 mg twice daily) showed a high rate of proximal DVT (12.5%) and no increase in PD parameters. Peak and trough plasma concentrations, AUC and PD parameters also increased in proportion with the dose. Higher dabigatran plasma concentrations were associated with lower DVT rates.[11]

It was concluded that the dabigatran etexilate demonstrates an acceptable safety profile, with a therapeutic window above 12.5 mg and below 300 mg twice daily. The low number of venous thrombo embolic events (VTE) events within each treatment group indicates a satisfactory antithrombotic potential, although the study was not powered for an efficacy analysis. Additional studies are ongoing to optimize oral absorption and the efficacy/safety balance.[11]

Phase 1 Trials

The phase 1 PK study was performed in 18 healthy volunteers in a three-way crossover study that included males between 18 to 55 years of age with a body mass index (BMI) between 18.5 to 30 kg/m^2. Treatment sequences consisted of a dabigatran 150mg capsule, administered after an overnight fasting period, in conjunction with pantoprazole 40 mg twice daily, started two days before administration of the study drug and following a high-fat, high-calorie breakfast.[1]

PK parameters were determined via plasma concentration versus time curves obtained from serial blood sampling over a 72-hour period after administration of the study drug.

Results were analyzed for all 18 subjects who were randomly assigned to treatment and who completed the trial. Co-administration with food demonstrated a delayed absorption of dabigatran etexilate, with the median T_{max} increasing from 2 to 4 hours. This delay did not result in decreased drug exposure, as expressed by a relatively unchanged AUC (fast-904 ng.hours/mL; fed-895 ng.hours/mL) and C_{max} (fast- 111 mg/mL; fed- 106 ng/mL). In contrast to these findings, co-administration with pantoprazole resulted in both a lower AUC (fast-904 ng.hours/mL, fed-705 ng.hours/mL) and C_{max} (fast-111 mg/mL; fed- 74.5 ng/mL). The T_{max} remained unchanged. The mean $t_{1/2}$ was decreased in both the pantoprazole and the fed patients, compared with the fasted patients: 7.8 hours (pantoprazole), 7.7 hours (fed), and 8.7 hours (fasted).[1]

Adverse Drug Events (ADEs) were mild to moderate in intensity. The most common ADE was headache. None of the ADEs were thought to be associated with the study drug.

Phase 2 Trials

The Phase 2 trial was an uncontrolled, open-label, multicenter PK study (BISTRO Ib) which was conducted in a total 62 consecutive patients scheduled for total hip replacement surgery in 11 sites in Sweden and Norway. Patients received a single oral dose of 150 mg of

dabigatran etexilate 1 to 3 hours after surgery. All concomitant medications prescribed and given at the investigator's discretion were considered acceptable. All patients received a dose of enoxaparin 40 mg subcutaneously in the evening or early morning prior to surgery. Continued VTE prophylaxis was given at the discretion of the investigator, and subsequent doses were given for a minimum of 10 hours after administration of the study drug. The investigators determined PK parameters by using plasma concentration versus time curves obtained from serial blood sampling over a 24-hour period after the study drug was administered. There were 4 pre-determined PK acceptance criteria for future use of the capsule formulation in the postoperative period.[1]

The results of a total 59 patients were analyzed and reported. In the majority of enrolled patients, the onset was immediate, with plasma levels of dabigatran measurable within 1 hour of administration. However, absorption was delayed by 4 to 6 hours following administration in two patients. The C_{max} (mean, 75.8 ng/mL) occurred at a median T_{max} of 6 hours, although the investigators noted that the T_{max} in 13 patients exceeded 10 hours. The mean AUC was comparable to that of healthy volunteers (962 ng.hours/mL and 904 ng.hours/mL, respectively). Inter-individual variability was also high in this study, with coefficients of variation greater than 65% for both the C_{max} and AUC_{0-24}.[1]

The most common ADEs were nausea and vomiting, although the investigators considered these ADEs to be related to the surgical procedure. One patient experienced moderate hypotension and a severe drop in hemoglobin, necessitating a blood transfusion, but these events were not considered to be related to the study drug. No patients died during the study. As a result of both phase 1 and phase 2 studies, the investigators concluded that oral administration of a capsule formulation of dabigatran etexilate resulted in an acceptable PK profile in healthy volunteers and in patients undergoing total hip replacement.[1]

Another multicenter, parallel-group, double-blind study of dabigatran etexilate was conducted in a total 1973 patients undergoing total hip or knee replacement, randomized to 6–10 days of oral dabigatran etexilate (50, 150 mg twice daily, 300 mg once daily, 225 mg twice daily), starting 1 to 4 hour after surgery, or subcutaneous enoxaparin (40 mg once daily) starting 12 hour prior to surgery. The primary efficacy outcome was the incidence of VTE (detected by bilateral venographic or symptomatic events) during treatment. Of the 1949 treated patients, 1464 (75%) patients were evaluable for the efficacy analysis. VTE occurred in 28.5%, 17.4%, 16.6%, 13.1% and 24% of patients assigned to dabigatran etexilate 50, 150 mg twice daily, 300 mg once daily, 225 mg twice daily and enoxaparin, respectively. A significant dose-dependent decrease in VTE occurred with increasing doses of dabigatran etexilate ($P < 0.0001$). Compared with enoxaparin, VTE was significantly lower in patients receiving 150 mg twice daily [odds ratio (OR) 0.65, P – 0.04], 300 mg once daily (OR 0.61, P = 0.02) and 225 mg twice daily (OR 0.47, P = 0.0007). Compared with enoxaparin, major bleeding was significantly lower with 50 mg twice daily (0.3% vs. 2.0%, P=0.047) but elevated with higher doses, nearly reaching statistical significance with the 300 mg once-daily dose (4.7%, P–0.051). Finally, concluded that the oral administration of dabigatran etexilate, commenced early in the postoperative period, was effective and safe across a range of doses. Further optimization of the efficacy/safety balance should be addressed in future studies.[12]

ADVERSE DRUG REACTIONS

Adverse drug events reported during above mentioned studies are already discussed and concluded. In another study of a total 22,126 patients, the safety of dabigatran etexilate has been evaluated. A total of 10,084 patients were exposed to at least 1 dose of dabigatran as study medication in four active-controlled clinical trials conducted to evaluate the safety and effectiveness of dabigatran etexilate in the prevention of VTE following major elective orthopedic surgery. Of these, a total 5,419 were treated with 150 mg or 220 mg daily of dabigatran etexilate, while a total 389 received doses of less than 150 mg daily, and a total 1,168 received doses in excess of 220 mg daily. Bleeding is the most relevant side effect of dabigatran etexilate.[3-5] Bleeding of any type or severity occurred in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery and in long-term treatment in 16.5 % of patients with atrial fibrillation treated for the prevention of stroke and systemic embolism.[3-5] Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes. As shown from previous clinical experience with ximelagatran, another safety concern with dabigatran etexilate is hepatotoxicity. Elevations in liver enzymes have been observed in patients during clinical trials. Although these elevations have been considered mild, further studies are required to determine the clinical significance of this kind of events.[13]

DRUG INTERACTIONS

The potential for drug interactions in conjunction with dabigatran etexilate has not been extensively studied in

clinical trials. Based on *in vitro* evaluation, neither dabigatran etexilate nor its active moiety, dabigatran, has been shown to be metabolized by the human CYP system, nor did they exhibit effects on human CYP isozymes. Concomitant use of dabigatran with treatment that interferes with hemostasis or coagulation increases bleeding risk. In the RELY trial, conducted in patients with atrial fibrillation, a two-fold increase in major bleeding was seen in both dabigatran study treatment arms, as well as that of the comparator, warfarin.[5] The concomitant use of dabigatran etexilate with P-glycoprotein (p-gp) inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibitors such as ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors.[4,5] On the basis of the results of the PK study evaluating the effect of co-administration of pantoprazole on the plasma concentrations and the AUC concentration of dabigatran, it appears that a high gastric pH decreases dabigatran exposure. Thus, it is expected that proton pump inhibitors, histamine blockers, and other agents that increase gastric pH would interact with dabigatran etexilate.[6]

PRECAUTIONS AND WARNINGS

Appropriate precautions required because as with all anticoagulants, dabigatran etexilate should be used with caution in circumstances associated with an increased risk of bleeding. Bleeding can occur at any site during therapy with dabigatran etexilate. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site. Use of dabigatran should be avoided in patients with bleeding diathesis or other coagulation disorders; trauma; thrombocytopenia; a history of gastric or duodenal ulcers; and the concurrent use of non-steroidal anti-inflammatory drugs, thrombolytic agents, and anti-platelet agents. Patients with renal insufficiency may require dosage adjustments to decrease the risk of bleeding[4,5,8,11].

DOSAGE AND ADMINISTRATION

The recommended dose of dabigatran etexilate is 220 mg daily, taken orally as 2 capsules of 110mg once a day in patients with intact renal function. Additional studies are required to determine the specific dose that will provide the greatest reduction in thrombo embolic events along with a minimal risk for bleeding[1,4,5,8,9,12].

CONCLUSION

In its current stage of clinical development, dabigatran etexilate shows promise in becoming the next orally available anticoagulant. Clinical trials have demonstrated timely efficacy without the safety concerns that have been associated with ximelagatran administration. Ongoing research will eventually confirm or refute these early findings and determine whether dabigatran etexilate has a role in the management of patients who require anticoagulation therapy and whether it might replace warfarin as the mainstay of therapy. The emergence of new oral anticoagulants, dabigatran has in recent years generated great expectations in the scientific community due to the similar clinical effectiveness of warfarin and enoxaparin over to a more predictable PK and PD and the adverse effects clinically less relevant. These new drugs appear as substitutes of coumarin anticoagulants and have the potential to change the standards of clinical practice in the prevention of DVT and pulmonary embolism.

REFERENCES

1. Stangier J et al. Pharmacokinetic profile of the oral direct thrombin inhibitor dabigatran etexilate in healthy volunteers and patients undergoing total hip replacement. J Clin Pharmacol 2005; 45:555–563.
2. Nisio MD, Middeldorp S, Büller HR. Direct thrombin inhibitors. N Engl J Med 2005;353(10):1028–1040.
3. Abrams P, Marzella N. Dabigatran (Rendix): A Promising New Oral Direct Thrombin Inhibitor. Drug Forecast. May 2007; 32(5):271-75.
4. Drug @ FDA. Prescription Information of Dabigatran Etexilate Capsules. (Link:http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022512s000lbl.pdf)
5. Product Monograph of Pr Pradax™ Dabigatran Etexilate Capsules 75 mg, 110 mg and 150 mg (Dabigatran Etexilate as Dabigatran Etexilate Mesilate) Anticoagulant. Boehringer Ingelheim Canada Ltd., October 26, 2010. (link: http://webprod.hc-sc.gc.ca/dpd-bdpp/info.do?lang=eng&code=79794)
6. Stangier J, Stahle H, Rathgen K and Fuhr R. Pharmacokinetics and Pharmacodynamics of the Direct Oral Thrombin Inhibitor Dabigatran in Healthy Elderly Subjects. Clin Pharmacokinet, 2008; 47 (1): 47-59.
7. Connolly SJ et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. The New England journal of Medicine, september 17, 2009; 361(12):1139-51.
8. Summury Product Characteristic of Pradaxa 110 mg hard capsules. (link:http://www.medicines.org.uk/EMC/medicine/20760/SPC/Pradaxa+110+mg+hard+capsules/)
9. Eisert WG, Hauel N, Stangier J, Wienen W, Clemens A, Ryn J. Dabigatran: An Oral Novel Potent Reversible Nonpeptide Inhibitor of Thrombin. Arteriosclerosis, Thrombosis, and Vascular Biology. 2010;30:1885-89.
10. Gómez-Moreno G, Aguilar-Salvatierra A, Martín-Piedra MA, Guardia J, Calvo-Guirado JL, Cabrera M, López-Gallardo C, Castillo T. Dabigatran and rivaroxaban, new oral anticoagulants. new approaches in dentistry. J Clin Exp Dent. 2010;2(1):1-5.
11. Eriksson BI et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. Journal of Thrombosis and Haemostasis, 2004; 2: 1573–80.

12. Eriksson BI et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. Journal of Thrombosis and Haemostasis, 2004; 3: 103–111.

13. Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. National Institute for Health and Clinical Excellence. Sep 2008.

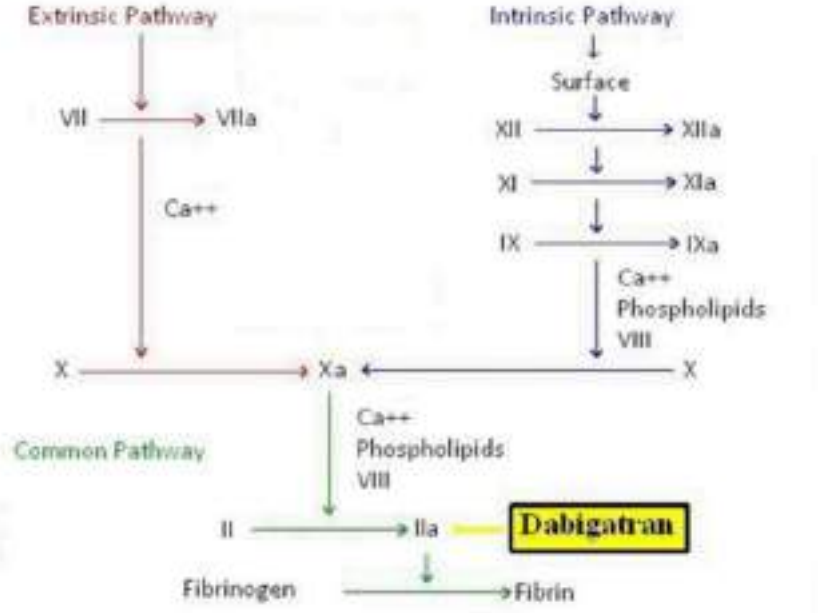

Figure 1: Mechanism of Action of Dabigatran[10]

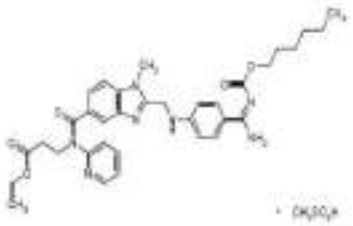

Figure 2: Chemical Structure of Dabigatran