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Dabigatran Etexilate: A Drug Update

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The Direct Thrombin Inhibitors are a new class of anticoagulants that binds directly to the thrombin enzyme and blocks its effect. DTI's prevents the conversion of fibrinogen to fibrin by binding the activity of thrombin. Pradaxa is used to help prevent strokes or serious blood clots in patients with atrial fibrillation. Dabigatran has shown efficacy in the prevention of thromboembolism in Phase 2 trials in orthopedic surgery and atrial fibrillation. Dabigatran has also undergone extensive Phase 3 clinical trials for the prevention of primary thromboembolism. FDA advisory committee recommends approval of Dabigatran Etexilate for prevention of Stroke in Atrial Fibrillation. Dabigatran has been licensed for the Total Hip Replacement and Total Knee Replacement in over 75 countries, including Europe and Canada. Hence, this paper reviews the existing safety and efficacy data for the use of dabigatran etexilate and discusses the potential role of dabigatran in the management of VTE, THR, TKR, atrial fibrillation.

Keyword: Oral anticoagulants, Dabigatran Etexilate, Venous thromboembolism, Pharmacokinetics, Hip replacement surgery, Total knee replacement surgery.

1. Introduction

Pradaxa is in a class of anticoagulant (or blood thinner) medications called direct thrombin inhibitors. It works by preventing blood clots from forming in the body.

1.1 Direct Thrombin Inhibitors (Dtis)

Direct Thrombin Inhibitors are a class of medication that acts as anticoagulants by directly inhibiting the enzyme thrombin. Some of the DTIs are already in the clinical use while other DTIs are undergoing clinical development.

1.2 Types of DTIs:-

There are 2 types of DTIs depending upon the interaction of DTIs with thrombin molecule.
Bivalent DTIs (hirudin) bind both to the active site and exosite, while univalent DTIs bind only to the active site.

1.2.1 Bivalent: - Hirudin and derivatives were originally discovered in *Hirudo medicinalis*.

- Hirudin
- Bivalirudin
- Desirudin

1.2.2 Univalent: - DTIs include

- Argatroban
- Melagatran (and its prodrug Ximelagatran)
- Dabigatran

Uses: - Pradaxa is used to help prevent strokes or serious blood clots in people who have non-valvular atrial fibrillation. Atrial fibrillation is a condition where the heart beats irregularly, thereby increasing the chance of clots forming in the body, which can lead to a stroke.

1.3 Stroke and Blood Clots: A stroke occurs when the blood supply to our brain is interrupted

or reduced. Strokes deprive our brains of oxygen and nutrients, which can cause our brain cells to die.

A stroke may be caused by a blocked artery (ischemic stroke) or a leaking or burst blood vessel (hemorrhagic stroke).

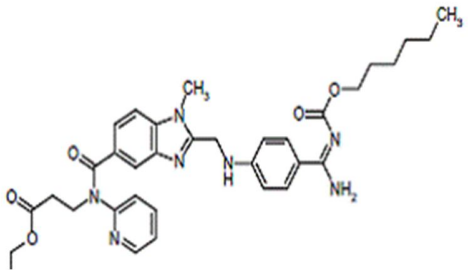

Fig 1: Structure of Dabigatran Etexilate

Chemical Name of Dabigatran Etexilate Mesylate
Ethyl 3-(1-{2-[({4-[amino({[hexyloxy)carbonyl]imino})methyl]phenyl}amino)methyl]-1-methyl-1H-1,3-benzodiazol-5-yl}-N-(pyridin-2-yl)formamido)propanoate methanesulfonate

1.4 Pharmacokinetics of Dabigatran Etexilate

It is administered orally as a prodrug that is rapidly and completely converted to the active entity dabigatran by unspecified plasma esterases[1]. Dabigatran binds directly to the clot-bound and free thrombin with high affinity and specificity[2]. In healthy volunteers, the PK profile is characterized by a time to peak plasma concentration. Within 2 hours, an absolute bioavailability of 3.5% to 5% is observed and a terminal half-life of 14-17 hours after multiple dose administration.

Dabigatran is excreted primarily via the renal system and is conjugated to activated glucuronic acid to form an acylglucuronide conjugate[3].

1.5 Different Dosage forms and Strengths

Capsule with a light blue opaque cap imprinted in black with the Boehringer Ingelheim Company symbol and a cream coloured opaque body imprinted in black with "R150 (150mg) or "R75 (75mg)[4].

1.6 Thrombin Specificity:

Thrombin is an endolytic serine protease that selectively cleaves the Arg--Gly bonds of fibrinogen to form fibrin and release fibrinopeptides A and B.

1.7 Mechanism of Action of Dabigatran:

All anti coagulants work by directly or indirectly inhibiting thrombin which plays a key role in thrombus formation[5,6,7,8].

1.8 Dabigatran Etexilate works by:

1. Specifically and selectively binding to thrombin and blocking its activity of conversion of fibrinogen to fibrin[9].
2. Blocking platelet activation by thrombin and activation of clotting factors V, VIII and XI by thrombin[10,11].
3. Blocking both free and clot- bound thrombin, providing effective inhibition of thrombin than other anti-coagulants like heparins which blocks mainly free thrombin.

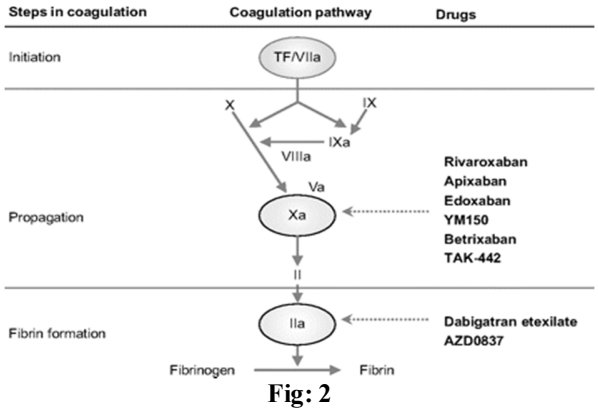

Fig: 2

Illustration showing the sites of action of new anticoagulants in the coagulation cascade. Vessel injury exposes tissue factor (TF), which interacts with activated factor (F) VII to initiate coagulation. Cleavage of prothrombin (factor II) by the prothrombinase complex (factor Xa and its cofactor, factor Va) leads to the generation of thrombin (factor IIa). Thrombin converts fibrinogen to fibrin and provides positive feedback through activation of factors V, VIII, and XI in the coagulation cascade. Factors Va, VIIIa, and XIa promote the production of additional thrombin, which leads to cross-linkage

of fibrin strands and the formation of a hemostatic plug. Thrombin also activates platelets through cleavage of the platelet membrane–bound protease-activated receptors 1, 3, and 4. Factor Xa inhibitors block the conversion of prothrombin (factor II) to thrombin (factor IIa) by factor Xa incorporated within the prothrombinase complex (the complex of factor Xa and factor Va bound to the activated platelet surface). Thrombin inhibitors block thrombin-mediated conversion of fibrin. These drugs also block thrombin-mediated feedback activation of factors V and VIII. Modified from Eriksson et al.[12].

1.9 Safety Profile of Dabigatran:

- The peptidomimetic dabigatran and its oral double prodrug dabigatran etexilate are highly selective univalent direct thrombin inhibitors that block the activity of thrombin by binding to the active sites via hydrophobic interactions.
- Other univalent direct thrombin inhibitors are:
  1. Argatroban
  2. Melagatran
  3. Prodrug of Melagatran i.e. Ximelagatran

Table I - Highly selective Univalent Direct Thrombin Inhibitors Under Active Clinical Development

Drug	Source	Clinical Trial Phase
Dabigatran Etexilate	Boehringer Ingelheim	III (For the prevention of deep venous thrombosis (DVT) after surgical intervention and for the prevention of stroke in patients with atrial fibrillation)
Argatroban	AstraZeneca	II
Melagatran	Mitsubishi Pharma	II

- Dabigatran has also shown efficacy in the prevention of thromboembolism in Phase 2 trials in orthopedic surgery and atrial fibrillation.
- Dabigatran has also undergone extensive Phase 3 clinical trials for the prevention of primary thromboembolism.

1.9.1 Formulations of Dabigatran Etexilate available in market:

Dabigatran is available in capsule form.
Lipophilic Prodrug

- Active drug has impaired absorption.
- Need acidic core to facilitate absorption.

1.9.2 Capsule containing pellets

- Do not open capsule for dysphagia
- GI irritation.
- Increased bioavailability.

According to FDA Pradaxa has strength of 75 mg and 150 mg as mentioned in the given table

Table 2: Formulations of Dabigatran Etexilate available in market.

Drug Name	Active Ingredients	Strength	Dosage form/Route	Marketing status
Pradaxa	Dabigatran Etexilate Mesylate	EQ 75 mg Base	Capsule, Oral	Prescription
Pradaxa	Dabigatran Etexilate Mesylate	EQ 150 mg Base	Capsule, Oral	Prescription

Table 3: Comparison of Efficacy and safety of the novel oral anticoagulants: Dabigatran, Rivaroxaban and Apixaban

Name of Drug	Key characteristics	FDA Status
Rivaroxaban	1. Direct, specific, competitive factor Xa inhibitor. 2. Rapid onset within 2-4 hours. 3. High bioavailability of ≥ 80%.	1. Xarelto® Trade name It is used for the prevention of DVT/PE after orthopedic surgery. 2. Dosage of Rivaroxaben approved by FDA is 10 mg in July 2011 3. Rivaroxaban is approved in the EU and Canada.
Apixaban	1. Direct, reversible FXa inhibitors. 2. Rapid onset of action, peak within 3 hours. 3. Bioavailability of Apixaban is 51-85%. 4. Half-life of Apixaban is long. 5. Metabolism occurs via CYP3A4, SULT1AA pathways.	1. Eliquis ® trade name 2. It is used for the prevention of DVT/PE after orthopedic surgery-No FDA approval yet. But Apixaban is approved in the EU.
Dabigatran	1. Specific, competitive, reversible univalent thrombin inhibitors. 2. Pro-drug converted to active form i.e. Dabigatran etexilate is converted to Dabigatran. 3. Rapid onset of action within 2 hours. 4. Renal clearance as glucouronic acid conjugate: 85%. 5. Metabolized by esterases catalyzed hydrolysis and P-gp transport mechanisms	1. Pradaxa® Trade name. 2. FDA approval is pending. It is an investigational oral thrombin inhibitor which is being studied in the prevention and treatment of acute and chronic thromboembolic diseases [13,14,15,16,17,18,19,20] 3. Pradaxa approved in EU and Canada. 4. For the prevention of stroke in patient with non-valvular atrial fibrillation. Pradaxa 150 mg BID FDA approved (Oct 2010)

1.10 FDA Advisory Committee Recommends approval of Dabigatran Etexilate for Prevention of Stroke in Atrial Fibrillation

About Atrial Fibrillation and Stroke

Atrial fibrillation is the most commonly significant heart rhythm disorder[21] and is associated with 15% of all strokes in the U.S[22].

The U.S Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee voted in favor of Dabigatran etexilate for prevention of stroke in patients with atrial fibrillation. For 50 years, warfarin has been the only oral anticoagulant in the U.S for stroke prevention in patients with atrial fibrillation. The RE-LY study established the safety and efficacy profile of dabigatran[13] without INR monitoring, dose adjustments or food restrictions[13].

1.11 RE-LY Trial

RE-LY was a global, Phase-III, randomized trial of 18,113 patients enrolled in 951 centers in 44 countries,[13] investigating whether dabigatran etexilate (two blinded doses) was as effective as well-controlled warfarin-INR 2.0-3.0-(open-label) for stroke prevention[13]. Patients selected for this study were equal to or greater than 75 years with atrial fibrillation and at least one other risk factor for stroke, age greater than or equal to 65 years with either diabetes mellitus, history of coronary artery disease, or hypertension[13] were enrolled in the study for 2 years with a minimum follow up period of 1 year[13].

The RE-LY trial utilized established PROBE (prospective, randomized, open label, blinded endpoint evaluation) clinical trial protocol[23], which has already been used in majority of trials of anticoagulation for stroke prevention in patients with atrial fibrillation[23].
Bleeding and gastrointestinal events were the most commonly reported adverse events in this trial[23].

1.12 Phase-III results for Dabigatran Etexilate, an investigational Oral Anticoagulant

Phase-III results from the RE-NOVATE trial demonstrated that oral anticoagulant dabigatran etexilate once daily, administered for 33 days was non-inferior to enoxaparin which is also administered for an average of 33 days in the prevention of venous thromboembolism (VTE) and all cause mortality after total hip and knee replacement surgery. In this trial the major risk factor of bleeding associated with dabigatran was similar to enoxaparin.In clinical trials; dabigatran was given orally and does not require titration or coagulation monitoring.
Results of the RE-NOVATE trial showed that both doses of dabigatran etexilate (oral dose) were non inferior to enoxaparin (injection) at reducing the risk of thromboembolic disease after primary elective hip replacement surgery when given for an average of 33 days. The incidence for the primary efficacy composite endpoint of total VTE and all cause mortality were 6.0% (dabigatran 220 mg), 8.6% (dabigatran 150 mg), and 6.7% (enoxaparin 40mg). Safety was evaluated for 3,463 patients receiving study treatment. The incidences of major bleeding events were similar in all treatment groups, 2.0% (dabigatran 220 mg), 1.3% (dabigatran 150 mg), and 1.6% (enoxaparin 40mg).
Pooled analysis of major VTE and VTE-related mortality after primary elective knee and hip replacement surgery across more than 8,000 randomized patients that were included in the phase-3 primary VTE prevention program (RE-MODEL, RE-MOBILIZE, and RE-NOVATE). The pooled analysis also concluded that dabigatran etexilate was non-inferior to enoxaparin in the prevention of major VTE and VTE related mortality after total knee and hip replacement.
RE-MODEL study was a multi national, randomized, double-blind, and non-inferiority trial involving 2,076 patients comparing dabigatran etexilate with enoxaparin in the prevention of VTE in patients undergoing primary elective knee or hip replacement surgery. Patients were randomized to either oral anticoagulant dabigatran 150 mg or 220 mg once daily or 40 mg enoxaparin administered by s.c.injection once daily[24].
RE-MOBILIZE study was a randomized, double-blind, non-inferiority trial involving 2,615 patients comparing 150 mg or 220 mg once-daily or 30 mg twice-daily enoxaparin administered by subcutaneous injection. Major VTE occurred at similar rates across all treatment groups (3.0% and 3.4% for 150 mg and 220 mg dabigatran etexilate versus 2.2% enoxaparin[25].

1.13 Oral thromboprophylaxis following Total Hip or Knee Replacement with Dabigatran Etexilate

Patients undergoing primary or secondary elective total hip replacement (THR) or total knee replacement (TKR) surgery have a risk of VTE, which presents a symptomatic deep vein thrombosis or pulmonary embolism[26]. Treatment with thromboprophylactic agents has been recommended for patients undergoing major orthopedic surgery[27].
Over 7,200 patients have been treated with dabigatran at the four centers: these are: Klinik fur Gelenkersatz; ENDO-Klinik; OCM Klinik; Center for endoprosthetic and reconstructive joint surgery. At the Klinik fur Gelenkersatz, over 2,500 patients received dabigatran between April 2008 and September 2010. The ENDO-Klinik treated over 1,500 patients with dabigatran between January 2009 and March 2010, while dabigatran has been in clinical use at the OCM Klinik since July 2008 and as of May 2010 over 2,600 patients had received the drug. At the Center for Endoprosthetic and Reconstructive Joint Surgery, Dabigatran was prescribed to approximately 600 patients between April 2009 and September 2010. Individual center patient

numbers and methods of examination and evaluation are not detailed due to their heterogeneity.

Dabigatran was directly compared to enoxaparin, as enoxaparin was the standard treatment in all centers before the study. The criteria for choosing to prescribe Dabigatran included: no contra-indications to therapy; no previous warfarin use; no severe bleeding disease; absence of a peridural catheter; the availability of a reduced dose for patient aged over 75 years, with renal insufficiency or receiving amiodarone therapy. The duration of treatment with Dabigatran was in accordance with European guidelines: 28-35 days for THR patients and 10 days in TKR patients.

Table 4: Advantages and disadvantages associated with the implementation and use of Dabigatran in clinical practice, as compared with Low Molecular Heparins

	ENDO-Klinik	OCM-Klinik	Center for Endoprosthetic and Reconstructive Joint Surgery	Klinik for Gelenkersatz
Advantages				
Good efficacy	*	*	*	*
Comparable efficacy to enoxaparin				*
Ease of use/oral dosing/single application/fixed flexible dosing	*	*	*	*
Time-saving		*		*
Can be taken by patients at home	*	*		*
High patient satisfaction levels	*	*		*
High staff satisfaction levels			*	*
Lack of haematoma		*		*
No risk of heparin-induced thrombocytopenia	*	*		*
No need for regular monitoring of coagulation parameters	*	*		*
No increase in DVT in first 8 days post-surgery	*	*		*
No increase in complications such as severe bleeding or need for wound revision	*	*		*
Reduced dosage available				*
Good safety profile	*	*	*	*
Clarity of protocol			*	
Fair pricing			*	*
Disadvantages				
Time consuming implementation	*	*		*
Limitations during spinal anaesthesia	*	*		*
Not suitable for use following DVT	*	*		*
No indication for treatment of DVT	*	*		*
Relative inaccuracy of laboratory coagulation parameters	*	*		*
No long-term experience	*	*		*
Severe nausea in some patients requiring change of therapy	*	*		*
Possible cost disadvantage	*			*
Large size of capsules				*

*Either data provided by the clinical supports this statement or an author from the clinic stated that they agree with the statement.

1.14 Safety and Efficacy Outcomes with Dabigatran

All advantages and disadvantages associated with the implementation of the new drug are summarized in table-4. In general, the efficacy and safety of dabigatran were deemed to be very good by the clinics and were thought to be comparable to the parenteral anticoagulants used. Dabigatran is administered orally as a fixed dose. No safety complications were reported at all the three centers. But rare cases of bleeding in intestinal tract were reported in one clinic reported case receiving dabigatran (which is the side-effect of dabigatran).

1.15 Patient Satisfaction with Dabigatran

Patients receiving Dabigatran were satisfied in all these clinical settings and in some centers better patient comfort was reported with Dabigatran. Satisfaction was high in case of those patients with having previous experience of LMWH; indeed, dabigatran's oral administration was preferable to the parenteral application of LMWH, which can be associated with abdominal haematomas.

2. Summary

Thromboprophylaxis is recommended following THR and TKR, and there has been a need for safe and effective but more convenient anticoagulant therapies. Dabigatran has been licensed for this indication in over 75 countries, including Europe and Canada. This experience with over 7,200 patients should provide useful and relevant information for surgeons considering dabigatran for the indication discussed. Overall, dabigatran was viewed as an effective oral alternative for thromboprophylaxis following major orthopaedic surgery, and its discussed advantages are likely to improve patient adherence to anticoagulant therapy.

3. Precautions and Warnings

The U.S. Food and Drug Administration (FDA) is informing health care professionals and the public that the blood thinner (anticoagulant) Pradaxa (dabigatran etexilate mesylate) should not be used to prevent stroke or blood clots (major thromboembolic events) in patients with mechanical heart valves, also known as mechanical prosthetic heart valves. Patients with renal insufficiency may require dosage adjustments to decrease the risk of bleeding[28].

3.1 Side-effects of Dabigatran Etexilate

- **Most common-** Bleeding in a critical area or organ, indigestion, nausea, upper abdominal pain, gastrointestinal bleeding and diarrhea.
- **Hypersensitivity-** Hives, rash and itching[3].
- **Contraindications** Contraindicated in patients with active bleeding and hypersensitivity.
- **Category C:** Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

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