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ORIGINAL ARTICLE

Role of new oral antithrombin in management of thrombophilia presented with multiple infarctions (cerebral, myocardial and pulmonary embolism)

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Mohamed Abdelwahab [a], Ayman El-Dib [a,*], Mohamed Hantera [a], Ayman A. Al-azzouny [b]

[a] Department of Chest Dis., Tanta University, Egypt
[b] Department of Neurology Medicine, Misr University for Sciences and Technology, Egypt

Abstract *Background:* Thromboembolic disease is a major cause of mortality and morbidity Current anticoagulant therapies have several caveats in the clinical use. New oral antithrombin (Dabigatran) provides comparable or superior thromboprophylaxis in multiple thromboembolic disease indications compared to standard of care.

Aim of this work: To evaluate the role of a new oral antithrombin, in management of thrombophilia presented with multiple infarctions (cerebral infarction, myocardial infarction, pulmonary embolism or infarction).

Patient and methods: This work was done on 100 patients with thrombophilia associated with multiple infarctions (cerebral infarction, myocardial infarction, pulmonary embolism or infarction). They were divided into 2 groups Group I: treated by LMW heparin. Group II: treated by dabigatran. The following was done for all patients. Thorough history taking, complete physical examination, investigations including CT, D Dimer, INR, APTT, Platelet count, Chest X ray P/A and lateral view, CT chest and/or Brain, ECG, CKMB and troponin when needed.

Results: The percentage of Stroke/TIA, AF/MI, PE, mixed and peripheral thrombotic events were 30, 24, 23, 26 and 6 patients respectively.

Introduction

Thrombin is a key serine protease and is the main effector protease in the blood coagulation cascade, exhibiting both pro- and anti-coagulant properties [1]. Thrombin (FIIa) is generated via proteolytic cleavage from inactive prothrombin (FII) by factor Xa (FXa) in the prothrombinase complex, which

* Corresponding author.

assembles when circulating coagulation factors come into contact with tissue factor (TF) on exposed extravascular tissues. Thrombin plays a central role in the initiation and propagation of thrombotic disease by activating platelets, catalyzing fibrinogen conversion into fibrin, and promoting clot stabilization [2]. Thrombin activates upstream factors in the cascade to amplify the coagulation response and enhance thrombin generation. Its activity is inhibited via endogenous circulating anticoagulants including antithrombin (AT), heparin cofactor II (HCII), and binding to cofactor thrombomodulin (TM) to activate the anticoagulant protein C [1].

Thromboembolic disease is a major cause of mortality and morbidity in the developed world and is caused by an excessive stimulation of coagulation. Since thrombin is a key serine protease in the coagulation cascade, numerous efforts have been made to develop safe and effective orally active direct thrombin inhibitors (DTIs). Current anticoagulant therapy includes the use of indirect thrombin inhibitors (e.g., heparins, and low-molecular-weight-heparins) and vitamin K antagonists such as warfarin. However there are several caveats in the clinical use of these agents including narrow therapeutic window, parenteral delivery, and food- and drug–drug interactions. Dabigatran is a synthetic, reversible DTI with high affinity and specificity for its target binding both free and clot-bound thrombin, and offers a favorable pharmacokinetic profile. Large randomized clinical trials have demonstrated that dabigatran provides comparable or superior thromboprophylaxis in multiple thromboembolic diseases compared to standard anticoagulant. Dabigatran is the first in a class of new oral anticoagulant agents from the class of the direct thrombin inhibitors to be licensed worldwide to prevent strokes in those with non-valvular atrial fibrillation, and at least one additional risk factor for stroke (congestive heart failure with left ventricular ejection fraction < 40%, elder age, hypertension, diabetes, and prior stroke or transient ischemic attack or systemic embolism), and to prevent the formation of venous thromboembolism in adults who have had an orthopedic surgery with total hip or knee replacement [3,4]. Except for the initial base line INR, Dabigatran does not require INR monitoring as it is unreliable in patients on dabigatran. This can be done through thrombin time (TT), activated partial thromboplastin time (aPTT) and ecarin clotting time (ECT) being the most sensitive parameter for anticoagulant activity. The thrombin time (TT) assay is extremely sensitive for accurate quantitative measurement of dabigatran activity [5]. If ECT or TT is not available, the aPTT test provides an approximation of dabigatran's anticoagulant activity, an aPTT of > 80 s at trough was associated with an increased risk of bleeding [6]. Dabigatran dosing is adjusted for kidney function as it is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min), to minimize the risk of bleeding. A dose reduction and close clinical surveillance should be considered in patients with moderate renal impairment (creatinine clearance 30–50 ml/min), particularly in those at an increased risk of bleeding, and patients older than 75 years [7]. Patients with active pathological bleeding or with a known serious hypersensitivity reaction (e.g., anaphylactic shock or reaction) to dabigatran. patients who have lesions or conditions at a significant risk of major bleeding such as current or recent gastrointestinal ulceration, recent brain or spinal injury, recent brain, spinal suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. It is contraindicated in severe hepatic impairment or liver disease as it is expected to have any impact on survival [8]. Dabigatran must not be used in patients taking oral or parenteral antifungal infections, ketoconazole and itraconazole, or the immunosuppressant medicines cyclosporine and tacrolimus [8]. Administration of a P-gp inducer (such as rifampicin, phenytoin or carbamazepine) is expected to result in decreased dabigatran concentrations and should be avoided, use of dabigatran is contraindicated with dronedarone, and with other anticoagulants, except when switching treatment to or from dabigatran, or with the use of unfractionated heparin for maintenance of venous or arterial catheter patency. The use of dabigatran during pregnancy or lactation is not recommended [4].

Aim of this work

To evaluate the role of new oral antithrombin, in management of thrombophilia presented with multiple infarctions (cerebral infarction, myocardial infarction, pulmonary embolism or infarction).

Patient and methods

This work was done on 100 patients with thrombophilia associated with multiple infarctions (cerebral infarction, myocardial infarction, pulmonary embolism or infarction). It was done in either the Chest or Neurology Department, Tanta University Hospital, Egypt from January 2011 to may 2013. The patients were divided into two groups, group I included 34 patients treated with LMW heparin and group II included 66 patients treated with dabigatran. All the patients started marevan after 3 days of treatment and continued together with LMW heparin or dabigatran for other 3 days, then marevan was given alone, some cases needed additional anti-platelet such as clopidogrel. The following was done for all patients: Thorough history taking, complete physical examination, the following investigations: Clotting time (CT), D Dimer, INR, APTT, platelet count, plain X-ray Chest P/A and lateral view. CT Chest and/or Brain when needed. ECG, CK MB and troponin when needed. Exclusion criteria were patients with severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months, recent or known bleeding disorders, uncontrolled hypertension, severe renal dysfunction with creatinine clearance < 30 ml/min, recent gastrointestinal ulceration, Esophageal varices, active liver disease and pregnant women.

Statistics

Statistical presentation and analysis of the present study were conducted, using the mean, standard deviation and t test linear Correlation Coefficient [r] and the SPSS V.16 (Figs. 1 and 2 and Tables 1–6).

Discussion

Thrombophilia is liability of blood to clot due to genetic or acquired causes and can be presented as CVA, MI, PE and peripheral thrombosis either single or mixed. In the present work the percentage of Stroke/TIA, AF/MI, PE, mixed and
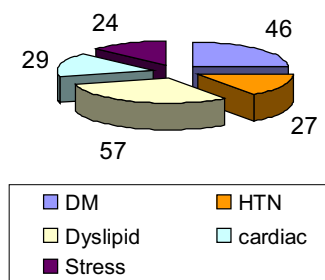
Figure 1 Showing percentage of risk factors of thrombophilia of the studied patients.
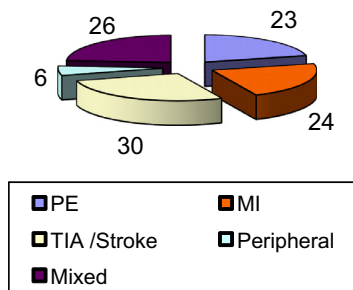

Figure 2 Showing percentage of Stroke/TIA, AF/MI, PE, mixed and peripheral thrombotic events were 30, 24, 23, 26 and 6 patients respectively.

Table 1 Some demographic data of the studied patients (Age, Sex and Body Weight).

Parameters	Range	Mean	±SD
Age	29–82	57.6	14.61
Sex (M/F)	64/36		
Body Weight	61–140	93.9	22.29

Table 2 Some hematological findings of the studied patients (Platelet, RBCs and INR).

Parameters	Range	Mean	±SD
Platelets	140–223	183.8	22.72
RBC	4.1–5.6	4.99	0.42
INR	1.1–2.1	1.58	0.34

Table 3 Risk factors of thrombophilia of the studied patients (DM, HTN, dyslipidemia, Cardiac, Stress).

+VE	N	%
DM	46	46
HTN	27	27
Dyslipidemia	57	57
Cardiac	29	29
Stress	24	24

Table 4 Percentage of Thrombotic events for the studied patients.

Thrombotic events	N	%
PE	23	23
AF/MI	24	24
TIA/stroke	30	30
Peripheral	6	6
Mixed	26	26

Table 5 Percentage of anticoagulants and antiplateletes (Dabigatran, LMWH, Coumarins and Clopidogrel).

+VE	N	%
Dabigatran	66	66
LMWH	34	34
Marevan	100	100
Clopidogrel	61	61

Table 6 Side Effects of different medications used in the studied patients.

	Dabigatran	LMWH	Marevan
Major Bleeding	0	2 GIT bleeding	0
Minor Bleeding	2 Epistaxis	3 SC Hematoma	3
Gastric upset	5	0	3

peripheral thrombotic events were 30, 24, 23, 26 and 6 patients respectively. This percentage of cases was explained by referral of cases to both neurology and pulmonology department [9].

Garnock-Jones, 2011 reported that dabigatran has a fast onset of action with peak plasma concentrations 2–3 h after ingestion with a half-life of 12–14 h. It does not require routine coagulation monitoring; it has no drug-food interactions, is not metabolized by cytochrome P 450 enzymes, and does not require dose adjustment for moderate liver disease [10].

Our study proved to be a safe convenient and effective anticoagulant activity in thrombophilia compared with other oral as well as LMWH, this was in accordance to Dahl et al. 2012; Eriksson et al. 2012 and Fuji et al., 2010 who studied in more than 10,000 patients in four phase trials of deep venous thrombosis (DVT) and pulmonary embolism (PE) prophylaxis in major orthopedic surgery using dabigatran demonstrated a good overall safety profile [11–13].

Contrary to our study Ginsberg et al., 2009 [14] compared dabigatran etexilate at 150 and 220 mg once daily (OAD) with enoxaparin 30 mg twice daily (BID), as prophylaxis of DVT or thrombus dissemination after total knee replacement (TKR), dabigatran was inferior due to a greater number of distal thromboses. However Eriksson et al., 2007 [15] found equivalence on comparing dabigatran to 40 mg of enoxaparin, for both thrombosis prevention and bleeding in total hip replacement (THR) and TKR.

Recently trials demonstrated its superiority in the prevention of major VTE (Friedman et al., 2010; Eriksson et al., 2011). In countries where dabigatran etexilate is approved for VTE prophylaxis it is recommended at a dose of 220 or 150 mg OAD for patients with renal impairment or taking a

Pgp inhibitor [16]. In the treatment of VTE 150 mg BID dabigatran etexilate was compared to standard warfarin treatment (Schulman et al., 2009). In the acute treatment setting, all patients received heparin or LMWH for a mean of 9 days prior to treatment with an oral anticoagulant. Dabigatran demonstrated the same efficacy in thrombosis prevention with significantly less minor bleeding and similar major bleeding. The extension studies RE-MEDY study (Dabigatran vs. warfarin) and RE-SONATE study (Dabigatran vs. placebo) showed a similar efficacy and improved bleeding profile compared to warfarin, and a 92% relative risk reduction of recurrent VTE with elevated clinically relevant non-major bleeding but no statistical difference in major bleeding compared to placebo (Schulman et al., 2011) [17–18]. In the RE-LY study, 18,113 patients with atrial fibrillation (AF) and at least one risk factor for stroke were randomized between warfarin, 110 or 150 mg BID dabigatran etexilate (Connolly et al., 2009). The 150 mg BID dose showed superior efficacy in stroke prevention and systemic embolism with similar major bleeding rate compared to well controlled warfarin. The 110 mg BID dose had a significantly lower major bleeding rate and the same efficacy as warfarin. Both doses showed a significant (up to 70%) reduction of intracranial hemorrhage and a reduction in life-threatening bleeding. There was a non-significant 12% mortality benefit ($p = 0.051$) with the 150 mg BID dose (Connolly et al., 2010) [19,20].

These results were consistent across all patient groups, including those with a prior history of stroke or transient ischemic attack (Diener et al., 2010), patients previously on warfarin, or those new to oral anticoagulation (Ezekowitz et al., 2010) [21,22].

For stroke prevention, the FDA recommends a lower therapeutic dose (75 mg BID) in patients with severe renal impairment [creatinine clearance 15–30 ml/min] and no use in patients with creatinine clearance under 15 ml/min. In Europe two doses (150, 110 mg BID) exist which enable tailored dosing and are contraindicated in patients with a creatinine clearance below 30 ml/min.

Conclusions

Dabigatran etexilate is an oral, reversible, direct thrombin inhibitor that inhibits both clot-bound and circulating thrombin. After oral administration, dabigatran has a fast onset of action, reaching peak plasma concentrations within 0.5–2 h, thereby potentially negating the need for initial treatment with a rapidly acting injectable anticoagulant. The presence of dabigatran in the blood can be detected by a prolonged TT or aPTT, but the anticoagulation response is sufficiently predictable that routine coagulation monitoring is not required. Dabigatran has a low potential for food and drug interactions, a half-life of 12–14 h in patients with normal renal function that permits once- or twice-daily administration, and a fast offset of action. About 80% of the drug is excreted unchanged by the kidneys.

Dabigatran etexilate has demonstrated non-inferiority and safety similar to once-daily enoxaparin for the prevention of VTE in patients undergoing hip and knee arthroplasty. Given its efficacy, safety profile, and attractive pharmacological characteristics, it has been approved for this indication in > 75 countries worldwide. Dabigatran has demonstrated noninferiority to and improved safety compared with warfarin for the treatment of VTE and noninferiority to warfarin at a lower dosage and superiority at a higher dose for preventing stroke and systemic embolism in patients with nonvalvular AF. Thrombin time (TT), has been approved for the quantitative determination of dabigatran plasma levels. For patients taking dabigatran who bleed, there is no specific antidote. Discontinuation of the drug and supportive measures usually suffice because the anticoagulant effect of dabigatran is short-lived. In emergencies, dabigatran can be dialyzed; failing that, nonspecific hemostatic agents such as rFVIIa and prothrombin complex concentrates can be considered. In case of overdose, the efficacy of early administration of activated charcoal and charcoal filtration is undergoing clinical evaluation.

Outstanding issues relating to the use of dabigatran etexilate include the lack of a test of anticoagulant activity, lack of an antidote, limited evaluation in patients with severe renal impairment, interaction with other drugs that are substrates of the p-glycoprotein transporter, and unknown long-term safety. The long-term safety of dabigatran etexilate is being evaluated in ongoing studies.

Conflict of interest

None declared.

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