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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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KEYWORDS

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Thromboprophylaxis;
Dabigatran

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

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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 nonvalvular 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