The Role of New Oral Anticoagulants for Prevention and Treatment of Arterial and Venous Thromboembolism

Essay

Submitted in Fulfillment of the Requirement for the Master Degree in Intensive Care Medicine

By

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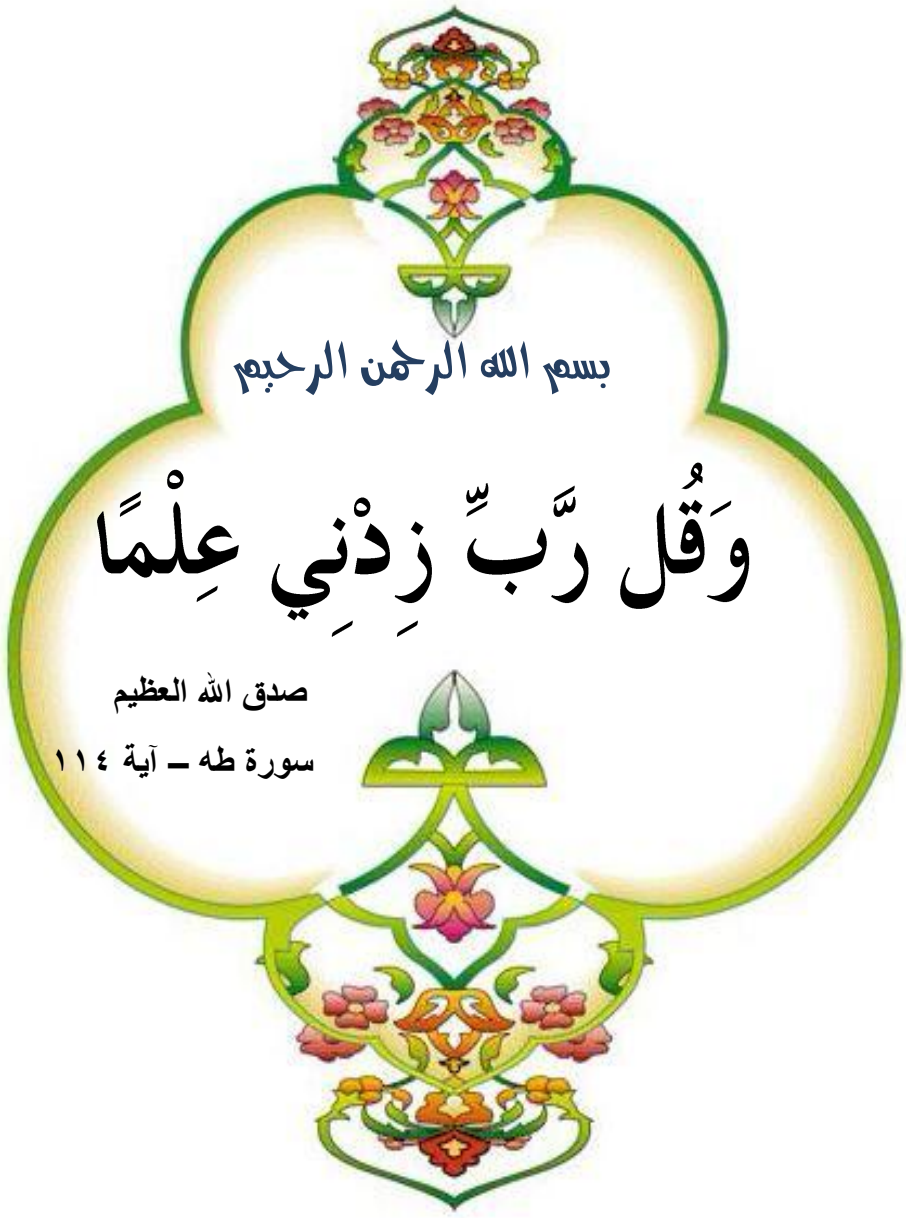
2014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سورة طه – آية ١١٤

Acknowledgment

Praise be to **ALLAH**, The merciful, The Compassionate for all the gifts **I** have been offered; One of the gifts is accomplishing this research work.

Words cannot adequately assure my deepest thanks and gratitude to ***Prof. Dr. Mohamed Hossam El-Din Shokeir***, Professor of Anesthesia and Intensive Care Medicine, Faculty of Medicine – Ain Shams University, for his continuous encouragement, constructive criticism and continuous assistance. I really have the honor to complete this work under his supervision.

I would like to express my deepest thanks and gratitude to ***Prof. Dr. Sherif Farouk Ibrahim,*** Professor of Anesthesia and Intensive Care Medicine, Faculty of Medicine – Ain Shams University, for his unlimited help, valuable guidance, continuous encouragement and forwarding his experience to help me complete this work.

I can't forget to thank with all appreciation and gratitude ***Dr. Dalia Fahmy Emam,*** Lecturer of Anesthesia and Intensive Care Medicine, Faculty of Medicine – Ain Shams University, for her valuable assistance, kind supervision, her great efforts and time she has devoted to this work.

Last but not least all thank and gratitude go to my **Family**, especially my Parents, for pushing me forward in every step in my life.

Aly Mohammed Abdullah

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Introduction

Arterial and venous thromboembolism disease is common and imposes a large clinical and economic burden on healthcare systems, with a substantial effect on patient's quality of life. Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) ***(Deitelzweig, 2012).***

The conventional management of acute VTE requires the use of a parenteral anticoagulant for 5 to 7 days, overlapping with longer term warfarin. Parental anticoagulants used in conjunction with warfarin include unfractionated heparin administrated intravenously, low molecular weight heparin administrated subcutaneously and fondaparinux administrated subcutaneously. Unfractionated heparin requires hospital admission and continuous monitoring and carries the risk of heparin-induced thrombocytopenia ***(Wysowski et al., 2007).***

The search has been ongoing for noval oral anticoagulants with equal efficacy, a wider therapeutic range, and less complex pharmacodynamics, thus precluding the need for routine laboratory monitoring. Over the past decade, several newer oral anticoagulant have emerged. These anticoagulants fall under two drug classes factor Xa (FXa) inhibitors and direct thrombin inhibitors (DTIs) ***(Fareed et al., 2007).***

Aim of the Study

To discuss pathophysiology, prevention, management of arterial and venous thromboembolism and the role of new oral anticoagulants.

Chapter (1)
Physiology of Blood Coagulation

Normal hemostasis

Hemostasis is a sequence of events that result in arrest of bleeding from a traumatized blood vessel. This system involves the interaction of four components, namely, the vascular endothelial cells, the platelets, the plasma coagulation system and fibrinolytic system ***(Colman., 1994).***

Role of blood vessel wall in hemostasis:

Normal blood vessel wall contains all the protective mechanics against thrombus formation as intact endothelium produces:

A- Thrombomodulin that activate protein C by the aid of thrombin and activated Protein C inhibits Va and VIIIa factors.

B- Heparin sulfate that acts as a co-factor for Antithrombin III which inhibits Xa factor and thrombin.

C- Dermatan sulfate which act as co-factor of heparin co-factor II which inhibit thrombin.

D- Prostacycline which inhibit platelets aggregation.

The vessel wall has an important role in arresting bleeding of a vascular injury by immediate reflex contraction

of the vessel wall. Endothelial cells can induce vasoconstriction as they secrete serine protease, which converts angiotensinogen to angiotensin I and contain their surface angiotensin converting enzyme (ACE), which converts vaso-inactive angiotensin I to vasoconstrictor angiotensin II, and inactivate the vasodilator bradykinin ***(Goldsmith and Cormick, 1994).***

Endothelial cells synthesize platelet-activating factor (PAF) when estimated by a variety of substances including thrombin, vasopressin, angiotensin, histamine and bradykinin. PAF is a potent activator of platelets. Polymorphic nuclear lymphocytes (PNLs) and monocytes. Subendothelial layers is an active component in platelet adhesion as deep injury of the subendothelium exposes the underlying region, releases the Von Willebrand factor (VWF) acting as a substrate for platelet attachment which rapidly becomes covered with a layer of platelets, which soon degranulate.

When endothelial cells become exposed to thrombin they react with factor VII and calcium and activate factor X, factor Xa in turn activates factor VII to factor VIIa. Endothelial cells synthesize factor V.***(Furies and Furies, 2005).***

Endothelial cells have fibrinolytic properties as they secrete several components of the fibrinolytic system, including plasminoge activator and plasminogen activator inhibitor ***(Shleef et al., 1988).***

Platelets maintain primary hemostasis by forming the hemostatic plug that occludes the site of vascular damage. They also -provide a surface for the assembly of the coagulation protein complexes that are responsible for the formation of thrombin ***(Weyrich., 2004).***

Two related roles are played by platelets in hemostasis. First by forming multicellular aggregates linked by fibrinogen. Second by accelerating rate at which coagulation proteins are activated. Phospholipids on platelets surface facilitate thrombin generation and fibrin strands formation.

After vascular injury, platelet adhesion to exposed subendothelial collagen occurs mediated by factor VIII-VWF polymers. Collagen induces configuration and biochemical alteration of platelets which include:

- Release reaction: which is the liberation of contents of platelets granules which are of two types: dense granules containing adenosine dipbosphate, serotonin and calcium which help more aggregation of platelets to the site of plug. And alpha granules containing platelets Factor IV, B-thromboglobin, platelets derived growth factor, that

play an important role in smooth muscle proliferation that may occur in response to the interaction of platelets with the vessel wall, factor VIII related. VWF, Factor V and others ***(Colman et al., 1994).***

- Liberation of arachidonic acid by phospholipase enzyme and oxygenated by cycloxygenase enzyme forming endoperoxidase prostaglandin G2 and prostaglandin H2 that form thromboxane A2, this enzyme induces more platelet aggregation and vasoconstriction (***Colman et al., 1994).***

Blood coagulation:

If is the rapid replacement of an unstable platelet plug with a chemically stable fibrin clot. A series of inter-dependent enzyme mediated reactions translate the molecular signal that initiate blood coagulation into major biologic event, the formation of fibrin clot ***(Furies and Furies, 2005).***

Coagulation Proteins:

Coagulation proteins are classified according to functional and structural similarities into several groups as, serine proteinase family, ceruloplasmin like binding proteins and serpin family. Most of coagulation proteins are synthesized by other cells as megakaryocytes, monocytes, macrophages and endothelial cells ***(Colman et al., 1994).***

By other way through factor VIIa, however, prolongation of the activated partial thromboplastin time occurs. Other pathway of activation of factor XI is Kallikrein. So activators of factor XI include XIIa, kallikrein and VIIa ***(Brewer, 2006).***

Activation of Factor X:

Activation of Factor X occurs by two separate mechanisms, the intrinsic pathway and the extrinsic pathway.

The intrinsic pathway:

In this pathway all components are intrinsic to blood. Activated Factor XI formed by contact system, will activate Factor IX to Factor IXa. Calcium ions are essential to this reaction ***(Davie., 1991).***

This reaction takes place in the solution phase without the need of membrane surface. Activated Factor IX forms a complex with Factor VIII and phospholipids (from platelets) which is called the Tenase complex on a membrane surface. This complex in the presence of calcium ions convert Factor X to its active form. In vivo hemostatic surface is provided, by platelets and to a lesser extent, fibroblasts- and vascular smooth muscle ***(Marker et al., 1994).***

The Extrinsic pathway:

In this pathway an. extrinsic component of blood is utilized. This is called tissue factor (Tissue Thromboplastin). It is a cellular receptor for Factor VII and VIIa, and is present in many cells as non-vascular cells and vascular cells ***(Broze, 1992).***

Tissue injury initiates activation of tissue factor pathway, as tissue factor is normally cryptic. Tissue factor forms a catalytic complex with factor VII or factor VIIa. This in presence of calcium ions will activate Factor X forming Factor Xa, which will activate Factor VII to Factor VIIa in the presence of tissue factor and phospholipids vesicles, leading to amplification of the clotting response ***(Brewer, 2006).***

It was discovered that tissue factor activates both Factor X and Factor IX, but activation of Factor X is more rapid than factor IX ***(Broze et al., 1992).*** So that physiologic role of tissue factor-dependent activation of Factor IX was not clear, but it has been showed that, the conversion of radiolabeled Factor X to factor Xa is heavily dependent on factors VIII and IX when a crude tissue extract or endothelial cells used as a source for tissue factor, implicating that on addition of tissue factor to plasma, the main flow of the

enzymatic reactions proceeds through factor VIII and IX ***(Furies and Furies, 2005).***

Common pathway

Active factor X in presence of Factor V, Ca^{++}, and phospholipid (all form a complex called prothrombinase complex), activates factor II (Prothrombin) to form thrombin. Factor V has a domain for binding factors Xa and II, Ca^{++} and phospholipid surface. Stimulated platelets contain discrete sites for factor V, the acceleratory role of platelets in Factor Xa-V-II reaction is called platelets factor II activity.

Factor V is more effective after it has been cleaved by Factor IIa, thus thrombin is initially generated at a sluggish rate- but once a small amount of thrombin is generated, it can cleave Factor V to more active form, so subsequent thrombin formation becomes rapid ***(Krishnaswamy and Mann, 1988).***