NEW ORAL ANTICOAGULANTS, RECENT TREND IN THE PERIOPERATIVE THERAPY

An Essay

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List of abbreviations

ACT	Activated clotting Time
ADP	Adenosine Diphosphate
AMI	Acute Myocardial Infarction
APA	Antiphospholipid Antibody
APC	Activated Protein C
APSAC	anisoylated plasminogen-SK activator complex
APTT	Activated Partial Thromboplastin time
CAMP	Cyclic AMP
CBC	Complete Blood Count
COAT	Collagen and Thrombin Stimulated platelets
COX-1	Cyclo-oxygenase 1
CrCl	Creatinine clearance
CYP	Cytochrome P
DIC	Dissiminated Intravascular Coagulopathy
DVT	Deep venous thrombosis
FDA	Food and Drug Association
FDP	Fibrin Degradation Products
GFR	Glomerular filtration rate
HIT	Heparin Induced Thrombocytopenia
HRT	Hormone Replacement Therapy
ICH	Intracranial Hemorrhage

ITP	Immune Thrombocytopenic Purpura
IgG	Immunoglobulin G
JAK-2	Janus Kinase 2
LA	Lupus Antibody
LMWH	Low Molecular Weight Heparin
MI	Myocardial Infarction
NOACs	New Oral Anticoagulants
PCC	Prothrombin Concenration Complex
PCI	Percutaneous Coronory Intervention
PF4	Platelet Factor 4
PGI2	Prostaglandin I 2
P-gp	Permeability glycoprotein
PL	Phospholipid
PV	Polycythemia vera
SSRI	Selective Serotonin Reuptake Inhibitor
TAFI	Thrombin Activatable Factor Inhibitor
TAX2	Thromboxane A 2
TF	Tissue Factor
TSOA	Target Specific Oral Anticoagulants
TIA	Transient Ischemic Attacks
TTP	Thrombocytopenic Purpura
TTR	Target Therapeutic Range

UH	Unfractionated Heparin
ULN	Upper Limit Normal
VKORC1	Vitamin K epoxide reductase complex subunit 1
VWF	Von Wallibrand Factor
VTE	Venous Thromboembolism
WBCT	Whole Blood Clotting Time

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Aim of the essay

The main aim of this essay is to enable practitioners to make informed evidence based decisions on the updated anesthetic perioperative strategies that may reduce morbidity and mortality in patients receiving oral anticoagulants.

Chapter 1

Pathohysiology of Coagulation System

Pathophysiology of Coagulation System

The term "hemostasis" means prevention of blood loss. Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms: (1) vascular constriction, (2) formation of a platelet plug, (3) formation of a blood clot as a result of blood coagulation, and (4) eventual growth of fibrous tissue into the blood clot closes the hole in the vessel permanently ***(Anderson et al., 2006)*.**

1. Vascular Constriction:

Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall itself causes the smooth muscle in the wall to contract; this instantaneously reduces the flow of blood from the ruptured vessel. The contraction results from (a) local myogenic spasm, (b) local autacoid factors from the traumatized tissues and blood platelets, and (c) nervous reflexes. The nervous reflexes are initiated by pain nerve impulses or other sensory impulses that originate from the traumatized vessel or nearby tissues ***(Anderson et al., 2006).***

In the resting state, blood is actively maintained in a liquid form by endothelial cells and circulating plasma protein inhibitors. When the vascular integrity is disrupted or the endothelium becomes inflamed, the thrombotic activity of the endothelial cells is triggered, through secreting platelet-activating factor, a substance that induces platelet

aggregation and synthesizes Von Willebrand factor (VWF), a cofactor necessary for platelet adherence to the subendothelium. In addition, the endothelium is able to secrete plasminogen activator inhibitor which inhibits the fibrinolytic system ***(Dittman and Majerus, 2001)***.

Endothelial cells have several anti-thrombotic mechanisms that protect against the unchecked action of thrombin, the terminal enzyme of the plasma coagulation system ***(Prescott et al., 2000)***.

Thrombomodulin is a surface protein that down regulates the coagulation system by binding to thrombin and activating the natural anticoagulant protein C. The endothelium also has heparin like molecules on its surface that potentiate the effect of antithrombin III, a plasma protein that inactivates thrombin ***(Prescott et al., 2000)***.

Thrombin itself induces endothelial cells to synthesize and release prostacyclin (PGI_2), a prostaglandin derivative that is a potent inhibitor of platelet aggregation; In addition, endothelial cells are capable of producing tissue type plasminogen activator which stimulates the fibrinolytic system ***(Prescott et al., 2000)***.

Damage to the endothelial monolayer exposes blood to a highly thrombogenic subendothelial connective tissue which initiates clot formation. This connective tissue consists of various types of compounds including fibrillar collagen, which is a potent stimulus for platelet activation and adhesion. Simultaneously, subendothelial components convert inactive

coagulation factors into powerful enzymes, initiating intrinsic stimulation of plasma coagulation system ***(Edward and Juan, 2000)*.**

2. Formation of the platelet plug:

Platelets have multiple and over-expanding role in hemostasis. They are recruited not only when vascular integrity is disturbed, but also they maintain the integrity of normal endothelium, as evidenced by the tendency of patient with platelet deficiencies to develop purpuric bleeding ***(Edward and Juan, 2000)*.**

Platelets respond through three steps:

1. Adhesion:

When platelets come in contact with a damaged vascular surface, especially with collagen fibres in the vascular wall, the platelets themselves begin to swell, assume irregular forms with numerous radiating pseudopods protruding from their surfaces, their contractile proteins contract forcefully and cause the release of granules that contain multiple active factors, they become sticky so that they adhere to collagen in the tissues and to a protein called Von-Willebrand factor that leaks into traumatized tissues from plasma ***(Anderson et al., 2006).***

2. Activation of Secretion:

With activation, platelets secrete granules and dense bodies. Granules contain platelet specific proteins that include fibrinogen, fibronectin, VWF, factor V, and factor IV. Dense bodies are rich in ionized calcium, adenosine diphosphate (ADP), epinephrine and serotonin. Following platelet activation and granule secretion, a phospholipid complex known as platelet factor 3, becomes exposed on the platelet surface, this complex provides a site where several clotting factors are able to bind with and ultimately form thrombin (table1-1) ***(Roberts et al., 2004).***

3. Aggregation:

The injured vascular wall and erythrocytes release adenosine diphosphate (ADP) which causes morphological change in the platelets leading to decrease of the electrostatic repulsion between the platelets leading to adhesion of platelets to each other. The release of thromboxane A_2 (TAX_2) and ADP leads to secondary platelet aggregation ***(Anthony and Barry, 2001).***

Platelet aggregation also results from bridging of fibrinogen molecules between many cells and requires the activation-dependent alteration in glycoprotein IIb/IIIa complex to permit binding of adhesive proteins ***(Anthony and Barry, 2001).***

3. Formation of a blood clot:

The third component of the hemostasis is the formation of the blood clot. The clot begins to develop in 15 to 20 seconds