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Anticoagulant Therapy to Prevent Embolization

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ABSTRACT
Aim: *This article aims at providing an overview regarding the anticoagulant therapy to prevent embolisation.*
Objective: *To provide a comprehensive review on anticoagulant therapy and other treatment options to prevent embolisation.*
Background: *An embolism is the lodging of an embolus, which may be a blood clot, fat globule, air bubble or foreign material in the bloodstream, resulting in a blockage of the blood flow to a paricular organ. Based on the organ affected, it is classified as pulmonary embolism, brain embolism, retinal embolism etc. Anticoagulants are a group of drugs that reduces the body's ability to form clots in the blood and thus they play a great role in both the prevention and treatment of established embolism. Therapeutic uses of anticoagulants include atrial fibrillation (AF), artificial heart valves, deep vein thrombosis (DVT), pulmonary embolism (PE), embolic stroke and myocardial infarction with a large mural thrombus etc. Anticoagulant drugs affect the blood's ability to clot and therefore there is also an increased risk of bleeding for people who are taking them. This article aims at providing information regarding anticoagulant therapy to prevent embolisation.*
Reason: *To know about the indications and use and disadvantages of anticoagulant therapy in various systemic diseases to prevent embolisation.*

INTRODUCTION

Thrombi are composed of fibrin and blood cells and may form in any part of the cardiovascular system, including veins, arteries, the heart, and the microcirculation. The complications of thrombosis are caused either by the effects of local obstruction of the vessel, distant embolism of thrombotic material, or consumption of hemostatic elements [1]. An embolus is most often a piece of a thrombus that has broken free and is carried toward the brain by the bloodstream. The term thromboembolus is used a lot because it turns out that most emboli arise from thrombi. However, bits of plaque, fat, air bubbles, and other material also qualify as emboli. Presumably an embolus floats along with the flowing blood until it encounters a narrowing in an artery through which it cannot pass. When the embolus gets stuck, it blocks the artery. This reduces blood flow to downstream tissues and causes them to become ischemic [2]. During routine homeostatic conditions, the human body maintains a constant balance between thrombus formation and destruction. This equilibrium is maintained by a complex interaction between platelets and the vascular endothelium, the coagulation cascade, and the fibrinolytic system [3]. Anticoagulants work by interrupting the process involved in the

formation of blood clots. Anticoagulants are the cornerstone therapy for thrombosis prevention and treatment.

PATHOPHYSIOLOGY

The coagulation cascade is triggered by tissue factor release from tissue trauma or vascular injury. Tissue factor forms a complex with factor VIIa in the presence of calcium and cleaves clotting factors X and IX to their activated forms Xa and IXa. The prothrombinase complex is then assembled on a phospholipid membrane and cleaves prothrombin to thrombin. Thrombin is one of the most potent activators of primary (platelet-mediated) and secondary (clotting factor-mediated) hemostasis. Thrombin may also potentiate clot formation by fibrin polymerization, platelet receptor activation, endothelium activation, and activation of factors V, VIII, XI, and XIII. Anticoagulant agents can inhibit thrombogenesis by altering various pathways within the clotting cascade or by targeting thrombin directly, attenuating thrombin generation. Indirect inhibitors, however, target and bind to naturally occurring plasma cofactors, such as antithrombin (AT), catalyzing their interaction with clotting enzymes. The coagulation cascade is comprised of the intrinsic pathway and the extrinsic pathway. Each pathway generates a series of reactions in which inactive circulating enzymes and their co-factors are activated. These activated factors then catalyze the next reactions in the cascade. Thrombin plays a pivotal role by triggering the conversion of soluble fibrinogen to insoluble fibrin monomers, which serve as the foundation for thrombus formation. Thrombin also activates factors VIII, V, and XIII. Factor XIII generates the covalent bonds that link fibrin strands ensuring structural integrity. Anticoagulants, either through their interaction with antithrombin or through a direct inhibition of thrombin, interrupt these enzymatic reactions [4].

ANTICOAGULANTS

HEPARIN

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are the anticoagulants of choice in acute thrombosis due to their rapid onset of antithrombotic activity. Since heparins are dependent on the presence of AT for clotting factor inhibition, they are considered indirect anticoagulants [5,6,7]. Heparins have no fibrinolytic activity and will not lyse existing thrombi. Heparins contain an active pentasaccharide sequence that binds to AT. Once heparin binds and activates AT, it can readily dissociate and bind to additional AT, providing a continuous anticoagulant effect. This binding produces a conformational change, accelerating AT binding and inactivation of coagulation factors XIIa, IXa, XIa, Xa and thrombin. LMWHs eg., Enoxaparin, Dalteparin, Tinzaparin, are administered in fixed doses for thromboprophylaxis, or in total body weight adjusted doses for therapeutic anticoagulation [8].

Clinical indications for UFH/LMWH include treatment of acute coronary syndromes (ACS), treatment or prevention of venous thromboembolism (VTE) and bridge therapy for atrial fibrillation (AF).

FONDAPARINUX

Fondaparinux selectively and irreversibly binds to AT. This results in neutralization of factor Xa, which ultimately inhibits thrombin formation and thrombus development. Fondaparinux has been proven to be at least as safe and effective as treatment of deep vein thrombosis(DVT), VTE and pulmonary embolism [9].

DIRECT THROMBIN INHIBITORS (DTIS)

DTIs exert their antithrombotic effect through direct, selective, and reversible binding to the active site of thrombin. This leads to inhibition of thrombin-catalyzed or -induced reactions, including fibrin formation, activation of coagulant factors V, VIII, XIII, protein C, and platelet aggregation. The hirudin analogs, desirudin and bivalirudin, and argatroban are three currently approved DTIs [10]. Argatroban and bivalirudin are indicated as an anticoagulant for thrombosis

prevention in patients undergoing percutaneous coronary intervention (PCI). Bivalirudin is indicated for use as an anticoagulant in the treatment of patients with moderate to high-risk ACS, unstable angina/non-ST-segment elevation myocardial infarction who are undergoing early invasive management, and in patients undergoing PCI [11].

ORAL ANTICOAGULANTS–VITAMIN K ANTAGONISTS

Vitamin K antagonists produce their anticoagulant effect by inhibiting vitamin K epoxy reductase, which is required for the conversion of vitamin K to its active form vitamin KH2. Vitamin K dependant proteins such as clotting factors II, VII, IX, and X require γ-carboxylation by vitamin KH2 for biological activity.

Warfarin is effective for the primary and secondary prevention of VTE, for the prevention of systemic embolism in patients with prosthetic heart valves or AF, for the primary prevention of acute myocardial infarction in high-risk men, and for the prevention of stroke, recurrent infarction, or death in patients with acute myocardial infarction [12].

TARGET-SPECIFIC ORAL ANTICOAGU-LANTS

Dabigatran, rivaroxaban, and apixaban are novel oral anticoagulants that offer major advantages over current agents. They have rapid onset and more predictable anticoagulants response that eliminates the need for monitoring. They are used in the prevention and treatment of the three leading causes of cardiovascular death: myocardial infarction, stroke, and VTE.

Dabigatran etexilate mesylate is a prodrug. After oral administration, non-specific plasma and hepatic esterases hydrolyze the compound into the active anticoagulant, dabigatran [13]. Dabigatran is DTI that exerts its action through reversible, competitive binding to the active site on thrombin. Furthermore, dabigatran indirectly exerts an anti-platelet effect by reducing thrombin's impact on promoting platelet activation and aggregation [14].

Rivaroxaban is an oral, highly selective, direct, competitive inhibitor of factor Xa [15]. Inhibition of factor Xa leads to interruption of the both intrinsic and extrinsic coagulation pathways, thus preventing thrombin generation and subsequent thrombus formation. Apixaban is used in Stroke and systemic embolism prophylaxis in non-valvular AF.

FIBRINOLYTICS

The antithrombotic effect of fibrinolytics, which include tissue plasminogen activator (tPA) and urokinase, is achieved by inducing the conversion of inactive plasminogen into the active enzyme plasmin, which degrades the fibrin matrix responsible for stabilizing a thrombus [16]. Alteplase, reteplase and tenecteplase are the most commonly used drugs in this class [17]. Common uses of these drugs include the treatment of acute cerebrovascular accidents (CVA), myocardial infarction, pulmonary emboli, as well as to dissolve thrombi in indwelling catheters.

USES OF ANTICOAGULANT THERAPY IN ATRIAL FIBRILLATION

Atrial fibrillation is a condition where the atria or the upper chambers of the heart beat irregularly. This could result in clot formation in the atria that could travel to different organs and produce stroke and other complications [18]. Antithrombotic therapy with oral anticoagulant has been shown to lower the risk of clinical thromboembolism in virtually all patients with AF, including all levels of risk and irrespective of type (paroxysmal, persistent, or permanent) [19]. Anticoagulants given during and a few weeks after atrial fibrillation prevent embolus formation.

IN STROKE

Ischemic stroke is the most frequent clinical manifestation of embolization associated with AF. It can occur at any point during the clinical course of AF. Systemic and pulmonary thromboembolism also occur, but are less commonly recognized. As a result, chronic antithrombotic therapy with either anticoagulation

(ie, a vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitor) or antiplatelet therapy is considered for most of these patients. Both therapies are effective in preventing systemic embolization, although anticoagulant therapy is far more effective and preferred in all but the lowest-risk patients [20].

Absolute indications for oral anticoagulation (primary and secondary stroke prevention) include the following:

- Mitral valve stenosis with any prior embolic event
- Left atrial myxoma
- Intraventricular thrombus
- Ventricular aneurysm with thrombus
- Mobile thrombus in the ascending aorta
- Dilated cardiomyopathy

IN PATENT FORAMEN OVALE (PFO)

Oral anticoagulation is indicated for patients with a large patent foramen ovale (PFO) under 3 circumstances:

- Recurrent cerebral ischemia while the patient was receiving aspirin, 300 mg/day
- Co-occurrence of PFO with atrial septal aneurysm
- Co-occurrence of PFO with deep venous thrombosis of the leg or abdomen [21].

IN UNSTABLE ANGINA AND MYO-CARDIAL INFARCTION

A patient may develop chest pain due to blockage to the flow of blood. This condition is called angina. If a clot completely blocks the flow of blood, it could result in a heart attack. Anticoagulants used for a short time may be beneficial in patients with unstable angina and heart attack [22].

IN INFECTIVE ENDOCARDITIS

The use of anticoagulant therapy (ACT) in patients with acute infective endocarditis (IE) remains a controversial issue. However, discontinuation of warfarin in IE patients with high cardioembolic risk (e.g., prosthetic valve or atrial fibrillation) can increase the probability of intracardiac clot formation and further embolization. The role of ACT in the prevention of embolism was limited in IE patients undergoing antibiotic therapy, although it seems to reduce the embolic potential of septic vegetation before treatment [23].

IN DVT

Deep vein thrombosis (DVT) is usually the formation of a thrombus in the deep veins of the leg. This can be caused by major surgery, prolonged sitting or bed rest, pregnancy and obesity. If a blood clot forms in the legs it can travel to the lungs and cause pulmonary embolism (PE). Heparin and warfarin are two types of anticoagulants that are used to treat DVT. Chronic anticoagulation is critical to prevent relapse of DVT or PE following initial heparinization [24].

IN PULMONARY EMBOLISM

Pulmonary embolism is where a blood clot blocks/occludes the pulmonary artery (the blood vessel that transports blood from the heart to the lungs). Traditionally, DVT and PE treatment is initiated with a fast-acting parenteral anticoagulant overlapping with VKA therapy (such as warfarin) for long-term and extended use. Low molecular weight heparin (LMWH) is the parenteral treatment of choice for most patients, although fondaparinux and unfractionated heparin (UFH) are also options [25].

IN ARTIFICIAL MECHANICAL HEART VALVES

Patients with artificial mechanical heart valves are at risk of embolism and the risk is even greater if they suffer atrial fibrillation. Precise anticoagulation appears to be of value in reducing thromboembolism from prosthetic valves. The anticoagulants used to prevent valve thrombosis and thromboembolic events in patients with prosthetic heart valves are vitamin K antagonists (generally for long-term therapy) and heparin (mainly unfractionated or low molecular weight

heparin; generally for short-term bridging therapy) [26].

IN DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

DIC is characterized by systemic activation of blood coagulation, which results in generation and deposition of fibrin, leading to microvascular thrombi in various organs and contributing to multiple organ dysfunction syndrome (MODS). [27] Anticoagulants are used in the treatment of clinically evident intravascular thrombosis when the patient continues to bleed or clot 4-6 hours after initiation of primary and supportive therapy. Heparin is the only currently available antithrombotic drug that has a role in the treatment of patients with DIC [28].

SIDE EFFECTS

Possible side effect of anticoagulants include [29];

- Excessive bleeding
- dizziness, headaches
- rashes
- itchy skin
- hair loss
- jaundice

CONCLUSION

Thus, the various anticoagulants have been studied and employed extensively for prevention and treatment of thrombosis and further embolization. Novel oral anticoagulants have emerged from clinical development and are expected to replace older agents with their ease of use and more favorable pharmacodynamic profiles. Hemorrhage is the main concerning adverse event with all anticoagulants. With their ubiquitous use, it becomes important for clinicians to have a sound understanding of anticoagulant pharmacology, dosing, uses, monitoring, and toxicity. Working knowledge becomes crucial for intercepting and averting problems [30].

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