The Selection of Antithrombotic Agents in the Prevention of Recurrent Ischemic Stroke

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Introduction

The selection of an antithrombotic agent for prevention of ischemic stroke may be based on two principles: knowledge of the individual patient's pathology for thrombotic-thromboembolism, or application of the rules from evidence-based medicine. The former decision base is rooted in the causal connection of the thrombotic-thromboembolic process to the individual patient who is to receive treatment. The latter is group-based in statistical correlation and removed from the individual patient's unique pathologic context, but is of epidemiologic importance [1••].

Pathophysiology of Thrombosis

The current model for hemostasis is Virchow's triad [2••,3••]. This triad consists of a causal nexus of interacting elements in the patient's body; vascular lining or endothelium, blood components, and flow dynamics interact to maintain integrity of the vascular system. In health, these elements interact to protect the patient from harmful hemorrhage and thrombosis. When the normal interaction of these elements responsible for hemostasis is upset because of their imbalance, thrombosis, hemorrhage, or both occur. Platelet activation and blood coagulation are complementary interdependent processes in thrombosis, hemostasis, and hemorrhage [3••].

Traditionally, the choice of antithrombotic agents for stroke in the acute, subacute, and chronic phase has been based on the idea of prevention of ongoing or further thrombosis, and divided between antiplatelet agents and anticoagulants. Thrombolytic agents are used for the acute treatment of stroke. Certain clinical situations have been considered to demand one or the other type of treatment in the past. However, combination therapy does make sense given the proper underlying pathology. Because thrombosis is a profoundly intricate process of interacting elements of Virchow's triad primed for survival of the individual under conditions of hemostasis, this process must be set uniquely to each individual's physiologic-environmental context [3••,4••]. When pathology of the vascular wall, blood, and flow components exist, thrombosis may work against survival of the patient and antithrombotic agents are chosen to counteract this process, depending on the pathologic context.

Although platelets and coagulation are complementarily activated and interdependent in the thrombotic process [3••], thrombi have been traditionally divided into two types, white and red, depending on their composition [5•]. There is evidence that the formation of thrombus...
type may occur on a continuum. Antiplatelet agents have been considered the agents of choice for prevention of white thrombi, and anticoagulants the antidote to red thrombi. There are patients who may be appropriate for one or the other therapy, but it is possible that most patients may harbor underlying pathology, calling for the use of both antiplatelet agents and anticoagulants together for effective thrombus prevention.

White thrombi form in fast-moving arterial streams where the endothelium is damaged. Red thrombi are predisposed to form in areas of stasis. Red thrombi contain fewer massed platelets and fibrin but more erythrocytes; white thrombi contain cellular debris, platelets, and fibrin, and only a few erythrocytes. A recent laboratory model for the formation of a continuum of red and white thromboembolism has been described and used to study the susceptibility to thrombolyis of clot subtypes [5•]. Other in vitro models have shown that white thrombi retract more than red thrombi, resulting in reduced permeability of thrombolytic agents into the clot, and decreased intraclot plasminogen, with increased fibrin per unit clot. In one study [5•], the ratio of plasma and erythrocytes determined the softness and size of the thrombus, with red thrombi being soft and pliable, lodging deeper into the vascular tree than the rigid white thrombi of the same size. The length of vascular occlusion was longer with red thrombi, and there was a retraction factor that was far less for red thrombi than white; red thrombi are more susceptible to thrombolytic agents.

Clinical situations in which one would expect white clots to form are atherosclerotic vessels, damaged cardiac valve surfaces, damaged endocardium, vasculitides, and other types of pathology where the arterial stream moves fast and past damaged endothelium. This latter situation may also exist in a tightly stenosed arterial vessel, where one also finds the situation of stasis. Platelet-rich thrombi are also expected to form when there is a situation of platelet activation, such as when the patient has defined hyperaggregable platelets. Red thrombi are expected to be the predominant thrombus type when a cardiac chamber is dilated, or there is decreased chamber function of sufficient degree given the “coagulability” state of the blood, spontaneous echo contrast is found on transesophageal echocardiography (TEE), there is a focal wall dyskinesia or atrial septal aneurysm with or without patent foramen ovale, or frank intracardiac thrombus. Cardiac arrhythmias are thought to produce to stasis and predispose to thrombus via this mechanism, as well as changes in the endocardium. Tight arterial stenoses where pre- or poststenotic flow abnormality is found, or when venous thrombosis itself has occurred in the intracranial venous sinuses, and where intravascular thrombus exists with flow interruption, are all red thrombus situations. Thrombophilias are associated with red thrombus formation, but may interact with the arterial wall to accelerate an atherosclerotic process or with lesser degrees of stasis or endothelial damage to promote thrombus formation. It is clear that there are many clinically detectable pathologies known to increase the risk of stroke where it is likely that both types of thrombi do occur.

Precise knowledge of the underlying pathologic basis for thrombus formation in the patient predisposed to vascular occlusion and ischemic stroke depends on thorough diagnostic testing and expertise in managing all types of antithrombotic medications in many different patients and situations [2••]. Without the knowledge of the elements of Virchow’s triad in the given individual to be treated and as best as can be determined through diagnostic testing, there is no sound basis by which to base the choice of antithrombotic agents for stroke prevention [2••]. This is because the wise therapeutic decision is based on the underlying presumed causative mechanism of future thrombosis-thromboembolism in the individual patient. This depends on a thorough diagnosis [2••]. The direct goal of antithrombotic administration in all instances is to prevent thrombosis. The potential benefit of successful therapy is prevention of vascular occlusion and stroke.

Evidence-based Medicine and Recommendations for Antithrombotic Therapy

The evidence-based recommendations for antithrombotic therapy for stroke prevention may be found in the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy [6]. Present day academic medicine considers scientific only that body of evidence derived from the collective of patients and interpreted through probability-based statistical analysis [6]. Yet it is clear that each patient has his own unique physiologic-environmental context of an infinite number of variables that interact with the hemostatic mechanism. Clinical decisions involve the individual patient, a fact that presents a paradox to the clinician who is forced to take group-based evidence as a basis for decision for treatment [1••.4••]. Thus, without consideration for any unique individual’s pathologic context, and using outcome from stroke as the endpoint, evidence-based medicine can find no reason to use anticoagulants such as heparin for acute thrombotic stroke. Likewise, multiple large, randomized clinical trials have been performed in the hope of finding the correct dose of aspirin for all. The hunt for the correct dose of aspirin for recurrent stroke prevention has continued in spite of mounting evidence that each person responds to a single dose of aspirin differently and the active biologic marker for clinical efficacy is either unknown or has not been measured in any clinical trial to ensure active dosage per each individual in the group. The denial of heparin efficacy for anyone has occurred in spite of biologic plausibility and positive evidence from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [6] and other smaller trials for efficacy where the underlying pathology makes sense [7•,8].