Why Thrombin Generation? From Bench to Bedside

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Key Words

Hemostasis · Thrombin generation · Treatment

Abstract

Intervention for clotting and bleeding disorders is costly, and clear-cut regimens undefined. The margin of safety between hemostasis and thrombosis is narrow and unpredictable. The use of a laboratory test to help define therapeutic regimens, dissect effects of these treatments, and to differentiate them are clearly needed. The current state of the art of thrombin generation is ready to do this.

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It is always important to translate basic science and its relevance not only to the public but to the very scientists carrying out the research. Both bleeding and clotting disorders can be the result of genetic and/or acquired risk factors as well as being initiated, prevented, or treated by medications or replacement therapy. At present, we are at a loss in being able to predict if hemostasis can be reached or whether a thrombotic event will take place. These issues puzzle hematologists, hepatologists, cardiologists, and neurosurgeons, to mention a few.

Bleeding and clotting occurs either separately or concomitantly in patients with uremia, liver disease, neurosurgery and disseminated intravascular coagulation. When and how to intervene is art and needs to be closer to science. The management of hematologic bleeding diseases is worthy of focus, as they are universal, extraordinarily costly, with the bulk of patients with hemophilia untreated. These patients, appropriately managed, can be maintained in a healthy productive state. Thrombocytopenia, a common entity, has perplexed clinicians as we cannot predict, in varying clinical settings, what platelet count is safe and that bleeding will not occur.

Genetic bleeding disorders consume billions of units of clotting factor to maintain hemostasis, costing billions of dollars (US). However, despite hemophilia being one of the oldest diseases described, our clinical endpoints for achieving hemostasis are, in the main, subjective. Severe patients bleed spontaneously about 35 times per year. Ten percent of these severe patients behave as though they were mild. We have no clue as to why this happens and how we can predict it at birth before bleeding episodes begin. The relationship to thrombophilia genes is controversial and unresolved.

With the introduction of recombinant biologics, we have recognized significant differences in the bioequivalence of both factor (F) VIII and FIX products, as com-

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pared to human-derived factors as well as their recombinant counterparts. Prophylactic therapy for hemophilia patients has been a part of management for some patients for over 25 years. The spectrum of regimens ranges from therapy once per week to every other day. As treatment is on a weight basis, there are enormous implications for both consumption of biologics and costs to patients, insurers, or governments. There is as yet no consensus as to which regimens are better. We have no endpoint to assure us that we have achieved hemostasis with any of these varied regimens.

Surgical procedures demand prolonged therapy and consume large resources of institutions and biologics. For FVIII and FIX- and FXI-deficient patients, we do not know the lowest level of achieved factor that will ensure hemostasis. Currently, it is empiric and not based on clinical trials or markers of hemostasis.

In contrast, up to 35% of FVIII- and 5% of FIX-deficient patients develop antibodies within a short time after exposure to replacement therapy. These inhibitor (neutralizing) antibodies make achieving a measurable factor level impossible. This has led to the production of bypassing agents such as APCCs and rVIIa. Thus, one cannot predict outcome. In addition, they have both been associated with thrombosis, both venous and arterial.

Von Willebrand's disease, the most common inherited bleeding disorder, is manifested by both an inability to

form a primary hemostatic plug and an FVIII deficiency. Treatments with DDAVP and biologics are also complicated by thrombosis.

These clinical entities raise significant unanswered questions. What is the key ingredient to ensure hemostasis, and can we attain a true endpoint for hemostasis? These are clearly more than academic questions.

The evolution of thrombin generation to the present has now engaged the minds and laboratories of many investigators. Its acceptance as a research tool has arrived. Its reproducibility from laboratory to laboratory and standards are yet to be defined. But its use in understanding pathophysiology of disease is clear. The contribution of platelets, endothelium, and various components of coagulation proteins and their inhibitors are being investigated. Exogenous anticoagulants (vitamin K inhibitors as well as heparin, low-molecular-weight heparins, and antithrombins) are also being evaluated.

It is clearly time to put this technique to use in understanding whether our current practices are correct or need to be modified. We need to understand the frequent narrow margin of safety our therapeutics provide between hemostasis and thrombosis. Will we be able to tailor therapy so we achieve our goals and potentially conserve our resources? The patients and treaters eagerly await the application of thrombin generation to help unravel these issues. Let the experiments go forth!