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Update on the Management of Bleeding Disorders Using Activated Recombinant Factor VIIa

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Recent evidence suggests that the normal clotting mechanism involves the initiation of coagulation with the tissue factor/factor VIIa complex (TF/VIIa). This complex first activates factor X and factor IX in the vicinity of the tissue factor-bearing cell. The factor Xa that is generated in this manner forms a complex with factor Va and, as a result, a very small amount of thrombin is generated around the TF cell. The amount of thrombin is insufficient to clot fibrinogen but is sufficient to: 1) activate platelets; 2) activate the co-factors, factor V and factor VIII; 3) activate factor XI and separate factor VIII from von Willebrand factor.

This “priming” dose of thrombin is very important in the initiating event. The factor IX activated by the tissue factor/factor VIIa complex does not remain in the vicinity of the TF cell but rather binds to the activated platelet so as to form a complex with factor VIIIa. As a result, this complex activates factor X on the surface of the platelets, which when in complex with its co-factor, Va, finally results in a burst of thrombin generation sufficient to clot fibrinogen and activate the thrombin-activatable fibrinolytic inhibitor (TAFI).

Excessive hemorrhage occurs when the normal clotting mechanism is altered. Deficiencies in the normal clotting process can be either hereditary or acquired. Deficiencies of any of the soluble clotting factors result in a form of hemophilia, for example, classic hemophilia, hemophilia B, factor XI deficiency, and so forth. There is now excellent treatment for factor VIII and factor IX deficiencies. These can now be treated with specific purified factor VIII or factor IX, respectively. However, in

the hemophilia A or hemophilia B patients who develop inhibitors, factor VIIa has been found to be of great benefit.

This is because factor VIIa can generate sufficient thrombin to augment hemostasis even in the absence of factors VIII and IX. Interestingly, factor VIIa has also been found to be extremely effective in other hereditary clotting factor deficiencies such as factor XI deficiency and factor VII deficiency. Factor VIIa has also been reported to be at least partially effective in factor V and factor X deficiency, even though these reports are rare and in most cases patients have not been severely affected.

Recombinant factor VIIa has also been found to be of benefit in acquired bleeding disorders, including those associated with injury, trauma, renal insufficiency, and a number of other conditions. Acquired bleeding disorders resulting from surgery and trauma usually result in “dilutional coagulopathy,” associated not only with low levels of soluble clotting factors but also thrombocytopenia and increased fibrinolysis. Factor VIIa has been found to be of benefit in both of these instances. Recent evidence from a clinical trial carried out in Europe and South Africa indicate that factor VIIa is effective in controlling bleeding in patients with trauma who are unresponsive to conventional therapy. The results of this trial will be discussed.

In addition, the mechanism of action of VIIa will also be discussed.

There are currently two main schools of thought regarding the mechanism of action. One is that factor VIIa can activate factor X in the absence of tissue factor; the other suggests

that the main action of recombinant factor VIIa is through the tissue factor mechanism. Recent results from our laboratory indicate that both mechanism are operative but that at pharmacological doses of recombinant factor VIIa, the direct activation of factor X by factor VIIa does plays a major role in increasing thrombin generation and accounts for the dose-response relationship.