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Emerging Off-Label Uses for Recombinant Activated Factor VII: Grading the Evidence

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Recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) is currently licensed in the United States for treatment of bleeding episodes in patients with deficiencies of factor VIII (FVIII) or IX (FIX) who are refractory to factor replacement because of circulating inhibitors. A 1999 report of its successful use to stop what was deemed to be lethal hemorrhage after an abdominal gunshot wound in a young soldier without pre-existing coagulopathy [1] has prompted exploration of other uses for rFVIIa. The virtual explosion of proposed uses of rFVIIa raises issues not only regarding our understanding of the coagulation system, but also regarding its efficacy, cost-effectiveness, and safety.

Recombinant FVIIa is a genetically engineered protein produced in cultured baby hamster kidney cells that is nearly identical to human plasma-derived FVIIa in structure and function. Where available, its use is rapidly replacing the use of activated prothrombin complex concentrates (APCCs) in the treatment of hemophiliac patients because of the decreased risk of viral transmission and the virtually absent risks of transfusion reaction, fluid overload, HLA antibody formation, and anaphylaxis compared with APCCs.

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Background

In addition to providing a new and highly efficacious treatment for hemophiliacs with inhibitors, rFVIIa has prompted a re-evaluation of our understanding of the coagulation system. Initially modeled in the 1960s as a cascade, two sequential series of reactions, the extrinsic (tissue factor/FVIIa-initiated) and intrinsic (FXII-initiated) pathways, share a common final pathway that culminates in the conversion of prothrombin to thrombin. Although this model provided an adequate explanation of the standard screening coagulation tests, prothrombin time (PT, a measure of the extrinsic pathway) and activated partial thromboplastin time (aPTT, a measure of the intrinsic pathway), it fails to explain some clinically observed problems such as hemophilia [2].

The coagulation cascade remodeled

Hoffman [2] has proposed a cell-based model of coagulation in which the reactions of the coagulation cascade take place in a cell-specific fashion and in three distinct but overlapping phases: initiation, amplification, and propagation. This process requires the participation of a tissue factor (TF)-expressing cell (usually found outside the vasculature and exposed upon endothelial injury) and platelets.

The initiation phase requires TF, thereby limiting the initiation of coagulation to the site of endothelial injury. FVII forms a complex with TF. The TF/VIIa complex cleaves FX to FXa, which binds to FVa on the surface of the TF-bearing cell. This Xa/Va complex cleaves prothrombin to thrombin, which is crucial in platelet activation, in releasing circulating FVIII from von Willebrand factor, and in activating FIX. The presence of inhibitors of FXa (tissue factor pathway inhibitor [TFPI]) effectively localizes this reaction to the surface of the TF expressing cell. However, the TF/FVIIa complex also activates FIX to FIXa, which is able to diffuse to activated platelets.

The amplification phase occurs on the surface of activated platelets binding to exposed collagen at the site of injury. Thrombin-activated platelets express surface binding sites (aka as PF3) for the tenase (FVIIIa/FIXa) and prothrombinase (FXa/FVa) complexes. The tenase complex is initially formed in part from FIXa, which has diffused from the TF-bearing cell in the initiation phase, but the initiation phase is rapidly inhibited by TFPI. The tenase complex generates FXa, which moves directly into complex with FVa to form the prothrombinase complex. This complex, in turn, generates the thrombin necessary to form enough fibrin to stabilize the platelet clot [3]. The clot becomes more resistant to fibrinolysis with increasing concentrations of fibrin. While TFPI modulates the activity of the TF/FVIIa complex, antithrombin and the protein C/S system modulate the activity of factors IIa, Xa, IXa, XIa, and Va and VIIIa, respectively.