

Recombinant Factor VIIa and its Clinical Applications

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More than 13 years ago, the Food and Drug Administration (FDA) approved the use of recombinant human coagulation factor VIIa (rFVIIa) for hemorrhage control in hemophilia A and B patients. Since that time, it has been administered in multiple situations other than those associated with hemophilia to achieve hemostasis. The rFVIIa is now being studied for its role in hemorrhage control of trauma patients with normal clotting factors. The U.S. military shares this interest and has been reviewing this pharmaceutical for possible future applications as a lifesaving tool for its front line troops.

Introduction

The pharmaceutical rFVIIa was approved by the FDA over 13 years ago as a hemostatic agent for use in hemophilia A and B patients. This medication has proven to be an important addition in the treatment of these hemophiliacs. Not only has rFVIIa been useful during bleeding episodes but it has also allowed these individuals to successfully receive high-risk surgical procedures where bleeding sequela would have probably led to mortality.

This medication has also been administered in many situations other than those associated with hemophilia A and B. This off-shelf use has grown in frequency and new applications are continually being described. The rFVIIa is now being studied for use in trauma patients who have normal clotting factors. This use has interested the U.S. military. The medication is now being reviewed for a possible future role as a lifesaving tool for front line troops.

To fully understand the clinical applications of this medication, a review of the clotting cascade should be completed. This review will make clearer the reasons why many consider rFVIIa a universal homeostatic agent.

The Clotting Cascade

At a glance, the clotting cascade follows this sequence: (1) formation of prothrombin activator; (2) prothrombin activator converts prothrombin (factor II) into the enzyme thrombin; (3) thrombin converts soluble fibrinogen (factor I) to insoluble fibrin, the structural basis for clot formation and our final goal of homeostasis. The initial formation of prothrombin activator occurs through both intrinsic and extrinsic pathways of blood clotting.

Intrinsic Pathway

The intrinsic pathway is concerned with homeostasis due

to damage within (intrinsic) blood vessels. When veins or arteries are damaged through some traumatic event, a protein called tissue factor (TF or factor III) is released. The TF is also known as thromboplastin and is found on the subsurface of the endothelial cells, which line these blood vessels. The TF is also located in cellular monocytes that circulate within the blood. The release of TF initiates clotting. This protein activates factor VII (FVIIa). Factor VII is normally found in circulating blood. Tissue factor and FVIIa then react with calcium ions and platelet phospholipids to activate factors IX and X. Factor X, now activated (FXa), produces small amounts of thrombin. This thrombin activates platelets and cleaves FV and FVIII. Factor VIIIa combines with FIXa, which activates X at a 50-100 fold increased rate than its formation after the TF and VIIa complex. Factor Xa with FVa and the proper membrane surface form together prothrombinase complex. Prothrombinase is then responsible for prothrombin production. This completes the intrinsic pathway of the clotting mechanism.

Extrinsic Pathway

The extrinsic pathway contains fewer steps than the intrinsic pathway. With fewer steps to proceed through, time is lessened with this cascade. When tissue is damaged outside the vascular system, the release of TF occurs, as seen in the intrinsic pathway. This TF is found on the surface of all cells of the body. Higher concentrations of this protein are located on the surface of intestinal, lung, and brain cells. The TF protein then converts FVII into an activated form. Activated factor VII then combines with FX, activating it. Factor Xa then reacts with FV and calcium ions to produce prothrombin activator. This completes the extrinsic pathway.

Common Pathway

The intrinsic and extrinsic pathways then converge into a common pathway. This pathway uses the prothrombin activator, with the addition of more calcium ions to convert prothrombin to thrombin. The thrombin next activates factors

VIII, V, XI, and platelets. These platelets change morphology to expose negatively charged phospholipids. These lipids, along with FVIII and FXI, become a template for the production of large quantities of thrombin.

In the final steps, thrombin, in the presence of calcium ions, converts soluble fibrinogen to insoluble fibrin. Thrombin also activates FXIII to stabilize the fibrin clot. Another effect of thrombin is to act as a positive feedback mechanism thus accelerating the production of more prothrombin activator.

How Does rFVIIa Work?

The rFVIIa works by supporting the normal pathway of the clotting cascade. Although we will now describe this reaction, the specific mechanism of this pharmaceutical and its results are not yet fully understood.

When TF is released from the sub-endothelial level of a blood vessel (intrinsic pathway) that has been injured, rFVIIa binds with it to begin the production of thrombin and fibrin deposition through the normal clotting cascade. In addition, thrombin affects platelets, inflammatory cells, and endothelium, all of which aid in the processes of homeostasis and inflammation.

It is also stipulated that the increased levels of rFVIIa compensate for decreased levels of platelets by stimulating additional nearby platelets to activate, which in turn, enhances platelet aggregation. This is proposed because increased levels of rFVIIa have shown to activate higher levels of FIX and FX, which then induce a thrombin burst. This burst facilitates a decreased time to fibrin clot, by activating platelets, which circumvents part of the intrinsic pathway of coagulation.

Lastly, it has been postulated that the fibrin plug formed by rFVIIa is stronger and more persistent than one that would be constructed in a heavily transfused patient. These individuals may have less effective thrombin due to the storage and age of the blood product given, thus forming a weaker plug.

The rFVIIa also promotes the extrinsic pathway of the clotting cascade. This is done in the presence of TF where it again binds to and begins the clotting mechanism. The start of this pathway also includes the activation of FIX and FX. This again induces a thrombin burst and the faster and stronger formation of fibrin clots at the site of injury.

The rFVIIa is structurally similar to FVIIa. This medication is derived from using the human gene for FVII, which is cloned by placing it in baby hamster kidney cells (BHK cells). The rFVII is then removed in its single-chain form and grown on a media, which contains newborn calf

serum. Using autocatalysis, it is developed into a two-chain form. A purifying process to remove all possible contaminants is then undertaken. The final product is supplied in a single-use vial as a white sterile powder ready for reconstitution. This pharmaceutical is a vitamin K dependent glycoprotein consisting of 406 amino acid residues. The vials come in the following volumes: 1.2 mg, 2.4 mg, and 4.8 mg.¹

This pharmaceutical is expensive. Approximate costs for the three volume vials are as follows: 1.2 mg (\$1,764.00), 2.4 mg (\$3,500.00), and 4.8 mg (\$7,000.00).

The rFVIIa must be kept refrigerated at 2-8°C / 36-46°F. Its pregnancy category is C and is contraindicated in patients with known hypersensitivity to mouse, hamster, or bovine proteins. Lastly, the package insert suggests dosing at 35-70 mcg/kg with evaluation for repeat dosage in 2.5 hours.

Shelf Use

The FDA-approved rFVIIa for use in the treatment of uncontrolled bleeding in individuals diagnosed with hemophilia A or B. These hemophiliacs have inhibitory antibodies against FVIII and FIX, which limits generation of thrombin. Platelets are able to increase production of thrombin when increased FVIIa is present. Normally FVII is found at 0.2 nM concentrations in the blood. When this is increased to 150 nM, thrombin generation appears at the level equal to those without any factor deficiencies. The rFVIIa has been used in patients with Hemophilia A or B during bleeding episodes, intracranial bleeds, joint bleeding, in the treatment of deep vein thrombosis, and liver disease.²⁻¹⁴ It has also been useful in the management of those patients during surgical procedures. Some of these procedures include orthopedic surgeries, elective surgery to correct retroperitoneal fibrosis and hydronephrosis, synovectomy, surgical treatment for gastric cancer, emergency placement of a central line, cataract surgery, and for the formation of a spinal epidural hematoma.¹⁵⁻²⁸

In hemophiliacs, the early use of this pharmaceutical by home administration has now been reported.²⁹⁻³² These reports demonstrate its safety, efficacy, and cost-effectiveness when used in this role.

Other Uses

Although designed specifically for the treatment of hemophilia A and B, rFVIIa has also been used many times in medical settings outside of this arena. This off label use has been increasing for a variety of conditions.

Some documented off label uses include the correction of hemostatic abnormalities related to liver disease/platelet defects

such as Glanzmanns thrombasthenia, Bernard-Soulier syndrome and type III von Willebrand's disease, reversal of oral anticoagulants, in Sever thrombocytopenia, and in dental extractions in cirrhotic patients.³³⁻⁴⁴ It has also been shown to have a use in treating intercranial hemorrhaging and severe uremic bleeding.⁴⁵⁻⁴⁸ In surgical procedures when the repeated use of blood products has failed to acquire reasonable hemostasis, rFVIIa again has proven its effectiveness. Some of these surgical procedures include interabdominal cases, orthopedic cases, liver transplants, in patients following bone marrow transplants, and bleeding associated with acute renal failure.⁴⁹⁻⁵⁸ This pharmaceutical has also been administered with success during heart procedures. These include intractable bleeding related to valvular repair, closure of atrial septal defect, De Vega's procedure, transposition of the great vessels, in support of bleeding abnormalities in patients with left ventricular assist devices, and during a transected aortic repair (author's own experience).⁵⁹⁻⁶³ In addition and not surprising, rFVIIa has been used in patients with antibodies against FVII.^{50, 64-67}

Adverse reactions identified after the administration of this pharmaceutical as of February 2001 include: 16 decreased therapeutic responses, 17 cardiovascular events of which seven were myocardial infarctions, six cerebrovascular events, six cases of venous thrombosis/thrombophlebitis, and one disseminated intravascular coagulation event. Seventeen of these patients died from reactions to this medication. It was also determined that eight individuals who were identified in this data may not have had a side effect caused by the administration of this medication. These responses were the total from an estimated 171,790 doses sold.⁶⁸

Use in Trauma Patients

In the past, rFVIIa has also been administered with success in trauma patients who were in hemorrhagic shock. Case reports concerning a 24-year-old female suffering from six stab wounds and a 19-year-old Israeli Soldier who was shot in the inferior vena cava have cultivated much attention.^{69,70} This interest led to studies using swine that received deliberate traumatic liver injuries.^{71,72} The reports generated from these studies demonstrated a decrease in mortality in the first hour (golden hour) and prolonged survival rates, compared to placebo groups, when rFVIIa was used. The data also demonstrated its safe use in swine. The information did support possible future uses in trauma patients when hemostasis cannot be achieved in preparation for surgical intervention. There is some concern of thrombotic events when trauma patients suffering blunt injuries or fractures are administered this medication. Additional studies need to be conducted to determine safe use in these types of insults.

rFVIIa and the Military

The U.S. military is also looking closely at the use of rFVIIa for a role in support of its combat forces. Studies have reported that from 50% to 70% of the trauma patients in urban settings who died, did so as a result of uncontrolled hemorrhage. These numbers are higher, from 80 % to 90%, when studying combat deaths related to the Vietnam War.⁷¹ Much of these injuries were torso in nature and at locations where direct pressure could not be administered in hopes of achieving hemostasis. Data is currently being collected to identify protocols for rFVIIa use to include when to administer and at what dose regiment. A Standard Operating Procedure, on the following page, by the U.S. Army Institute of Surgical Research, Fort Sam Houston, TX, was included to outline their views in rFVIIa administration, and suggests an initial dosing of 120 mcg/kg intravenous bolus.

If studies continue to be positive, the military may wish to have this lifesaving product carried by its front line providers. Unfortunately, the price of this medication is an issue, along with the need for temperature control, as is typical for many medications used during field operations.⁷³ Discussions are ongoing between the manufacturer and the U.S. Army in an attempt to rectify some of these concerns. I have been told that our forces do have this product in some of the Level 3 medical facilities located in Iraq, however, I am not aware of its clinical use there. Lastly, the FDA is considering the approval of a prospective human trial. With use of this medication being considered in multiple clinical settings, it is not surprising that some are looking at rFVIIa as a universal hemostatic agent.^{40,62,74,75}

Conclusion

The role of rFVIIa has varied greatly since its approved use by the FDA 13 years ago. The initial use was for hemorrhage in hemophilia A and B patients. Since that time it has been found to be safe and effective in multiple situations gaining a status in some circles as a universal hemostatic agent. The next step for this medication may go beyond its current off label use as a pharmaceutical administered as a "bail out" when multiple transfusions of blood products have failed to achieve acceptable hemostasis. A protocol, which might eliminate the initial infusion of multiple blood products before rFVIIa is used, could be imagined. This would decrease the percentage of reactions and transmitted viruses associated with repeated transfusions. Also, it would circumvent depletion of bloodstocks by some of the bigger trauma cases. As research and dialogue continues over the use of this medication, it is important for all providers to understand its limitations and situational applications.

Standard Operating Procedure for Use of Recombinant Factor VIIa

1. **Background:** Recombinant factor VIIa is FDA approved for use during critical bleeds or surgery in hemophilic patients with inhibitors to FVIII or FIX. Recently, FVIIa has been shown to decrease transfusion requirements in humans with life-threatening hemorrhage including patients with hypothermia (30-33 degrees centigrade, pH 6.99-7.2) In the forward surgical setting, rFVIIa should be considered for administration in patients that require damage control maneuvers in the presence of poorly controlled hemorrhage.

2. **Mechanism:** Recombinant factor VIIa is activated in combination with tissue factor at sites of endothelial injury. High doses of FVIIa result in the accelerated generation of thrombin. The resulting clots are stronger and more resistant to fibrinolysis than normal clots. The potential effectiveness of rFVIIa degrades with time in the patient with poorly controlled hemorrhage due to platelet and coagulation factor consumption. These patients may require clotting factors and platelet supplementation prior to administration of FVIIa. In the forward surgical setting this supplementation is available by the administration of fresh whole blood.

3. Guidelines for administration in the forward surgery setting:

a. Consider use in patients undergoing damage control procedures, those with coagulopathic bleeding, difficult to control bleeding associated with hypothermia or significant pelvic hemorrhage.

b. Consider administration of 2 units of fresh whole blood before giving rFVIIa in patients with possible depletion of clotting factors and/or platelets.

c. Dose is 120 ug/kg intravenous push.

d. Consider re-dosing at 20-60 minutes if hemorrhage continues.

e. Consider administration of 2 units of fresh whole blood if bleeding not controlled with the initial dose of rFVIIa. This should serve to replenish the platelets and fibrinogen in the coagulopathic patient.

f. Application of fibrin sealant to site of hemorrhage may be useful after hemorrhage is controlled due to the relatively short half-life of rFVIIa (2 hours).

4. Storage:

a. Refrigeration at 4 degrees centigrade (range 2-8 degrees centigrade).

b. Reconstitution is with sterile water for injection at room temperature.

c. The reconstituted solution may be used up to 3 hours after reconstitution.

5. **Contraindications:** The use in patients with known atherosclerotic disease is a relative contraindicated.

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