

Possible Anaphylaxis Due to Recombinant Factor VIIa Administration During Thoracic Aortic Surgery

To the Editor:

This letter reports the possibility of an anaphylactic reaction to recombinant factor VII activated (rFVIIa; NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) administered during thoracic aortic surgery for the management of severe coagulopathy. To the best of the authors' knowledge, this possibility has not been reported in patients undergoing thoracic aortic surgery.

The patient was a 69-year-old man who presented with an acute Stanford type-A aortic dissection that commenced at the sinotubular junction and extended into the abdominal aorta. He had no known allergies. The aortic root architecture was preserved, with normal function of the native aortic valve. According to the Penn classification of acute type-A dissection, the patient's clinical presentation was complicated by malperfusion, as evidenced by severe abdominal pain and a cold extremity.¹

The surgical procedure consisted of replacing the ascending aorta while on cardiopulmonary bypass with a period of deep hypothermic circulatory arrest (DHCA) for an aortic arch replacement. Because of extensive dissection of the arch and all three brachiocephalic arteries, a total aortic arch replacement was required, with antegrade cerebral perfusion during the DHCA period. This complex thoracic aortic repair required a cardiopulmonary bypass time of 5.5 hours and a DHCA time of 100 minutes. The details of the DHCA protocol have been reported previously.²

After successful separation from cardiopulmonary bypass, the severe coagulopathy persisted after heparin reversal. This coagulopathy proved refractory to a protocol-based intervention with aminocaproic acid, desmopressin, and a transfusion of platelets, cryoprecipitate, and fresh frozen plasma.² At this point, because of the refractory coagulopathy, rFVIIa was administered intravenously at a dose of 90 $\mu\text{g/kg}$ to gain hemostasis, as has been reported previously.³

Approximately 30 seconds after the administration of the rFVIIa, the patient developed acute severe systemic vasodilation complicated by cardiac arrest. Complete circulatory recovery followed within 3 minutes because of direct cardiac massage and intravenous epinephrine (150 μg total). There was no evidence of cutaneous erythema or acute bronchospasm during this episode. Immediate echocardiographic assessment showed no thrombus in the aorta or cardiac chambers and no new regional wall motion abnormalities to suggest an acute coronary thrombosis.

The remainder of the intraoperative course was uneventful. Hemostatic control was achieved after the administration of rFVIIa. The patient remained hemodynamically stable and was admitted to the cardiac and vascular intensive care unit, with no further complications.

Although rFVIIa is an effective hemostatic adjunct for the management of life-threatening coagulopathy after the surgical repair of an aortic dissection, this application remains off label.³ The risk of clinical thrombosis in this setting has been

described, suggesting that rFVIIa therapy be reserved for rescue from life-threatening coagulopathy.⁴

Anaphylaxis may present as a sudden and isolated acute circulatory collapse.⁵ The authors' working diagnosis was anaphylaxis because of this acutely vasoplegic presentation within moments after the intravenous administration of rFVIIa. In support of this diagnosis was the rapid recovery after prompt therapy with epinephrine. Although a circulatory collapse because of acute thrombosis has been described in this setting, this syndrome is characterized by a large clot burden in the aorta or cardiac chambers.⁶ This diagnosis was excluded rapidly by transesophageal echocardiography.

Although anaphylaxis to recombinant factors VIII and IX has been reported in hemophiliacs, this possibility for rFVIIa has, to the best of the authors' knowledge, not been reported.^{7,8} A detailed review of the rFVIIa production process shows that this recombinant molecule has potential triggers for anaphylaxis.

According to the package insert (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark), the gene for rFVIIa is cloned and expressed in hamster kidney cells. The rFVIIa protein is secreted into culture media containing calf serum. Commercial rFVIIa is supplied as a lyophilized powder. It is reconstituted with a histidine solution in water immediately before administration. Consequently, rFVIIa contains trace amounts of animal proteins derived from this production process. The antigenic production process for rFVIIa may explain the potential for anaphylaxis to this protein.

In summary, hemodynamic collapse after the administration of rFVIIa may be characterized by acute vasoplegia. It responds to titrated epinephrine and likely is an anaphylactic reaction. Further research is required to confirm this hypothesis and to investigate the mechanisms of this life-threatening syndrome associated with rFVIIa.

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