

Successful Desensitization Protocol in an Infant Following Anaphylaxis Secondary to Recombinant Factor VIIa

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Background: Recombinant factor VIIa (rFVIIa) is a highly purified recombinant protein. It is approved for the treatment and prevention of bleeding episodes associated with congenital factor VII deficiency, congenital hemophilia with inhibitors, and Glanzmann's thrombasthenia. The most commonly reported adverse events are thrombolytic in nature. In this report, we present a successful desensitization protocol administered to an infant with a history of anaphylaxis to rFVIIa.

Case: A male infant with a history of gingival bleeding at the age of 6 months was diagnosed with factor VII deficiency with a factor VII level of 1%. His sister also had diagnosis of factor VII deficiency. Our patient was hospitalized at 10 months of age with generalized petechiae and bloody stools. Twenty minutes after administration of rFVIIa, he developed anaphylaxis that responded to epinephrine and supportive care. Subsequently he was evaluated at the allergy clinic, where a skin prick test with rFVIIa was negative. However, the intradermal skin test, applied with 1/1,000 (1 µg/1 mL, 0.1 mL) dilution of rFVIIa, showed induration of 8 mm (positive reaction). Because there is no alternative treatment for factor VII deficiency, we developed a successful 13-step desensitization protocol with rFVIIa (NovoSeven®). Desensitization was performed an additional 2 times using the same protocol, one of which was for a head injury and the other for a swollen knee since the period between the doses was ~3 months.

Conclusion: Allergic reactions, such as anaphylaxis can occur without prior exposure. This can be due to the high molecular weight and structural property of the biological agent. In this report, we present an effective desensitization protocol for an infant with a history of anaphylaxis to rFVIIa. Desensitization protocols in this age group should be carried out in a medical facility and with specialized staff and equipment prepared to care for anaphylaxis.

Keywords: desensitization, drug allergy, factor VIIa

Introduction

FACTOR VII DEFICIENCY is the least common of the coagulation defects.¹ It may cause fatal intracranial hemorrhage during a patient's lifetime.^{2,3} The ideal replacement therapy for factor VII deficiency is the administration of recombinant factor VIIa (rFVIIa) concentrate (NovoSeven®).⁴ rFVIIa concentrate is also used for the treatment of bleeding episodes and prevention of bleeding in adults and children who have congenital hemophilia with inhibitors or Glanzmann's thrombasthenia.⁵⁻⁷

Serious adverse reactions to recombinant factor VII include thrombosis, pain, thrombophlebitis, pulmonary embolism, decreased therapeutic response, cerebrovascular disorder, angina

pectoris, disseminated intravascular coagulation, anaphylactic shock and abnormal hepatic function. There have been no confirmed reports of inhibitory antibodies against rFVIIa or FVII in patients. rFVIIa (NovoSeven RT, Novo Nordisk A/S, Bagsvaerd, Denmark) is a highly purified recombinant protein. Hypersensitivity reactions, including anaphylaxis,⁷ may occur. Croteu et al. reported a total of 285 adverse drug reactions (including pyrexia, pain, nausea, pruritus, headache, vomiting, decreased therapeutic response, rash, hypertension, edema, and increased body temperature), which are considered to be related to the administration of rFVIIa in 88 pediatric patients.⁸

Adverse drug reactions are an important clinical problem for children.⁹ Drug desensitization is defined as the induction

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of a temporary state of clinical unresponsiveness to a compound responsible for a drug allergy.¹⁰ The desensitization procedure should always be considered when the offending drug is essential and there are either no alternative treatments or those that are available are unsatisfactory. It should be remembered that the tolerance induced by desensitization is temporary. Desensitization is performed in individuals with a history of immediate anaphylaxis when the patient's medical condition warrants administration of the offending agent. For delayed reactions, European Academy of Allergy and Clinical Immunology (EAACI)-Drug Allergy Interest Group (DAIG)/European Network for Drug Allergy experts recommend desensitization only for uncomplicated exanthems or fixed drug eruptions.¹¹ There are several cases of successful administration of desensitization in the literature for antibiotics, antiepileptics, biologic agents, and antithymocyte globuline.¹²⁻¹⁴

In this report, we present a successful desensitization protocol used in an infant with rFVIIa allergy.

Case Presentation

A 6-month-old boy, born to unrelated parents at 38 weeks gestation, was admitted to hospital with a history of gingival bleeding and was diagnosed with factor VII deficiency with a factor VII level of 1%. His sister also had factor VII deficiency. When he was 10 months old, he was admitted with a generalized petechial rash and bloody stool. rFVIIa was used for the first time. Twenty minutes after administration he developed confusion, tachycardia, and periorbital edema. His symptoms resolved after the administration of intramuscular adrenaline for anaphylaxis. Results of the cranial-computerized tomography, performed to evaluate the possibility of intracranial bleeding, were normal. Corticosteroids and antihistamines were also administered. The following day, he was treated with tranexamic acid, after which there were no bloody stools and he was discharged. He had no prior history of allergic symptoms or disease (sneezing, cough, respiratory distress, asthma, urticaria, runny nose, etc.). There was no history of allergy in his family and no inhibitor was detected against factor VII.

He was referred to our clinic for the evaluation of rFVIIa allergy. We performed a skin prick test, which was negative. The result of the intradermal skin test, which was performed using 0.02–0.05 mL of 1/1,000 (1 µg/1 mL, 0.1 mL) dilution of rFVIIa, was positive with a wheal diameter of 8 mm. The

positive control was histamine (10 mg/mL), and the negative control was 0.9% sodium chloride. In laboratory tests, the total serum IgE level was found to be 27.9 IU/mL (reference range: 2–34 IU/mL). The aeroallergen sIgE-phadiatop and food panel (fx5; wheat, egg, cow's milk, soya, peanut, and fish) were negative. Skin prick test for cow's milk was negative.

Two months later, he was admitted to the pediatric hematology clinic with restlessness and agitation. The physical examination was normal, but the stool examination was positive for blood. Desensitization was performed for the first time. Total dose of rFVIIa was calculated to be 410 µg for the patient who weighed 13.5 kg (calculated by 30 µg/kg/dosage). Three different solutions (A, B, and C), with 3 different drug concentrations, were prepared with 0.9% NaCl. Solution A was 1/1,000 diluted, solution B was 1/100 diluted, and solution C was 1/10 diluted.

Premedication regimen was not given to the patient before the desensitization protocol. Desensitization was started with 1/1,000 dilution 1 mL (0.001 mg) rFVIIa intravenously, and the dosage was increased in 20-min intervals by 1/1,000, 1/100, 1/10 dilutions, respectively. A 13-step desensitization protocol was performed using an initial dose of 0.001 mg followed by incremental doses administered at 20-min intervals over a course of 4 h. Solution A was used in steps 1–4, solution B in steps 5–8, and solution C in steps 9–14 (Table 1).

He was monitored during the desensitization period. His body temperature, respiratory rate, heart rate, and blood pressure were recorded every 30 min. There were no problems during the desensitization procedure, and the same doses were applied the following days.

rFVIIa desensitization was performed 2 more times using the same protocol, one of which was for a head injury and the second for a swollen knee because the period between the doses was ~3 months.

Discussion

Drug hypersensitivity reactions (DHRs) are adverse effects of drugs. DHRs are currently increasing with the widespread use of new therapeutic agents.

In the absence of an alternative therapeutic option, desensitization is considered for individuals with severe hypersensitivity reactions.¹⁵ It is performed with the administration of increasing doses of the medication until the cumulative therapeutic dose is achieved and a temporary hyporesponsive state

TABLE 1. THIRTEEN-STEP DESENSITIZATION PROTOCOL FOR 30 µg/KG DOSE (410 µg) OF RECOMBINANT FACTOR VIIa

Administration time, min	Solution type	Step of dosage	Solution dose, mL (mg)	Cumulative dose (mg)	Tolerance
0	A (1/1,000)	1	1 mL (0.001 mg)	0.001	Tolerated
20	A (1/1,000)	2	2 mL (0.002 mg)	0.003	Tolerated
40	A (1/1,000)	3	3 mL (0.003 mg)	0.006	Tolerated
60	A (1/1,000)	4	4 mL (0.004 mg)	0.01	Tolerated
80	B (1/100)	5	0.5 mL (0.005 mg)	0.015	Tolerated
100	B (1/100)	6	1 mL (0.01 mg)	0.025	Tolerated
120	B (1/100)	7	1.5 mL (0.015 mg)	0.04	Tolerated
140	B (1/100)	8	2 mL (0.02 mg)	0.06	Tolerated
160	C (1/10)	9	0.25 mL (0.025 mg)	0.085	Tolerated
180	C (1/10)	10	0.5 mL (0.05 mg)	0.135	Tolerated
200	C (1/10)	11	0.75 mL (0.075 mg)	0.21	Tolerated
220	C (1/10)	12	1 mL (0.01 mg)	0.31	Tolerated
240	C (1/10)	13	1 mL (0.01 mg)	0.41	Tolerated

is induced.¹⁰ It should be reserved for selected cases because it is a treatment modality that involves the risk of anaphylaxis.

It has been observed that desensitization is a rapid, safe, and effective technique for patients who demonstrate hypersensitivity to beta-lactam antibiotics and requires therapy with these medications, and it has been performed successfully for years.^{16,17} After the desensitization procedure was successfully applied using antibiotics, other empirical protocols were developed for type 1 hypersensitivity reactions to essential drugs such as chemotherapeutic and biologic agents (eg, monoclonal antibodies, cytokines, and fusion proteins), when alternative agents are not available in allergic patients.^{18–21}

There is limited data on desensitization protocols with coagulation factors. We present a successful 13-step desensitization protocol for an infant with an anaphylactic reaction to rFVIIa.

We were unable to evaluate the tryptase level due to laboratory limitations. However, the involvement of 2 systems with clinical resolution of symptoms with adrenaline, supported the diagnosis of anaphylaxis. We also know from the literature that a low tryptase level does not exclude anaphylaxis.²²

The epicutaneous skin prick test, which was performed to evaluate drug hypersensitivity, was negative, but the intradermal test with 1/1,000 dilution of rFVIIa was positive. The intradermal test supported the determination that the anaphylactic reaction was immunoglobulin E-mediated. We were unable to identify any published data on sensitivity, specificity, or nonirritating concentration of the rFVIIa. Owing to ethical guidelines, we could not perform skin prick or intradermal tests with rFVIIa on healthy control groups to find nonirritating concentration, which is a limitation of the study.

In our patient, anaphylaxis occurred after his initial exposure to rFVIIa. In some cases, patients become sensitized to drugs with similar molecules in different ways, which can be the case in this study. In addition, this may be an IgG-mediated reaction to very low level of factor VII.

Dioun et al. reported 2 children on whom they performed factor IX desensitization.²³ When the intradermal test was performed on these 2 patients using factor IX, the test was not positive with 1/100 dilution but was positive with 1/10 dilution.²³ For our patient, the intradermal test was positive with 1/1,000 dilution, and as it was highly diluted, we did not attribute this positivity to irritation.

There is limited data for IgE-related reaction of coagulation factors and desensitization protocols. Mediawake et al. reported anaphylaxis with human prothrombin complex concentrate for a 3-year-old girl with Lupus Anticoagulant Hypoprothrombinemia Syndrome.²⁴ Her factor II level was low and it was thought that the anaphylaxis was due to the factor II in human prothrombin complex. Anaphylaxis had not been previously reported against recombinant factor VII concentrates in children.

There have been successful cases of desensitization for factor IX deficiency in the literature.^{25,26} Dioun et al. presented 2 patients (2- and 9-year-old boys) with histories of anaphylaxis to factor IX where a desensitization protocol was successfully applied.²³ Anaphylactic reactions to factor IX are more prevalent in patients with severe hemophilia B (<1% factor IX), who are also predisposed to developing inhibitors (neutralizing antibodies) to factor IX.^{27,28}

Alexander et al. performed a successful factor IX desensitization to a 9-year-old boy with severe hemophilia B.²⁵

Wyckoff et al. reported an adult with possible anaphylaxis to factor VIIa during a thoracic aortic surgery, but desensitization was not required in this case.²⁹

To our knowledge, this is the first report of a successful desensitization protocol for factor VIIa hypersensitivity in a young child. Our experience can be useful in the diagnosis and management of similar patients with rFVIIa hypersensitivity.

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Author Disclosure Statement

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