CASE REPORT

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Successful desensitization for the anaphylaxis due to F8/vWF extract in the youngest patient

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Abstract

Von Willebrand disease is a genetic disease with the possibility to cause hemorrhage in various areas of the body. vWD type 3 is a rare hemorrhagic diathesis and plasma-derived F8/vWF extract is used for the treatment. While the two years old male patient diagnosed with vWD type 3 has been administered with F8/vWF extract (Haemate P®500 IU) for the fourth time, he had complaints of flushing on his body, angioedema on lips and eyelids, shortness of breath, coughing and cyanosis within the fifth minute of the infusion. The patient was treated with IM adrenaline, oxygen, short-acting beta 2 agonist and antihistamine. The symptoms disappear after these treatments. As the patient is required to be administered with F8/vWF extract and due to lack of any alternatives, desensitization is decided. During and after the desensitization protocol, no reaction has been observed. In this presentation, a successful desensitization protocol for F8/vWF extract in the youngest patient was discussed.

Keywords: Anaphylaxis, Desensitization, F8/vWF extract.

INTRODUCTION

Von Willebrand Disease (vWD) is an inherited hemorrhagic disorder, progressing with the decreased blood level or function of the von Willebrand factor (vWF). We may clinically encounter this disease with the symptoms of nose bleeding and mucocutaneous bleeding, also with menorrhagia and excessive hemorrhage in the post-trauma period [1, 2]. The disease is classified into three main groups; type 1, type 2 and type 3 [3, 4]. vonWillebrand type 3 is a rare subtype of the disease. The treatment varies based on the subtypes of the disease. In type 3 vWH, as the F8 level is low in blood in addition to the vWF level, factor extracts including F8/vWF is used in the treatment [3]. Alloantibodies are formed in time in the patients with vWH type 3 with the multiple blood products infused. These alloantibodies with Ig G type may result in severe life-threatening anaphylactoid reactions [5, 6]. In addition, Ig E mediated anaphylaxis due to factor extract can be rarely seen [7]. In this presentation, a successful desensitization protocol for F8/vWF extract in the youngest patient was discussed. Written consent was obtained from the patient's parents for all procedures to be done.

CASE REPORT

The two years old male patient diagnosed with vWH type 3 had developed complaints that were flushing on his body, angioedema on lips and eyelids, shortness of breath, coughing and cyanosis in the fifth minutes of F8/vWF extract (Haemate P®500 IU) infusion. The oxygen saturation of the patients has been measured as 88% and the arterial blood pressure as 55/29 mm Hg. In the physical examination, respiration rate per minute was 60 and pulse rate was 145. Rhonchus has been identified in the pulmonary auscultation. The patient was diagnosed with anaphylaxis and treated with IM adrenaline 0.01 mg/kg, oxygen, nebulized salbutamol and antihistamine.

There was no history of similar reaction previous three infusion of F8/vWF extract. The patient have no comorbid allergic disease. F8/vWF extract diluted at the ratio of 1/10 and skin prick test have been done for the purpose of revealing that the reaction developed is Ig E mediated Saline was used as negative control. The patient has developed flushing, cough and wheezing three minutes after the skin prick test. The patient was treated with IM adrenaline 0.01 mg/kg, oxygen, nebulized salbutamol and antihistamine. In the skin prick test, induration developed with redness around 5x5 mm. Since the patient needs to take the F8 / vWF extract continuously and there is no alternative, we decided to desensitization with F8/vWF. Three different solution were prepared ranging from the stock solution of 500 IU/ml to a saline-diluted concentration of 5 IU/ml (Solution A, B and C). The initial dose was 1/50.000 of the therapeutic dose (1/50.000 of total dose: 500 IU/50.000 = 0.01 IU). This initial amount of F8/vWF extract with 0.01 IU/ml concentration was calculated as 0.05 ml. The doses were increased two fold increments every 15 min. Therefore, the infusion rates were also increased by two fold every step. However, the concentration was increased every hour. For the next concentration, the remaining factor in the set was thrown and another infusion set was prepared for the consecutive concentration. Desensitization protocol was shown in the Table 1. Premedication has been performed with phenyramine, methylprednisolone and ranitidine prior to the initiation of desensitization protocol. During and after the desensitization protocol, no reaction has been observed.

Table 1: Desensitization protocol with 12 steps applied to the patient with Haemate P® 500 IU

Step	Concentration	Infusion rate (mL/hour)	Time (min)	Volume infused per step (ml)	Dose administered with this step (IU)	Cumulative dose (IU)	Fold increase per step
1	1/100*	2.0	15	0.50	0.01	0.010	1
2	1/100	5.0	15	1.25	0.25	0.035	2.5
3	1/100	10.0	15	2.5	0.5	0.085	5
4	1/100	20.0	15	5	0.1	0.185	10
5	1/10**	5.0	15	1.25	0.25	0.435	25
6	1/10	10.0	15	2.5	0.5	0.935	50
7	1/10	20.0	15	5	1	1.95	100
8	1/10	40.0	15	10	2	3.935	200
9	1/1	10.0	15	2.5	5	8.935	500
10	1/1	20.0	15	5	10	18.935	1.000
11	1/1	40.0	15	10	20	38.935	2.000
12	1/1	75.0	162	202.5	409.6	500	40.960

***Solution A:** Includes 5 IU factor with 1/100 concentration

****Solution B:** Includes 50 IU factor with 1/10 concentration

*****Solution C:** Includes 500 IU factor with 1/1 concentration

DISCUSSION

VWF deficiency is a hematological disease that impairs quality of life and can cause serious clinical conditions with bleeding. Various plasma derived factor products are used for the treatment of this disease. Anaphylactoid reactions due to complement activation may occur in patients administering these products for a long period. Inhibitors developing based on long-term use of the plasma derived products cause this condition [5]. Development of an Ig E-mediated anaphylaxis reaction against factor extracts is rare. Cases reported so far are generally associated with adult ages, however, although rarely, reactions have also been reported in pediatric age group [7]. In Ig E-mediated drug reactions, antigens of the drug used cause specific Ig E formation in patients as a result of repeated treatments[8]. In the subsequent medication intake, certain inflammatory mediators are released from mast cells and basophils by drug antigens binding to specific Ig E bound to Ig E receptors in mast cells and basophils. Those are histamine, tryptase, prostaglandins and leukotrienes. Certain symptoms are revealed upon the release of such mediators. Organ systems such as skin, respiratory, cardiovascular and gastrointestinal system may be affected, and mortality due to anaphylaxis may be experienced in advanced cases [9]. The diagnosis of hypersensitivity reaction to the drug is made by evaluating the history and clinical findings. Whenever possible,

diagnosis should be supported by skin tests, in-vitro tests and provocation tests. The history of the reaction development time (at what dose and how long the reactions develop after the drug is started to be administered) should be carefully evaluated if the symptoms are compatible with drug allergy. In our patient, anaphylaxis developed at the fourth dose of the drug and 5 minutes after the drug was administered. The skin prick test we performed for the diagnosis was found positive

In patients with drug allergy, desensitization is administered only if it is absolutely required to administer the medication and no alternative treatment is available. The objective of the desensitization in such patients is to temporarily suppress the response of the body to the medication. The patient is ensured to be administered with the medication without developing any reaction by administering the medication starting with minor and then incremental doses. General rules related to the desensitization have been published by European Network for Drug Allergy and European Academy of Allergy and Clinical Immunology [10]. Desensitization protocols is required to be based on general rules and be simple, safe, easy and amendable in accordance with the response of the patient [10-12]. The initial dose for desensitization is required to be determined by taking into account the severity of the reaction. Typically; the initial dose is required to be within the range of 1/100.000 and 1/100 of the complete therapeutic dose. Based on the severity of the reaction of the patient, it can be initiated with lower doses. Increase of dose is performed in two or three times following the initial dose. There is a risk of developing reaction at any stage of the steps. If the reaction develops in the intermediate steps, the relevant step is stopped and returned to a lower step [10-12]. We have initiated the dose of 1/50.000 of the factor extract administered by our patient and reached to complete therapeutic dose increasing the dose by two-fold. No reaction has been developed at the desensitization steps.

In conclusion, although rarely, life-threatening Ig E mediated reactions can be experienced against the factor extracts in infant patients diagnosed with vWD type 3. Desensitization is vital and inevitable for vWD tip 3 patients who develop anaphylaxis to vWF extract. The protocol that we propose here encompasses the general rules of desensitization: a regimen that is safe, simple, and effective. Although desensitization procedures have been conducted by different specialists, for the patient's safety, allergists should develop, review, and supervise treatments.

Acknowledgments

We thank the parents of the patient for giving written consent for publication of this case report

Statement of Ethics

Written informed consent to publish the case, was given by the patient's parents.

Conflict of interests

The authors declare that they have no conflict of interests.

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REFERENCES

1. Sadler JE, Budde U, Eikenboom JC *et al*. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost. 2006; 4:2103-14.
2. Federici AB. Diagnosis and classification of von Willebrand disease. Hematol Meeting Reports. 2007; 1:6-19.
3. Budde U, Metzner HJ, Müller HG. Comparative analysis and classification of von Willebrand factor/factor VIII concentrates: impact on treatment of patients with von Willebrand disease. Semin Thromb Haemost. 2006; 32:626-35.
4. Patzke J, Schneppenheim R. Laboratory diagnosis of von Willebrand disease. Hamostaseologie. 2010; 30:203-6.
5. Bergamaschini L, Mannucci PM, Federici AB, *et al*. Posttransfusion anaphylactic reactions in a patient with severe von Willebrand disease: role of complement and alloantibodies to von Willebrand factor. J Lab Clin Med. 1995; 125:348-55.
6. Batlle J, Loures E, Vila P *et al*. Alloantibody from a patient with severe von Willebrand disease inhibits von Willebrand factor-factor VIII interaction. Ann Hematol. 1997; 75:111-5.
7. Beken B, Celik V, Gokmirza PO *et al*. Successful Desensitization of a Patient with Possible IgE-Mediated Anaphylactic Reaction to FVIII/VWF Concentrate. Pediatr Allergy Immunol Pulmonol. 2019; 32:81-4.
8. Solensky R. Drug hypersensitivity. Med Clin North Am. 2006; 90: 233-60.
9. Vadas P, Gold M, Perelman B *et al*. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. N Engl J Med 2008; 358:28-35.
10. Cernades JR, Brocrow K, Romano A, *et al*. General considerations on rapid desensitization for drug hypersensitivity:

a consensus statement. Allergy. 2010; 65:1357-66.

11. Liu A, Fanning L, Chong H *et al*. Desensitization regimens for drug allergy: state of the art in the 21st century. Clin Exp Allergy. 2011; 41:1679-89.
12. Celik G, Pichler WJ, Adkinson Jr NF. Drug allergy. In: Adkinson Jr NF, editor. Middleton's allergy principles & practice. 7th ed. Philadelphia: Mosby. 2009; p. 1205-26.