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CASE REPORT OPEN ACCESS

Successful desensitization with FVIII/Von Willebrand Factor concentrate in Type III Von Willebrand Disease

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Abstract
Von Willebrand Disease (VWD) Type 3 is a rare and severe bleeding disorder characterized by an almost complete deficiency of Von Willebrand Factor (VWF). Plasma-derived Factor VIII (FVIII)/VWF concentrates are used both on demand and for prophylactic treatment. However, allergic reactions to these products pose significant challenges in clinical management. A 40-year-old female patient with VWD Type 3 presented to our clinic with symptoms including jaw numbness and tightness, chills, fatigue, nausea, and dyspnea following administration of a FVIII/VWF concentrate (Haemate® P). Skin prick tests and intradermal tests were performed for diagnostic evaluation and were found to be negative. The hypersensitivity reaction was assessed as an immediate type and non-IgE-mediated reaction. As there were no alternative treatment options, we decided to perform desensitization. A 14-step desensitization protocol was successfully administered. The patient is now able to self-administer Haemate® P at home three times a week. This case highlights the importance of desensitization and multidisciplinary approach in the case of drug hypersensitivity in patients with VWD Type 3. Our desensitization protocol with FVIII/VWF concentrate is highly effective and safe.

Introduction

Von Willebrand Disease (VWD) is an inherited bleeding disorder in which platelet adhesion and aggregation are defective and is associated with decreased activity of Von Willebrand Factor (VWF) in blood.[1] VWF is also a carrier protein for the coagulation Factor VIII (FVIII).[1,2] There are three types of this disease associated with either quantitative or qualitative deficiency of VWF, of which VWD Type 3 is a quantitative defect resulting from an almost absolute

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lack of VWF and is the most severe type of the disease.[3] VWD is most commonly inherited in an autosomal dominant manner, whereas Type 3 VWD, inherited in an autosomal recessive manner, is rare, being detected in <5% of all cases.[1,4]

Symptoms of VWD may vary according to the residual VWF level, gender, age, and subtype of the disease. In adults, hematoma, menorrhagia, prolonged bleeding after surgery, and tooth extraction are frequently seen.[1] Intrartricular bleeding is a serious problem, especially in Type 2N and Type 3 patients, although it is mostly reported in patients with hemophilia.[5] Treatment is based on normalization of VWF and FVIII levels and varies according to the subtype of the disease.[1] VWF-Factor VIII or VWF concentrate is used in Type 3 VWD. Prophylactic factor infusion is used in patients with VWD, and successful patient series are available in the literature.[6,7]

Although hypersensitivity reactions to FVIII/VWF concentrates are rarely reported in the literature, their management represents a significant clinical challenge due to the limited availability of alternative therapeutic options.[8-10] Here, we present the case of a patient who experienced an immediate hypersensitivity reaction to Haemate® P, a plasma-derived FVIII/VWF concentrate, in the absence of viable treatment alternatives. This case highlights desensitization protocol as a successful management strategy.

Case Report

We report a 40-year-old woman who was diagnosed with VWD Type 3 at the age of 14 months after an oral mucosal bleeding that could not be stopped. She had no concomitant allergic disease. She is on perindopril + indapamide, drospirenone, and magnesium supplements. On prophylactic therapy, she was self-administering Haemate® P (FVIII/VWF concentrate) 1500 IU 3 days a week for 12 years. She was known to have an inhibitor of factor for 8 years. After the last two Haemate® P infusions, she had complaints compatible with immediate-type hypersensitivity reactions and was referred to our allergy clinic. On the first reaction day, immediately after the drug infusion was completed, she had numbness and contraction in the jaw, tremor, feeling of weakness, nausea, and shortness of breath. She was admitted to the emergency department, and her complaints resolved within 1 h after diphenhydramine administration. Two days after this event, the drug was administered in the Hematology Clinic, where she was followed up with a premedication consisting of methylprednisolone and diphenhydramine. Near the end of the infusion, she had itching, a feeling of weakness, numbness in the chin, dyspnea, chest tightness, and chest pain. There was no deterioration in vital signs. Her complaints resolved without additional medical treatment. Infusion was stopped, and her complaints resolved spontaneously.

Since both reactions were suggestive of Haemate® P-associated hypersensitivity reaction, we formed a diagnostic evaluation and treatment plan. Initially, skin prick tests and intradermal tests with Haemate® P were performed to evaluate an IgE-mediated allergic reaction; however, they were negative (Table 1). For the skin prick test, 500 IU of FVIII/VWF concentrate was diluted with 10 mL of its own solvent to obtain a solution with a final concentration of 50 IU/mL. Both this solution and its 1:10 dilution were used. For intradermal tests, solution A (250 cc 0.9% NaCl + 15 IU Haemate® P) and solution B (250 cc 0.9% NaCl + 150 IU Haemate® P) were used.

The hematology clinic where she followed up stated that there was no alternative treatment option, and the drug should be used absolutely. Although an IgE-mediated reaction could not be confirmed, due to the severity of the reactions and the need for treatment, we decided to perform desensitization procedure. Desensitization procedure was performed as shown in Table 2. The protocol was created using the 3-bag 12-step desensitization protocol described by Brigham and Women's Hospital.[11] We used a 14-step protocol to shorten the infusion time, and the process was completed in a total of 292.28 min. Written informed consent was obtained before desensitization procedure. We also obtained consent and permission to publish the case report.

The patient was ensured to receive treatment 3 days a week, on Monday, Wednesday, and Friday. On the 1st day, the desensitization procedure was completed without any reaction with a total dose of 1361.85 IU Haemate® P. We planned to start the infusion rate on the third day at a lower dose instead of starting at the last step rate, due to the short half-life and the concern that desensitization may be lost 2 days after desensitization. On the 3rd day, 1500 IU Haemate® P was added into 250cc SF to form a "stock solution," and the protocol shown in Table 3 was performed. Again, considering the half-life of Factor VIII and VWF and with the concern that the temporarily created tolerance may have disappeared, 14-step desensitization was performed on Day 7 (Table 2). On Day 9, the protocol in Table 3 was performed. On the 11th day, the infusion was completed by giving the "stock solution" at 75 cc/h for 15 min and the remaining solution at 150 cc/h. On the 14th day, "stock solution" was administered at a rate of 150 cc/h. On the 16th and 18th days, 1500 IU Haemate® P was administered slowly over 1 h without dilution. No reactions developed in any of the drug administrations. The patient is currently self-administering 1500 IU Haemate® P at home as a slow infusion over 30 min.

Table 1 Skin Prick and Intradermal Test Concentrations and Results.

	Skin Prick Test Result	Intradermal Test Result
Haemate P®	1:1 Negative (50 IU/ml) 1:10 Negative (5 IU/ml)	0.6 IU/ml (A Solution) Negative 6 IU/ml (B solution) Negative

Table 2 14 Step Desensitization Protocol to Haemate P®.

Step	Concentration	Infusion rate (mL/hour)	Time (min)	Volume infused per step (ml)	Dose administered with this step (IU)	Cumulative dose (IU)
1	A	2	15	0.5	0.03	0.03
2	A	5	15	1.25	0.075	0.105
3	A	10	15	2.5	0.15	0.255
4	A	20	15	5	0.3	0.555
5	B	5	15	1.25	0.75	1.305
6	B	10	15	2.5	1.5	2.805
7	B	20	15	5	3	5.805
8	B	40	15	10	6	11.805
9	C	10	15	2.5	15	26.805
10	C	20	15	5	30	56.805
11	C	40	15	10	60	116.805
12	C	75	45	18.75	112.5	229.305
13	C	150	30	37.5	225	454.305
14	C	200	52.28	151.25	907.5	1361.85

A Solution: 250 cc % 0.9 NaCL + 15 IU Haemate® P
B Solution: 250 cc % 0.9 NaCL + 150 IU Haemate® P
C Solution: 250 cc % 0.9 NaCL + 1500 IU Haemate® P

Table 3 Drug Administration Scheme.

Step	Concentration	Infusion rate (mL/hour)	Time (min)	Dose administered with this step (IU)	Cumulative dose (IU)
1	A	40	15	60	60
2	A	75	15	112.5	172.5
3	A	150	88.5	221.25	1500

***A solution**: 250 cc % 0.9 NaCL + 1500 IU Haemate® P (stock solution)*

Discussion

VWD Type 3 is an autosomal recessive disorder characterized by an almost absolute deficiency of VWF. Haemate® P, a plasma-derived FVIII/VWF concentrate, is used both prophylactically and on demand in this patient population.[1] Here, we report a patient with VWD Type 3 who had an immediate-type hypersensitivity reaction and anaphylaxis with Haemate P® and successful management of the patient with a defined desensitization procedure. The patient's initial reaction was characterized by symptoms including numbness and tightness in the jaw, tremor, generalized weakness, nausea, and shortness of breath. As these symptoms did not fulfill the diagnostic criteria for anaphylaxis according to current anaphylaxis guidelines, the reaction was classified as an immediate hypersensitivity reaction. However, the patient's second reaction, which involved generalized pruritus and dyspnea, fulfilled the diagnostic criteria for anaphylaxis as defined by The European Academy of Allergy and Clinical Immunology (EAACI) Anaphylaxis Guidelines and the World Allergy Organization (WAO) Anaphylaxis Guidance 2020.[12,13] Additionally, according to the modified WAO Grading System for severe allergic reactions, the severity of anaphylaxis was classified as Grade 3, where Grade 1 represents the mildest and Grade 5 the most severe form of the reaction.[14] We consider this reaction to have been self-limiting, likely due to the premedication administered in advance. Hypersensitivity reactions to Haemate P® are rare and pose a challenge in patient management due to limited alternatives.

The exact mechanism of hypersensitivity reactions to these concentrates is unknown. One of the proposed mechanisms is the development of alloantibodies (usually polyclonal IgG) called inhibitors after repeated exposures.[9–11,15] Alloantibodies cause a decrease in the hemostatic response after infusion. A relationship between inhibitor development and hypersensitivity reactions such as anaphylaxis has been reported.[9–11,16] In addition, these antibodies have been associated with immune complex development and complement activation.[15,17] Complement activation was thought to be responsible for HSRs and anaphylactoid reactions due to complement activation, with repeated plasma-derived treatments being associated with inhibitor development.[15]

Another proposed mechanism is that these HSRs are IgE-mediated allergic reactions. Although there are no standardized test concentrations defined with these extracts, there are pediatric cases in the literature where skin test positivity is shown and IgE-mediated HSR is confirmed.[10]

There are cases in the literature where skin prick tests and intradermal tests were negative and non-IgE-mediated HSR was reported, as in our patient.[9] Our patient was also known to have inhibitor antibodies, and the hypersensitivity reaction in this case may be associated with possible complement activation.

Drug desensitization is the process of inducing the development of tolerance to the drug causing the hypersensitivity reaction, and is a high-risk procedure as it carries the risk of anaphylaxis. Although drug desensitization has long been recognized as an effective strategy in the management of IgE-mediated HSRs, it has also gained a role in the treatment of non-IgE-mediated immediate HSRs. These reactions occur through alternative immunologic pathways, such as direct mast cell activation, basophil activation, or complement activation. Non-IgE-mediated immediate HSRs can lead to significant clinical manifestations, including cutaneous, respiratory, gastrointestinal, and systemic symptoms—potentially progressing to anaphylaxis in severe cases.[18,19] Although the underlying mechanisms are less well-defined, successful rapid drug desensitization protocols have been reported in patients with negative skin tests who are classified as having non-IgE-mediated immediate hypersensitivity reactions. These protocols have been applied effectively with chemotherapeutic and biologic agents, as well as with certain non-β-lactam antibiotics and sulfonamides. Such approaches represent a significant advancement in the management of these patients.[8,18,20] In our case, the patient experienced a non-IgE-mediated immediate hypersensitivity reaction, and due to the lack of an alternative treatment option, desensitization was applied.

The general principles of desensitization have been previously reported. Before initiating any desensitization protocol, a thorough assessment of the individual risk-benefit ratio is essential. Desensitization should be conducted in a controlled clinical setting under the close supervision of an experienced physician, ensuring immediate availability of cardiopulmonary resuscitation and anaphylaxis management.[18] In this protocol, the dose escalation scheme was started according to the protocol defined by Birmingham Women's Hospital.[8] Fourteen consecutive infusion steps were performed using three separate solutions, each containing 250 mL of 0.9% NaCl. Solution A, administered in Steps 1 through 4, represented a 1:100 dilution of the final target concentration. Solution B used in Steps 5 through 8 represented a 1:10 dilution of the target concentration. Solution C, administered in Steps 9 through 14, contained 1500 IU of Haemete P® dissolved in 250 mL of 0.9% NaCl. The infusion rate was increased in the last 2 steps, reaching up to 200 mL/h.

Desensitization with Haemete P® is very limited in the literature.[9-11] To the best of our knowledge, our case represents the first desensitization procedure performed in an adult patient. Platt et al. reported successful desensitization and graded challenge experiences after non-IgE-related allergic reactions in two children with VWD Type 3.[9] In addition, hypersensitivity reactions and desensitization protocols due to FVIII/VWF concentrate, which are thought to be IgE-mediated and confirmed by skin test positivity, have been reported in pediatric patients.[10,11] We successfully performed a 3-bag 14-step desensitization procedure in an immediate-type allergic reaction, which was thought to be non-IgE-mediated. We found that this method was effective and safe.

Conclusion

In conclusion, this case shows the importance of desensitization and a multidisciplinary approach in desensitization in patients with hypersensitivity reactions, which is one of the rare bleeding disorders. Desensitization is absolute in the absence of alternative treatment in patients with VWD who develop a hypersensitivity reaction. Our protocol is effective and reliable and covers the general rules of desensitization. Uncovering the mechanisms underlying the transient tolerance induced by desensitization may improve the safety of this high-risk intervention.

Competing Interests

The authors had no relevant financial interests to disclose.

Author's Contribution

All authors contributed equally to this article.

Conflict of Interest

None.

Funding

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