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CASE REPORT

Anticoagulation Therapy Considerations in Factor VII Deficiency

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Abstract Factor VII (FVII) deficiency is the most prevalent rare bleeding disorder in the USA and affects approximately 1 out of every 500,000 people. Warfarin inhibits the synthesis of FVII, in addition to other clotting factors. Warfarin is contraindicated in patients with bleeding tendencies or blood dyscrasias; therefore, the literature regarding the use of warfarin in FVII deficiency is very limited. We report a successful re-challenge of warfarin therapy in a patient with FVII deficiency. A 70-year-old woman with FVII deficiency experienced a significant decrease in FVII activity and subsequent vaginal bleeding roughly 5 weeks after starting warfarin for atrial fibrillation. The patient was switched to aspirin therapy. Nearly 4 years later, warfarin therapy was re-attempted by a different haematologist. After 9 months, FVII activity remained in an acceptable range and no bleeding events had occurred. In addition, once the maintenance dose was established, the international normalized ratio remained within the goal range (1.5–2.0) for the majority of assessments. Regarding future considerations, we hypothesize that anticoagulants that do not directly affect FVII, such as the direct oral anticoagulants, would carry less risk of bleeding complications and therefore may be safer alternatives to warfarin to reduce the risk of thromboembolic stroke in patients with atrial fibrillation and FVII deficiency.

Key Points

We observed a successful re-challenge of warfarin therapy in a patient with atrial fibrillation and factor VII (FVII) deficiency.

Challenges with using warfarin therapy in FVII deficiency include lack of a defined optimal target international normalized ratio range and a poor correlation between the degree of FVII deficiency and bleeding risk.

We hypothesize anticoagulants which do not directly affect FVII, such as the direct oral anticoagulants, may carry less risk of bleeding complications than warfarin to reduce the risk of thromboembolic stroke in patients with atrial fibrillation and FVII deficiency.

Introduction

The coagulation pathway is a complex system and is an essential part of haemostasis [1]. It involves a number of enzymatic steps, which activate circulating clotting factors, ultimately leading to clot formation (see Fig. 1). Coagulation is typically initiated through the extrinsic pathway when tissue injury exposes tissue factor. Circulating factor VII (FVII) binds to tissue factor, and the resulting complex becomes activated FVII (FVIIa). FVIIa then directly catalyses the conversion of factor X to factor Xa (FXa) in the common pathway and indirectly via the

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Fig. 1 Effects of multiple anticoagulant medications on the coagulation cascade
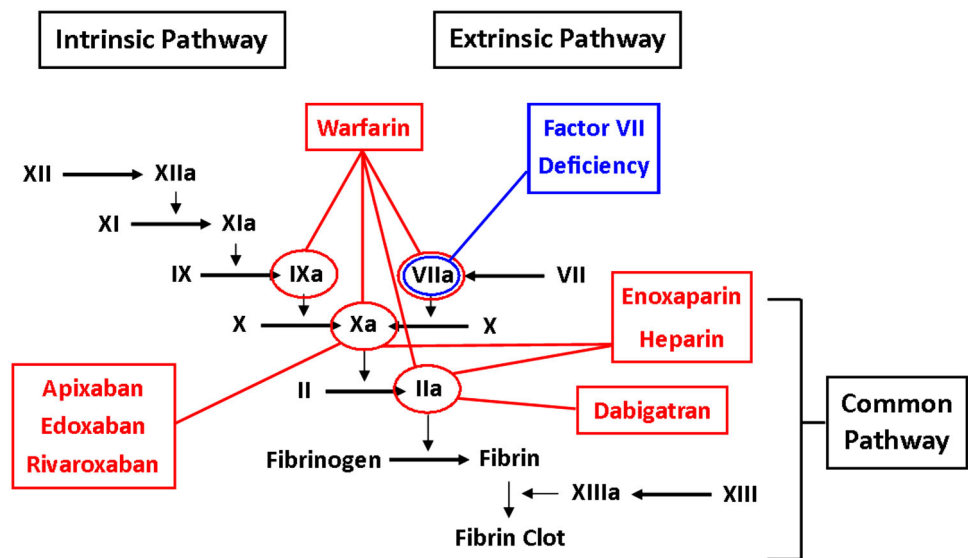
activation of factor IX to factor IXa. While the extrinsic pathway initiates haemostasis, sustained haemostasis is dependent upon the continued and amplified procoagulant action of the intrinsic pathway, which involves factors VIII, IX, XI and XII [2, 3].

Given the complex nature of the coagulation pathway, one can appreciate the complexity of coagulation disorders. Classical bleeding disorders include haemophilia A and B; however, a number of rare bleeding disorders (RBDs) exist [4]. RBDs represent only about 3–5 % of inherited coagulation deficiencies and include deficiencies in fibrinogen; factors II, V, V + VIII, VII, X and XIII; and a combination of the vitamin K-dependent factors [5]. The most prevalent RBD is FVII deficiency, which affects approximately 1 out of every 500,000 people in the USA, and the prevalence varies in other countries [6]. FVII deficiency is an autosomal-recessive bleeding disorder. The hallmark of FVII deficiency is a prolonged prothrombin time (PT) and an elevated international normalized ratio (INR) in the setting of normal liver function and a normal activated partial thromboplastin time (aPTT) [7].

Managing an FVII-deficient patient presents several challenges. First, FVII can potentially exist in several different forms, and measuring FVII is further complicated by the many different assays available [8–10]. For the purposes of this article, FVII is reported as FVII coagulation activity (FVIIc), expressed as a percentage, with normal activity being 50–150 %. Our institution utilized a one-step clotting assay, with the result being normalized to determine the percentage activity. Second, determining disease severity on the basis of FVIIc is also difficult, as there is a poor correlation between FVIIc and bleeding risk, as some patients with moderate to severe deficiency may remain asymptomatic, while others with mild deficiency may

experience major bleeding events [11]. Disease severity may be better classified on the basis of the location and frequency of bleeding events [7, 12]. A recent retrospective analysis of 83 patients with FVII deficiency undergoing surgical procedures recommended using FVII levels, the bleeding history and the type of surgery to help estimate bleeding risk and guide perioperative management [13]. Lastly, gene analysis is also difficult to interpret, as there are over 130 known mutations, with many still lacking defined phenotypic characteristics [11]. Progress is being made as national and international registries for RBDs continue to provide information about FVII deficiency.

Although RBDs inherently limit coagulation and may predispose patients to bleeding, patients with FVII deficiency may still require anticoagulation therapy if indicated. A case series analysed thromboembolic events in patients with FVII deficiency and concluded that those with mild FVII deficiency should not be precluded from receiving antithrombotic prophylaxis [14]. Historically, warfarin has been the initial treatment of choice in this limited patient population. Warfarin works by blocking the regeneration of vitamin K epoxide, thus inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX and X, as well as the anticoagulant proteins C and S. There is evidence to suggest that not all of the vitamin K-dependent clotting factors are affected equally by warfarin, with FVII and factor IX being suppressed to a greater degree than factors II and X [15]. The PT is used to monitor warfarin therapy and is converted to an INR for standardization. The PT reflects the functionality of several different clotting factors, including the vitamin K-dependent clotting factors; however, a prolonged PT is not seen until one of the clotting factors has decreased to <30–40 % [16]. For conventional patients who are stable on warfarin

therapy, the INR should accurately represent variations in coagulation factor activities [17]. However, in the presence of FVII deficiency, the INR may not as accurately represent the degree of coagulation ability, given the inherent decrease of FVII in this RBD. Monitoring treatment through FVII activity may also prove to be difficult, as the minimal levels needed to sustain haemostasis are not well established [7]. There is limited published literature to guide anticoagulation therapy and monitoring in this population due to the rare nature of the disorder.

Three case reports involving the use of vitamin K antagonists for atrial fibrillation in patients with FVII deficiency have been published:

- The first case was a 50-year-old male with a prolonged PT and an INR of 1.5 at baseline [18]. He developed an INR of 19.6 after four doses of warfarin 5 mg, which prompted discontinuation. Two weeks later, laboratory analysis revealed an FVIIc of 43 %, which led to the diagnosis of mild FVII deficiency. Warfarin was re-started at a higher INR goal of 2.5–3.5 to ensure adequate anticoagulation in the presence of an elevated baseline INR. After 18 months, no bleeding or thrombotic events were reported, despite the INR being in the therapeutic range only 32 % of the time.

- The second case was a 77-year-old female [19]. She developed an INR of 6.0 after two doses of warfarin 10 mg, which prompted discontinuation. Thirteen days later, her INR was 2.2. Warfarin was re-started, and over the next few months, the patient's INR ranged from 2.2 to 3.8 with doses ranging from 0.5 to 4 mg weekly. When warfarin was withheld for 2 weeks and the patient's INR remained elevated at 3.5, she was evaluated for an RBD. Laboratory analysis revealed an FVIIc of 14 %. It was concluded that the risks with warfarin outweighed the benefits, and the patient was switched to aspirin.

- The third case was an 80-year-old male with a baseline INR of 2.1 and an FVIIc of 10 % [20]. His INR goal was set at 2.5–3.0. While his INR was within the goal range, his FVIIc decreased to 5 % (equal to a 50 % decrease from baseline), whereas none of the other vitamin K-dependent clotting factors decreased more than 30 % in comparison with baseline. Given the risk of bleeding and perceived inadequate anticoagulant effect, warfarin was discontinued, and enoxaparin (a low molecular weight heparin [LMWH]) was initiated, which was monitored using anti-FXa activity. The patient received enoxaparin for 3 months without any bleeding symptoms before undergoing successful cardioversion.

In summary, although none of these patients developed major bleeding symptoms with vitamin K antagonist therapy, all encountered challenges with monitoring and accurate assessment of the anticoagulant effect. Such challenges lead to uncertainties in how to implement anticoagulation therapy in patients with this RBD, as further highlighted by the case summary below.

Case Report

A 70-year-old African American female with atrial fibrillation was referred to haematology in 2010 for evaluation of a mildly prolonged PT with persistent vaginal bleeding. Laboratory test results revealed a decreased FVIIc of 33 % (reference 50–150 %), and FVII deficiency was diagnosed. The patient underwent endometrial cryotherapy, and after 4 months without recurrent vaginal bleeding, haematology cleared the patient to start warfarin therapy, with an INR goal of 2.0–3.0. Haematology recommended discontinuing warfarin if FVIIc decreased to 10 % or less. The patient's baseline INR was 1.4, and warfarin was conservatively started at 2 mg daily. The INR remained at 1.4 for the first 4 weeks of therapy, despite gradual dose increases. Nearly 6 weeks into therapy, the patient made a dosing error, which caused her INR to increase to 2.5. She developed recurrent vaginal bleeding, and her FVIIc was found to be 10 %, which prompted warfarin discontinuation. She was switched to aspirin 81 mg daily.

In 2014, she was evaluated by a different haematologist. Her FVIIc was 44 %, with a baseline INR of 1.2. It was decided to re-attempt warfarin therapy with a lower INR goal of 1.5–2.0, as the risks of stroke without anticoagulation seemed to outweigh the risks of bleeding with anticoagulation. The patient's risk factors for stroke had not changed since her initial warfarin course. Haematology recommended discontinuing warfarin if FVIIc decreased to <15% or if the patient developed any clinical signs of bleeding. A total weekly dose of 40 mg was found to maintain her INR in the range of 1.6–1.8. The FVIIc varied between 24 and 28 % during the first 6 months of warfarin therapy. During the seventh month, the patient's FVIIc decreased to 15 %, with a corresponding increase in her INR to 2.4, despite no change in her weekly dose. The patient denied any signs of bleeding during this second treatment course. Her weekly doses, INR results and FVIIc results are shown in Table 1.

Discussion

Our case report describes a successful re-challenge of warfarin therapy in a patient with FVII deficiency. However, we must recognize the varying degrees of FVIIc and the corresponding bleeding risk among patients with FVII

Table 1 Case patient dose, international normalized ratio (INR) and factor VII coagulation activity (FVIIc) results

Date	Dose (mg/week)	INR	FVIIc (%)	Comments
September 27, 2010	None	1.3	33	First haematology consultation
April 11, 2011	None	1.4	–	Warfarin 2 mg daily started—1st attempt
May 5, 2011	24	1.4	37	
May 23, 2011	56	2.5	10	Dose error, recurrent vaginal bleeding, warfarin discontinued
March 26, 2014	None	1.2	44	Second haematology consultation
June 19, 2014	None	1.2	–	Warfarin 2 mg daily started—2nd attempt
August 11, 2014	32	1.4	24	
October 7, 2014	40	1.7	28	
December 11, 2014	40	1.7	32	
January 27, 2015	40	2.4	15	No signs/symptoms of bleeding, warfarin dose decreased to 38 mg/week
March 3, 2015	38	1.6	30	

deficiency. When our case is compared with the two patient cases that required vitamin K antagonist discontinuation, our patient had a more mild FVII deficiency and maintained higher FVIIc activity during anticoagulation therapy. For patients with lower FVIIc at baseline or who experience bleeding events or significant decreases in FVIIc with warfarin therapy, alternative therapies could be considered.

Our patient was initially treated with warfarin in 2011. At that time, evidence-based practice guidelines recommended long-term antithrombotic therapy with either warfarin or aspirin, since the patient had only one major risk factor—hypertension [21, 22]. In 2014, however, updated guidelines now favoured anticoagulation therapy for our patient, despite no change in her risk factors [23, 24]. The American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) 2014 guidelines recommend using the CHA_2DS_2-VAS_c scoring system to assess stroke risk. The CHA_2DS_2-VAS_c score for our patient was 3, due to hypertension, female sex, and age $\geq$65 years. For scores $\geq$2, anticoagulation therapy is recommended (warfarin: level of evidence—A; dabigatran, rivaroxaban, apixaban: level of evidence—B) [24]. These changes in treatment guidelines are significant for our patient, as aspirin is no longer considered an acceptable treatment option on the basis of her risk factors.

The new agents mentioned above represent a new group of anticoagulants known as direct oral anticoagulants (DOACs). This group currently includes direct thrombin (factor II [FII]) inhibitors (dabigatran) and direct FXa inhibitors (rivaroxaban, apixaban and edoxaban). The mechanisms by which both classes of agents act target a clotting factor only in the common pathway of the coagulation cascade, independent from FVII. Laboratory analysis has shown that these agents do not inhibit FVII [25, 26]. In contrast, warfarin inhibits FVII in the extrinsic pathway. Clinical studies have shown dabigatran, rivaroxaban, apixaban and edoxaban to be comparably safe and effective in comparison with warfarin therapy for the treatment of atrial fibrillation, although patients with FVII deficiency and other RBDs were excluded from the trials [27–30]. However, because these agents provide therapeutic anticoagulation by targeting clotting factors below FVII in the clotting cascade (Fig. 1) and do not directly affect FVII activity, they may theoretically carry less bleeding risk than warfarin in patients with FVII deficiency.

This suggestion to choose an anticoagulant that does not affect FVII activity is supported by the case report [20] in 2009, which emphasized heparin use in patients with FVII deficiency. In that case, LMWH was safely tolerated throughout the duration of maintenance therapy. However, at that time, the DOACs were not approved or available for use. Interestingly, the DOACs have mechanisms of action similar to those of heparin, targeting FXa and/or FII. While heparin remains a viable option, it must be administered parenterally, which is a disadvantage in comparison with orally administered medications. One important difference between LMWH and the DOACs is the ability to monitor the anticoagulant effect beyond the FVIIc activity assay, as LMWH can be monitored using anti-Xa levels, which correlate with the actual bleeding risk. This ability (not requirement) to monitor the anticoagulant effect may serve as an advantage in this population at higher risk of bleeding, as it gives the clinician a method to objectively assess the degree of anticoagulation being provided. The DOACs rivaroxaban, apixaban and edoxaban are FXa inhibitors and, although anti-Xa level monitoring is not performed clinically, it would seem reasonable that it could be utilized

with these agents as well [31]. Lastly, the initial lack of antidotes or reversal agents for the DOAC class was considered to be a disadvantage but, recently, highly specific reversal agents have been developed and studied with positive results in clinical trials [32, 33]. Before reversal agents were available, a subgroup analysis from the ROCKET-AF trial of 779 patients who experienced major bleeding revealed no differences in outcomes in patients treated with rivaroxaban versus warfarin, including death (20.4 vs 26.1 %; hazard ratio 0.69, 95 % confidence interval 0.46–1.04). There was also less use of prothrombin complex concentrate (PCC) and significantly less use of fresh frozen plasma (FFP) with rivaroxaban compared with warfarin [34]. This information supports the consideration of DOACs as a potential alternative to vitamin K antagonists, even in unique and high-risk patient situations.

Conclusion

Warfarin has been the treatment of choice for thromboembolic conditions for multiple decades, but the data are limited in patients with RBDs. We have described a successful re-challenge of warfarin therapy in a patient with FVII deficiency. However, compared with our patient case, patients with more severe FVII deficiency at baseline or those who experience lower levels of FVII activity during warfarin therapy may not observe the same positive response. The emergence of the DOAC group of anticoagulants has provided more options for clinicians when treating patients with RBDs in the outpatient setting. Based on their mechanisms of action in relation to the coagulation cascade, it would seem DOACs could potentially be safer alternatives to warfarin for patients with FVII deficiency by providing similarly therapeutic anticoagulation with less bleeding risk. Future studies would be helpful to evaluate the safety and effectiveness of DOAC therapy in patients with FVII deficiency. However, because of the rare nature of the disorder, it is not feasible to conduct prospective, randomized studies. Large clinical trials of anticoagulants typically exclude patients with FVII deficiency and other RBDs, although this would be an excellent way to obtain more data. It is imperative for clinicians to publish case reports and other retrospective data to guide future therapy in this population.

Compliance with Ethical Standards

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent may be requested for review from the corresponding author.

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