

# Therapeutic Management of a Patient With a Unique Factor IX Sensitivity to Warfarin

Salvatore Scialla, MD<sup>1</sup>  
 Ronald Rubin, MD<sup>2</sup>  
 Kristin M. Liptock, DO<sup>1</sup>

<sup>1</sup> Scranton Temple Residency Program, Scranton, Pa  
<sup>2</sup> Temple University School of Medicine, Philadelphia, Pa

Warfarin sensitivity and resistance is a commonly encountered clinical problem. By far the most common mechanism of this sensitivity and resistance involves albumin binding interactions, and most importantly, warfarin metabolism interactions in the hepatic mixed-function oxidative p450 microsomes.<sup>1</sup> On rare occasions, unique biochemical resistance and/or sensitivity mechanisms such as altered affinity of the warfarin receptor<sup>2</sup> and factor IX propeptide mutations<sup>3</sup> have been encountered.

We report a case of exquisite warfarin sensitivity related to an abnormal factor IX, which resulted in standard warfarin dosages causing hemophilic levels of factor IX with a subsequent bleeding diathesis consistent with this condition. Upon making the correct diagnosis, warfarin was monitored by factor analysis rather than international normalized ratio (INR) measurements with excellent clinical results at 4-year follow-up.

The patient is a 74-year-old man who presented to the hospital with left leg pain and swelling. He had recently undergone surgery for aortic valve replacement and coronary artery bypass grafting. He was placed on warfarin prophylaxis with monitoring by INR. He achieved a prothrombin time (PT) of 25 seconds, with an INR of 2.38 by postoperative day 5 at a dose of 5 mg daily. His INR remained stable in the range of 2–3.

The patient presented after four weeks with significant swelling of the left thigh with ecchymotic discoloration from hematoma. Ultrasound studies confirmed a large deep hematoma and warfarin treatment was discontinued. The coagulation studies returned to normal with a PT of 12.7 seconds, INR of 1.3, and activated partial thromboplastin time (aPTT) of 28.9 seconds. A subsequent trial of warfarin coagulation resulted in another bleeding episode with a deep thigh hematoma. At the time of the second episode, INR was 1.87, PT was 15.5 seconds, and aPTT was 44.1 seconds. Factor analysis was performed and revealed the following activities: factor II, 50%; factor VII, 52%; factor VIII, greater than 200%; factor X, 29%; factor XII, 81%; and factor IX, 1%.

An inferior vena cava filter was inserted, and the patient was cautiously restarted on warfarin. APTT, factor

II, and factor IX activities rather than INR were closely monitored. Maintaining factor IX activity in the range of 20–40% has prevented further bleeding or thrombosis at 4-year follow-up.

## Discussion

This patient was found to have a unique sensitivity to warfarin. Chu and colleagues<sup>3</sup> described a patient with a factor IX mutation that resulted in increased warfarin sensitivity because of reduced affinity of the gamma-glutamylcarboxylase for the factor IX propeptide precursor. The patient described by Chu and colleagues had a factor IX activity of over 100% when off warfarin and 1% on warfarin, at a point where other vitamin K-dependent factors were at 30–40% activity.

Remarkably, our patient was later found to be related to the patient studied by Chu and colleagues. The defect appears to be located on the X chromosome. This rare mutation is estimated to occur in less than 1.5% of the population<sup>1</sup>; as such there is a lack of studies in the literature to suggest definitive management and screening options.<sup>4</sup>

In our patient, we continued warfarin therapy, adjusting dosage according to monitored aPTT, factor II, and factor IX levels. By lowering the factor IX activity to 20–40% we were able to prevent aortic valve-induced thrombosis. Data from the past three years demonstrate that the aPTT is not sensitive enough for management. At a factor IX activity of 25%, the aPTT was in the normal range at 36 seconds. At a factor IX activity of 11%, the aPTT was 48.6 seconds. The factor II activity has been approximately 50% during the use of warfarin in this patient.

Warfarin management in our patient has required factor IX analysis in order to prevent bleeding complications while maintaining lower factor IX activity. Thus far the approach has been successful for four years in that no thromboses or bleeding complications have occurred. Although the incidence of this unique situation is low, a spot aPTT in a patient with unusual bleeding while on

warfarin with a reasonable INR may be a helpful screen. Depending on the sensitivity of the reagent, the aPTT is a better monitor because the PT will not reflect the dramatic drop in factor IX levels.

Our patient showed similar clinical and laboratory characteristics to the patient discussed by Chu and colleagues. Our patient was also found to be genetically linked to their patient, and almost assuredly shares the propeptide mutation in factor IX. This case report demonstrates a strategy of warfarin management incorporating vitamin K–dependent coagulation factor analysis.

## References

1. Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic management. *Chest*. 2001;119:8S-21S.
2. Alving BM, Strickler MP, Knight RD, et al. Hereditary warfarin resistance. *Arch Intern Med*. 1985;145:499-501.
3. Chu K, Wu SM, Stanley T, et al. A mutation in the properties of factor IX leads to warfarin sensitivity by a novel mechanism. *J Clin Invest*. 1996;8:1619-1625.
4. Jorgensen MJ, Cantor AB, Furie BC, et al. Recognition site directing vitamin K-dependent gamma-carboxylation resides on the propeptide of factor IX. *Cell*. 1987;48:185-191.

## Review

Elizabeth Blanchard, MD

Jack Ansell, MD

*Boston University School of Medicine*

The coumarin-type anticoagulants are vitamin K antagonists that interfere with the synthesis of the functional coagulation factors II, VII, IX, and X.<sup>1</sup> These vitamin K–dependent factors require gamma carboxylation of the glutamate residues on the N terminus of the respective polypeptides in order to function properly; vitamin K is a cofactor for this carboxylase reaction. This reaction requires reduced vitamin K<sub>1</sub>, which is oxidized in the process and subsequently reduced for recycling. Warfarin inhibits one of the reductase enzymes and leads to the accumulation of oxidized vitamin K epoxide and less of the reduced form of vitamin K. The resulting vitamin K–dependent factors are undercarboxylated and exhibit reduced procoagulant function.

The key to safe and effective therapy with warfarin is to maintain the patient in a therapeutic INR range. This is challenging because of the many factors that influence response to warfarin including other medications, diet, concomitant illnesses, and other factors. Medications may influence warfarin pharmacokinetics by enhancing or inhibiting its major metabolic enzyme, cytochrome

P450 2C9. Diet can lead to changes in warfarin's effect by containing a variable vitamin K content. Lastly, concomitant illnesses may influence liver function and warfarin metabolism or coagulation factor synthesis, or may affect diet and lead to reduced vitamin K intake.

Chu and colleagues described a case of warfarin sensitivity as a result of a mutation in the gene coding for the factor IX protein.<sup>2</sup> This patient, on warfarin for an aortic valve replacement, developed significant bleeding with extremely low factor IX activity (<1%), while factor VII activity was only modestly reduced. Off of warfarin, the patient's factor IX levels returned to normal but fell again to very low levels once warfarin was restarted. Chu and colleagues found a base pair substitution mutation in which threonine was substituted for alanine at position -10 in the propeptide portion of factor IX. The propeptide portion is the recognition site for the carboxylase enzyme and a mutation in that area appears to result in the decreased affinity of the carboxylase enzyme for factor IX. With reduced carboxylation, there is reduced activity and apparent sensitivity for additional defects in carboxylation such as those that occur with warfarin therapy.

Scialla and colleagues describe a similar case of warfarin sensitivity as a result of an apparent factor IX dysfunction in a patient who, as it turns out, is related to the patient described by Chu and colleagues. This case is that of an elderly man receiving anticoagulation for an aortic valve replacement who had significant bleeding manifested by a deep thigh hematoma on 2 occasions. After the second bleeding episode, factor levels were measured and factor IX activity was 1%, while other vitamin K–dependent factors were only moderately reduced (29–52%). Distinct from the previous case, the aPTT was not severely prolonged. Subsequent long-term management of this patient was achieved by monitoring factor IX activity levels and maintaining a level of 20–40%. The patient remained free of thrombotic complications during the follow-up period of 4 years. The authors note that the aPTT was not sensitive enough to use for management and the aPTT remains in the normal range in this patient when factor IX levels drop as low as 25%.

This interesting case raises several questions. Does this indeed represent a mutation in the gene coding for factor IX similar to the case described by Chu and colleagues? Can using factor IX levels in such a case provide adequate anticoagulation? The authors propose this to be a case of a mutation in factor IX causing increased sensitivity to warfarin by the findings of a severely diminished factor IX with only modestly reduced levels of other vitamin K–dependent factors during warfarin therapy. This proposed cause is further supported by the fact that this second case is actually a relative of the patient described by Chu and colleagues. However, no data are provided to

exclude a mild hereditary factor IX deficiency as the cause of this patient's clinical picture. Measuring factor IX levels off therapy might resolve this possibility.

One wonders whether adequate anticoagulation in a patient with a mechanical heart valve can really be achieved by maintaining factor IX levels in the range of 20–40% as the authors did thereafter. By reducing the dose of warfarin to achieve this level of factor IX, one would expect the other vitamin K–dependent factors to be considerably higher ( $\geq 50\%$ ). This would allow for a relatively normal extrinsic pathway of coagulation (factors VII, X, V, II, I) to operate and might allow for coagulation/thrombosis to occur. However, this patient appears to have stood the test of time, as he was without thrombotic or bleeding complications during the four years of follow-up.

Alternative approaches to anticoagulation in a case like this might be to use an anticoagulant that is a non-vitamin K antagonist such as a low-molecular weight heparin (LMWH), although only short-term use of LMWH in

patients with mechanical heart valves has been studied to date.<sup>3,4</sup> Lastly, one might eventually consider one of the newer antithrombotic agents in clinical trials as a suitable alternative. These include the indirect factor Xa inhibitor idraparinux (Sanofi-Aventis/Organon), a synthetic heparin pentasaccharide, or other oral direct Xa inhibitors or IIa inhibitors, such as ximelagatran (Exanta, AstraZeneca).<sup>5</sup>

## References

1. Hirsch J, Dalen JE, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest*. 2001;119:8S-21S.
2. Chu K, Wu SM, Stanley T, et al. A mutation in the propeptide of factor IX leads to warfarin sensitivity by a novel mechanism. *J Clin Invest*. 1996;98:1619-1625.
3. Ferreira I, Dos L, Tornos P, et al. Experience with exoxaparin in patients with mechanical heart valves who must withhold acenocumarol. *Heart*. 2003;89:527-530.
4. Montalescot G, Polle V, Collet JP, et al. Low molecular weight heparin after mechanical heart valve replacement. *Circulation*. 2000;101:1083-1086.
5. Ansell J. New anticoagulants and their potential impact on the treatment of thromboembolic disease. *Curr Hematol Rep*. 2004;3:357-362.