Warfarin resistance in a patient with mechanical valve prosthesis

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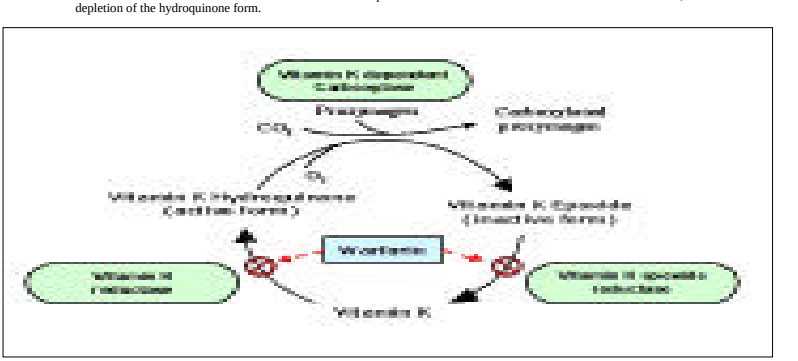
The term warfarin resistance is usually reserved for patients who require warfarin in excess of 20 mg/day to maintain the International Normalized Ratio (INR) within the therapeutic range. It is usually encountered at the start of therapy, however, it may also occur in patients who have been already on warfarin therapy. Both diet and the co-administration of certain drugs can have a marked effect on the anticoagulant efficacy of warfarin.

A 45-year-old lady who had a mechanical mitral valve prosthesis (Tilting Disc Prosthesis) 12 years ago presented with chest pain and shortness of breath on moderate exertion. She was maintained on warfarin until 3 years ago when she developed left hemiparesis. Since then there have been difficulty in getting her adequately anticoagulated and she was labeled as having "warfarin resistance". Despite giving her up to 35 mg of warfarin a day, her INR never reached a therapeutic level. She has not been on any medications that could have interfered with the action of warfarin. Subsequently, she was shifted to enoxaparin 80 mg subcutaneous injection twice a day and was even offered to have her metallic mitral prosthesis changed to a tissue valve in order to avoid the need for anticoagulation. Her physical examination showed a regular pulse of 82/minute and the mitral prosthesis metallic click was heard. The rest of her examination was unremarkable. Her investigations showed normal complete blood count and chemistry with an INR of 0.9, electrocardiogram was normal and her chest x-ray was clear. Transesophageal echocardiogram revealed satisfactory function of the mitral valve prosthesis with no evidence of valvular thrombosis, pulmonary artery systolic pressure was 30 mm Hg. High resolution computed tomography (CT) scan of the chest showed features consistent with pulmonary hypertension and mild bronchiectasis. Cardiac catheterization revealed normal coronaries. She was recommenced on warfarin and followed up regularly in the hematology clinic, however, warfarin resistance was evident again with an INR remaining between 0.9-1.1 despite increasing the warfarin dose gradually up to 40 mg per day. She strongly denied non-compliance with her medications and was not on any vitamin supplements, diet or drugs that could depress the effect of warfarin. She was then maintained on enoxaparin and warfarin. Two months later, she was admitted to our hospital with a transient ischemic attack. She had left sided hemiparesis that resolved within 12 hours with no residual focal neurological deficit. She was in sinus rhythm and her INR was 0.94. Brain CT scan was normal. Clinical suspicion

Figure 1 - Vitamin K cycle and site of inhibition by warfarin. Vitamin K is reduced to vitamin K hydroquinone by vitamin K reductase. This reduced form of vitamin K is a cofactor for the vitamin K-dependent carboxylase which is responsible for the conversion of glutamic acid residues (of vitamin K dependent coagulant proteins) to γ-carboxyglutamic acid. During this reaction vitamin K hydroquinone is oxidized to vitamin K epoxide. This inactive form of vitamin K is salvaged by an enzyme, vitamin K epoxide reductase, and is recycled back to vitamin K. Vitamin K reductase and vitamin K epoxide reductase are both sensitive to warfarin inhibition, this leads to the depletion of the hydroquinone form.



of non compliance with warfarin was raised and she was therefore kept in hospital for supervised administration of warfarin. Surprisingly, after a 20 mg loading dose of warfarin taken in front of the doctor followed by daily doses of 7.5 mg, her INR increased to 2.5 in less than 5 days. She admitted then to the fact that she has not taken her warfarin tablets for more than 3 years. Her INR remained within a therapeutic level of 3-3.5 on 7.5 mg per day. She was then evaluated by the psychiatrist who felt that she was suffering from depression and started her on citalopram 20 mg once daily. The seriousness of the issue was discussed with her and her family. She was subsequently followed in the hematology clinic and her INR remained within the therapeutic range with a dose of 7.5 mg daily.

Warfarin is a vitamin K antagonist that inhibits the synthesis of functionally active vitamin K-dependent coagulation factors. Vitamin K works as a cofactor for the enzymes that carboxylates the glutamic acid residues of factors II, VII, IX, and X as well as the natural anticoagulants; protein C and its cofactor, protein S. Warfarin interferes with the regeneration of reduced form of vitamin K by inhibiting reductase enzymes (vitamin K reductase and vitamin K epoxide reductase). **Figure 1** details the recycling process of vitamin K and the site of warfarin action.

The INR (International Normalization Ratio) reflects the balance between vitamin K status and the warfarin dose. Lowered response to warfarin may be secondary to poor compliance, poor absorption, diet or coadministration of drugs that may interact with warfarin; depressing its effect. Examples of drugs that depress the effect of warfarin are Barbiturates, Carbamazepine, Chlorthalidone, Cholestyramine, Digitalis, Ethanol, Estrogens, Glutethimide, Griseofulvin, Haloperidol, Oral Contraceptives, Phenobarbital, Rifampin and Vitamin K-containing Preparations.

Warfarin resistance can also occur when warfarin is given concurrently with enteral feeding.[1] Patients and physicians may not be aware of vitamin K supplements that patient is taking, such as parenteral nutrition or vitamin K-containing multivitamins. Patients taking large amounts of cruciferous vegetables like cabbage, spinach and broccoli may also exhibit resistance to warfarin because of the high vitamin K content in these products.[2,3] Excess dietary vitamin K can cause life-threatening consequences in patients on warfarin. Myocardial infarction after diet-induced warfarin resistance in a patient with prosthetic aortic valve was described.[4] If excess vitamin K supplement, as well as concomitant use of drugs that counteract the effect of warfarin have been ruled out, other causes of warfarin resistance are extremely rare. Warfarin resistance, presumably secondary to malabsorption in a patient with mechanical mitral valve prosthesis was reported and this was treated with replacement of the mechanical valve by a biological valve, thereby eliminating the need for anticoagulant therapy.[5] This option was offered to our patient when she developed warfarin resistance but she refused such option. Hereditary warfarin resistance is one of the rare causes that appear to involve epoxide reductase, an enzyme involved in the synthesis of vitamin K-dependent clotting factors, which is less sensitive to the inhibitory effect of warfarin.[6]

Compliance to medications that patients are supposed to take life-long is always problematic, particularly when such medication requires frequent follow up and laboratory monitoring. Brief noncompliance to warfarin is a common problem in daily practice, but prolonged intentional noncompliance with the intention of self-harm is rare, and should be considered, despite patient's denial, if other more common causes of warfarin resistance are excluded.

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References

1. Howard PA, Hannaman KN. Warfarin resistance linked to enteral nutrition products. ***J Am Diet Assoc*** 1985; 85: 713-715.
2. Kempin SJ. Warfarin resistance caused by broccoli. ***N Engl J Med*** 1983; 308: 1229-1230.
3. Ovesen L, Lyduch S, Idorn ML. The effect of a diet rich in brussels sprouts on warfarin pharmacokinetics. ***Eur J Clin Pharmacol*** 1988; 34: 521-523.
4. Gotze JP, Thorsen S, Haunso S. Acquired warfarin resistance in a patient with mechanical heart valve. ***Ugeskr Laeger*** 2001; 163: 7075-7076.
5. Lara LF, Delgado LL, Frazee LA, Haupt KM, Rutecki GW. A subtherapeutic international normalized ratio despite increasing doses of warfarin: could this be malabsorption? ***Am J Med Sci*** 2000; 320: 214-218.
6. Alving BM, Strickler MP, Knight RD, Barr CF, Berenberg JL, Peck CC. Hereditary warfarin resistance. Investigation of a rare phenomenon. ***Arch Intern Med*** 1985; 145: 499-501.