Elmer Press

Case Report J Hematol. 2014;3(4):116-117

# Warfarin-Induced Pseudo-Allergy

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## Abstract

Most common adverse reactions to warfarin are fatal and nonfatal hemorrhage from any tissue or organ. Despite bleeding complications being the most feared concern, non-bleeding events can also occur from warfarin therapy. These non-bleeding events, which account for less than 1%, include but are not limited to skin necrosis and dermatological hypersensitivity reactions. We describe a rare case of "warfarin allergy" in a 77-year-old female patient admitted for coronary bypass grafting and mitral/aortic valve replacement. The patient came with a history of valvular heart disease, embolism (occlusion of distal superficial femoral artery) and atrial fibrillation with documented "warfarin allergy" described as dermatitis and anaphylaxis witnessed during earlier hospital admission. Given double valve replacement and atrial fibrillation ($CHA_2DS_2$-VASc score of 9), she was deemed a candidate for lifelong warfarin. Significant renal impairment and recent valve replacement narrowed the choice of anticoagulant to warfarin. To rule out the possibility of dye allergy, patient was re-challenged with dye free warfarin with close monitoring. Patient was able to tolerate dye free (white) warfarin with no allergic manifestation. The purpose of this report is to increase awareness of possibility of allergic reaction to dye in medications and recommend possibility of dye free medications as an option in such cases.

**Keywords:** Warfarin; Pseudo-allergy; Adverse reaction

## Introduction

Warfarin sodium acts by inhibiting the synthesis of vitamin K-dependent clotting factors, which include factors II, VII, IX, and X, and the anticoagulant proteins C and S [1]. Commonly indicated for prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism, prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement and reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction [1]. For patients with a bioprosthetic valve in the mitral position and atrial fibrillation a target INR of 2.5 is recommended (range, 2.0 - 3.0) for life [1].

Most common adverse reactions to warfarin are fatal and nonfatal hemorrhage from any tissue or organ [1]. Although dermatological allergic reactions with warfarin are rare and reported in few cases, it makes it difficult to manage patients when drug is essential and newer alternatives are not options due to unlabeled indications or other comorbid conditions like severe renal impairment. Few case reports in medical literature describe the cutaneous reactions in patients taking warfarin. Reported adverse reactions, such as urticarial, maculopapular, vesicular, and pruritic skin eruptions in all cases involved coumarin derivatives [2-9]. Onset of maculopapular rash was described as occurring within 40 min to 4 weeks after warfarin ingestion with pruritus and urticarial lesions [3, 4, 10].

## Case Report

A 77-year-old female patient was transferred from another facility to our tertiary center for cardiac surgery for double valve replacement and coronary artery bypass surgery. She was known to have severe aortic stenosis associated with moderate aortic insufficiency in addition to heavily calcified mitral valve with moderate mitral valve stenosis. Other comorbid disease states included diabetes mellitus, chronic renal insufficiency, atrial fibrillation, heart failure, hypertension, dyslipidemia and hypothyroidism. Patient underwent mitral valve replacement (perimount 25 mm biological prosthesis) aortic valve replacement (perimount 21 mm, biological prosthesis) and coronary artery bypass grafting.

Due to combination of valvular heart disease and embolic events (Doppler study was showing occlusion of distal superficial femoral artery) 3 years earlier (2011), she was deemed appropriate for anticoagulation. She was initially maintained

Manuscript accepted for publication November 11, 2014

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doi: http://dx.doi.org/10.14740/jh173w

on low molecular weight heparin and subsequently started on oral warfarin. The patient, however, did not tolerate warfarin and developed allergic reaction manifesting as skin rash and anaphylaxis. Warfarin was therefore discontinued and replaced with dabigatran. However, patient developed rectal bleeding, hemoptysis and mild epistaxis. Dabigatran was therefore stopped and patient was maintained on aspirin and pentoxyfylline alone. Patient required blood transfusions to correct her hemoglobin to her initial baseline level.

Three years later, she presented with atrial fibrillation and double valve replacement. Calculated $CHA_2DS_2$-VASc score of 9 corresponded to a high risk of stroke in atrial fibrillation. Yearly risk of stroke without warfarin treatment was estimated at 15.2%; consequently she was deemed a candidate for lifelong warfarin. With known documented history of warfarin allergy and unlabeled indication of newer anticoagulants, following options were considered: 1) re-challenge patient with warfarin. 2) Dabigatran or rivaroaxaban after first 3 months of therapeutic enoxaparin (given biological valve replacement these drugs are not labeled for use within first 3 months). However given fluctuating renal function (CrCl range 15 - 30 mL/min) and patient's previous history of bleeding with dabigatran, it was not considered as the first option (apixaban not included in formulary). 3) Clopidogrel 75 mg daily for atrial fibrillation with close monitoring and follow-up for bleeding.

Hematologist was consulted and decision was made to re-challenge patient with warfarin given the high risk of embolism. Hospital formulary included coumadin from Germany, of which 5 mg was a white tablet without dye. Patient was challenged with 5 mg white warfarin in critical care unit with close monitoring. No anaphylaxis or rash was observed. Patient was followed for 3 months with close monitoring without any allergic manifestations.

## Discussion

Although rare, dermatological reaction and anaphylaxis to warfarin can present great challenge in managing patients with atrial fibrillation especially in patients where the use of newer anticoagulants remains unlabeled. Cutaneous reaction attributing to inactive ingredient like dye in warfarin was also reported in a case study by Bogart et al [11]. Most recently, there were documented cases of skin rash with sinemet that were recognized to yellow dye (D&C yellow 10 and FD&C yellow 6) [11, 12]. Patients experiencing rash on sinemet were re-challenged with levodopa and were able to tolerate forms of levodopa not containing the dye. Similarly, urticaria was reported as a reaction to blue dye in synthroid tablets [11, 13]. Allergic manifestation to inactive ingredients like dye in medications may be more common than anticipated. Possibility of dye allergy should be evaluated in patients before changing the drug regimen when possible.

## Acknowledgement

The authors would like to acknowledge and thank Dr. Nameer Al Saadawi for his time and effort critiquing and editing this paper.

## Financial Support

No sources of financial support.

## Conflicts of Interest

The authors have no conflict of interest to disclose.

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