Warfarin Allergy: An Easy Solution

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Introduction

Allergic cutaneous reactions in patients on warfarin are uncommon but represent a clinical dilemma when the drug is essential for management. The usual approach to treating these reactions in the past has been discontinuation of warfarin and use of alternative oral anticoagulants which include either another coumarin derivative or an indandione like anisindione. Since other oral vitamin K antagonists (eg, phenindione, anisindione) are no longer available in the United States and orally administered direct thrombin inhibitors (eg, ximelagatran) have not yet passed the scrutiny of the United States Food and Drug Administration, subcutaneous administration of low molecular weight heparins offer another alternative. However, patients generally prefer and are more compliant with oral drug administration. The cutaneous reaction to warfarin tablet can either be due to the active ingredient (ie, warfarin) or an inactive ingredient like dye. However, the possible allergic reaction to the dye in a warfarin tablet is not widely appreciated and in a significant number of cases, warfarin is an essential part of long-term therapy. The purpose of this report is to increase the awareness of allergic reaction to the dye and propose a simple solution.

Case Report

A 53-year-old African American male presented for evaluation of chest pain and was found to have atrial fibrillation. The patient had a history of atrial fibrillation since 1983 and had multiple cardioversions. His past history was significant for "warfarin allergy" and he had been told not to take this drug. The allergy was manifested by hives. His daily medications were diltiazem 360 mg, atenolol 50 mg, and aspirin 325 mg. His examination revealed atrial fibrillation and was otherwise unremarkable. A dobutamine echocardiogram showed mild left ventricular hypertrophy, mild left atrial enlargement, but no evidence of ischemia. Transesophageal echocardiography revealed a small mobile density in the left atrial appendage, consistent with thrombus.

Because of the warfarin allergy, a decision was made to treat the patient with enoxaparin 1 mg/kg every 12 hours subcutaneously while an alternative oral antithrombin was sought. The PharmD service was consulted and it was suggested that the rash might be due to the dye in the warfarin tablet. Since the 10 mg tablets do not contain dye, this was suggested as a possible solution. After careful

explanation and informed consent, the drug was initiated with one-half of the 10 mg tablet. No rash appeared. The patient has been maintained on this formulation of the drug for 6 months with no adverse effects.

Discussion

Dermatologic adverse reactions to warfarin are rare, however with the widespread use of the drug, many health care professionals may encounter it. Various types of warfarin-induced skin reactions have been reported including vesicular, maculopapular, and urticarial lesions. More serious dermatologic skin conditions caused by warfarin include skin necrosis and "purple-toe syndrome." Practitioners must distinguish these more serious cutaneous conditions from a nonthreatening maculopapular rash.¹

It is possible, but rare, to have an allergic type reaction to a color additive. The Food and Drug Administration (FDA) regulates dyes added to drugs. In many cases the type of dye must be identified on the drug labeling so consumers who are sensitive to the dye may avoid it. Warfarin is manufactured by Mallinckrodt Pharmaceuticals and coumadin is manufactured by Bristol-Myers Squibb. Both pharmaceutical companies use the same strength tablets with identical coloring. The tablets differ only in shape. Warfarin is oval and coumadin is round. The Table lists the specific dye used in each strength tablet.²⁻³

There have been numerous case reports of skin eruptions after administration of warfarin.⁴⁻⁹ The rash was most often described as a pruritic, maculopapular eruption that resolved with cessation of the drug and recurred with rechallenge.⁵⁻⁷ In 1 case, rechallenge with warfarin was not done for ethical reasons⁸ and in another case, rechallenge with warfarin was not done because skin tests were not confirmatory.⁴ In 1 case, the patient had the same reaction to acenocoumarol which contained a coloring agent and warfarin and phenprocoumon (uncolored tablet). The etiology of the rash in this case was thought to be an immunologic reaction vs a metabolic idiosyncrasy.⁹

Most recently, there were documented cases of skin rash with sinemet that were actually attributed to yellow dye (D&C yellow 10 and FD&C yellow 6). Patients experiencing a rash on sinemet were rechallenged with levodopa and were able to tolerate forms of levodopa not containing the dye.¹⁰ Similarly, urticaria was reported as a reaction to blue dye in synthroid tablets.¹¹ These situations¹⁰⁻¹¹ are analogous to the case report described in this article.

Table 1. Types of Dyes Present in Different Coumadin (Warfarin Tablets)

	Coumadin (Warfarin) Tablets for Oral Use Also Contain:
All strengths	Lactose, starch, and magnesium stearate
1 mg (pink)	D&C Red No. 6 Barium Lake
2 mg (lavender)	FD&C Blue No. 2 Aluminum Lake and FD&C Red No. 40 Aluminum Lake
2.5 mg (green)	D&C Yellow No. 10 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
3 mg (tan)	FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, and FD&C Red No. 40 Aluminum Lake
4 mg (blue)	FD&C Blue No. 1 Aluminum Lake
5 mg (peach)	FD&C Yellow No 6 Aluminum Lake
6 mg (teal)	FD&C Yellow No. 6 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
7.5 mg (yellow)	D&C Yellow No. 10 Aluminum Lake and FD&C Yellow No. 6 Aluminum Lake
10 mg (white)	Dye Free

Clearly, the lesson learned in this case is to think about dye in medications as a potential source of maculopapular

eruptions before changing the anticoagulation regimen. As an initial step in management, a simple change to an uncolored tablet of the same drug may readily relieve the patient of their symptoms and provide a long-term solution for clinical management.

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