Warfarin or excipient allergy: a clinical dilemma resolved

"it is possible to have dermatological adverse reactions to the colouring dyes in warfarin"

A 57-year-old Asian woman was referred for surgical ablation of atrial fibrillation (AF), coronary revascularisation and mitral valve surgery. She had a history of paroxysmal AF, previous stroke, coronary artery disease and severe mitral regurgitation. In the work-up for surgery, she developed recurrent, pruritic maculopapular rashes involving her trunk and upper limbs on two occasions within 3 days of initiating oral anticoagulation with warfarin (Marevan, Aspen) for AF. There were no other changes to the patient's longstanding medication regimen during this period. Her regular medications consisted of aspirin 100 mg and perindopril arginine 2.5 mg in the morning, and atorvastatin 80 mg at night. Long-term anticoagulation with warfarin was necessary due to planned mechanical valve replacement and ongoing paroxysmal AF. Subsequently, she was referred to a clinical immunologist for assessment of her reaction to warfarin. Since allergic reactions to warfarin are rare, a reaction to one of the dyes in the tablet was considered.

The patient had been taking all three strengths of Marevan tablets (1 mg, 3 mg and 5 mg), which contain a number of excipients (Box). Initial drug challenge commenced with Coumadin 1 mg (Bristol-Myers Squibb) tablets, as these did not contain any shared excipients. She tolerated this for 1 week and subsequently the dose was increased to three 1 mg tablets of Coumadin. She remained symptom-free and reached a therapeutic international normalised ratio. It was therefore deemed safer to avoid Marevan 1 mg and 3 mg tablets and the Coumadin 2 mg tablet, which shared the colouring constituent indigo carmine (132). She later underwent mitral valve replacement with a mechanical valve, closure of the left atrial appendage, surgical ablation and coronary revascularisation. She currently remains rate-controlled at 7 months follow-up with therapeutic anticoagulation on Coumadin 1 mg tablets.

"Warfarin allergy" can be due to the coumarin structure or the excipients introduced for colouring and safety.[1] While this has previously been documented, excipients are rarely considered as a possible cause of allergic reaction in common practice.[1,2] Importantly, not all allergies are attributed to the coumarin structure, and it is possible to have dermatological adverse reactions to the colouring dyes in warfarin.[1,3] In our patient, we strongly suspect indigo carmine (FD&C Blue No. 2). Blue dyes have previously been implicated as the cause of urticarial rashes in patients taking synthyroid tablets.[4] Although there was no objective confirmation of causality (eg, patch testing), the clinical presentation coupled with a high score of 9 on the Naranjo probability scale is compelling, although not conclusive.[5] With this in mind, we suggest that excipient allergy should be considered in patients with a reaction to warfarin, and dye-free preparations can be administered as a therapeutic alternative.

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References are available online at www.mja.com.au.

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Excipient dyes used in Coumadin and Marevan brands

Brand/strength	Tablet colour	Active ingredient	Dye
Coumadin 1 mg	Light tan	Warfarin sodium	Amaranth (123) Quinoline Yellow (104)
Coumadin 2 mg	Lavender	Warfarin sodium	Amaranth (123) Indigo Carmine (132)
Coumadin 5 mg	Green	Warfarin sodium	Quinoline Yellow (104) Brilliant Blue FCF (133)
Marevan 1 mg	Brown	Warfarin sodium	Iron Oxide Yellow (172) Iron Oxide Red (142) Indigo Carmine (132)
Marevan 3 mg	Blue	Warfarin sodium	Indigo Carmine (132)
Marevan 5 mg	Pink	Warfarin sodium	Erythrosine (127)

Other excipients (all strengths): Coumadin — lactose, starch (tapioca, stearic acid and magnesium stearate); Marevan — lactose, starch (maize and pregelatinised maize, sodium starch and magnesium stearate). ◆

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