

Induction of Tolerance to Warfarin after Anaphylaxis with a Desensitization Protocol

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Established Facts

- Hypersensitivity to warfarin has been rarely reported, with previous reactions largely involving the skin.
- Long-term anticoagulation with warfarin is the preferred treatment for recurrent thromboembolic disease.
- No cases of desensitization to warfarin have been published.

Novel Insights

- A novel case of anaphylaxis to warfarin is reported.
- Desensitization to warfarin is possible using a graded oral administration procedure.

Key Words

Allergy · Anaphylaxis · Desensitization · Hypersensitivity · Warfarin

Abstract

Warfarin hypersensitivity is exceedingly rare. A 59-year-old male with acute renal infarction and a history of allergy to warfarin underwent evaluation, confirming presence of warfarin hypersensitivity. Induction of tolerance to warfarin was successfully completed using an oral desensitization protocol, which has not previously been reported.

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Introduction

Crystalline warfarin sodium (Coumadin) is an anticoagulant that acts by inhibiting vitamin K-dependent coagulation factors. Warfarin is indicated for the prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation. Warfarin is also indicated to reduce the risk of thromboembolic events such as stroke. There are many documented potential adverse reactions to Coumadin therapy. Hypersensitivity reactions to warfarin, however, are exceedingly rare, with only 2 case reports indicating maculopapular rash in one and urticaria in another patient [1, 2]. There have been no documented attempts of desensitization in patients with warfarin allergy.

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0008–6312/10/1153–0174\$26.00/0

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Case Report and Methods

We report on a 59-year-old male with a medical history of atrial fibrillation, congestive heart failure, three-vessel coronary artery bypass grafting, cerebrovascular accident and new-onset right-sided renal infarction. The patient had a 3-year history of oral warfarin treatment but was discontinued from the medication due to severe pruritus and urticaria that had occurred several days after the initiation of the drug. He had full resolution of symptoms once warfarin was stopped. Due to the patient's significant co-morbidities and the high risk of recurrent thromboembolism, it was felt that he would most benefit from long-term anticoagulation with warfarin.

The patient was referred for evaluation of warfarin allergy. The history of pruritus with urticaria suggests an IgE-mediated process. Informed consent was given, and skin testing and a drug challenge were performed. The patient underwent skin prick testing with full-strength warfarin (2 mg/ml), as well as histamine (1 mg/ml) and glycerol-saline controls. Percutaneous testing was negative. A drug challenge was then initiated, which began with 0.2 mg i.v. warfarin, followed by 0.5 mg warfarin and 2.0 mg at 30-min intervals. The patient developed flushing, sweating and shortness of breath during the drug challenge. His examination revealed mild edema of the back and wheezing at the lung bases bilaterally. Intramuscular epinephrine, and oral and intravenous diphenhydramine were administered, with full resolution of symptoms.

After discussion with the patient and treating physicians, the patient consented to oral warfarin desensitization. There are no existing protocols for warfarin desensitization due to the rarity of warfarin allergy. Oral desensitization was performed with pre-medication (prednisone 20 mg orally, ranitidine 150 mg orally and diphenhydramine 50 mg orally, administered 24 h prior), according to the dose escalation protocol (table 1).

The following day, the patient was administered 5.0 mg warfarin. The patient remained stable with no adverse events, and was

Table 1. Oral desensitization protocol to warfarin sodium

Time, h	Dose, mg
0:00	0.25
0:20	0.50
0:40	0.75
1:00	1.00
1:20	1.50
1:40	2.00

discharged on 5.0 mg of warfarin with an international normalized ratio in the therapeutic range. Two weeks later, the patient presented to the outpatient clinic and complained of mild itching, which was further controlled with cetirizine once daily. He had improvement of renal function and no further thromboembolic episodes during the 6-month follow-up.

Discussion

Persons with acute renal infarction are known to have a high risk of recurrent thromboembolic phenomena with a 30-day mortality rate of 11% [3]. Adequate anticoagulation is mandatory to restore renal function and decrease short- and long-term morbidity and mortality [4]. This case illustrates a rare report of allergy to warfarin. In cases of warfarin hypersensitivity, successful induction of tolerance to the drug can be achieved through oral desensitization.

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