IJAHSP™ .nova.edu
The Internet Journal of Allied Health Sciences and Practice
A Peer Reviewed Publication of the College of Health Care Sciences at Nova Southeastern University
Dedicated to allied health professional practice and education
http://ijahsp.nova.edu Vol. 11 No. 4 ISSN 1540-580X

Warfarin Induced Generalized Dermatitis – A Case Study

Corinne Floyd, PharmD[1]
Simon Leung, MS, PharmD, BCPS[2]

1. Clinical Specialist, Department of Pharmacy, Memorial Regional Hospital, Hollywood, Florida
2. Clinical Coordinator in Cardiology, Department of Pharmacy, Memorial Regional Hospital, Hollywood, Florida

United States

CITATION: Floyd C, Leung S. Warfarin Induced Generalized Dermatitis. *The Internet Journal of Allied Health Sciences and Practice*. Oct 2013. Volume 11 Number 4.

ABSTRACT

Despite bleeding concerns, other non-bleeding events can also occur from warfarin therapy. These non-bleeding events, occurring in less than 1%, include but are not limit to skin necrosis, "purple toe syndrome," and dermatologic hypersensitivity reactions. Dermatologic adverse reactions from warfarin are uncommon and rarely reported in the literature. In this article, a rare case is described of warfarin induced generalized dermatitis in a 73-year-old female patient who was admitted for COPD exacerbation but later had paroxysmal atrial fibrillation ($CHADS_2$ score of 2) and experienced an acute dermatological reaction during the initial and subsequent re-challenge of warfarin therapy. Both episodes of hypersensitivity reaction were managed by standard support care. The purpose of this communication is to increase awareness of this adverse event, review prior case studies, and address alternative anticoagulation agents in the event of a similar dermatologic reaction. To our knowledge, this is the first report of warfarin induced generalized dermatitis.

INTRODUCTION

Warfarin sodium (Coumadin and Jantoven) is a vitamin K antagonist used to reduce the synthesis of coagulation factors II, VII, IX, and X, as well as proteins C and S.[1] Common clinical uses of warfarin include prophylaxis and/or treatment of thromboembolism (i.e., deep vein thrombosis and pulmonary embolism) and thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.[2] Anticoagulation with warfarin is used to reduce the risk of death, recurrent myocardial infarction, stroke, and systemic embolization after myocardial infarction.[2] Warfarin is listed as a high alert medication by the Institute for Safe Medication Practices because of the heightened risk of adverse drug events from complex warfarin dosing, a narrow therapeutic window, and other monitoring parameters like hemoglobin, hematocrit, and platelet counts. For these reasons, the Joint Commission has set national patient safety goals to reduce the likelihood of patient harm associated with the use of anticoagulant therapy.[3]

Bleeding is the major adverse event associated with warfarin therapy.[1] A recent pooled analysis of 1455 warfarin patients from multiple clinical trials had reported the rate of major bleeding as 4.7% (95% confidence interval of 3.8% to 6%).[4] When compared to aspirin patients, although not statistically significant, the same analysis noted an increase in major bleeding in warfarin patients resulting from a pooled odds ratio of 1.27 (95% confidence interval of 0.83 to 1.94).[4] Careful interpretation and extrapolation of these results are warranted because management of anticoagulation therapy is more vigilantly coordinated in clinical trials than in actual clinical practice. In addition, the bleeding risk of warfarin can also be influenced by the intensity of anticoagulation, concomitant therapies, especially antiplatelet drugs, high risk versus low risk bleeding patients, history of bleeding, other comorbidities and advanced age.[1]

Despite bleeding concerns, other non-bleeding events can also occur from warfarin therapy. Non-bleeding events, occurring in less than 1% and include but are not limit to skin necrosis, "purple toe syndrome," and dermatologic hypersensitivity reactions.[2] Dermatologic adverse reactions from warfarin are uncommon and rarely reported in the literature. Potential dermatologic adverse effects include alopecia, bullous eruptions, dermatitis, rash, pruritus, and urticaria.[2] Herein is reported a suspected case of warfarin induced generalized dermatitis with the hopes to increase awareness of this adverse event. Additionally, prior case studies and alternative anticoagulation agents in the event of a similar dermatologic reaction were reviewed.

CASE REPORT

A 73 year old female (90 kg) presented to the emergency department with shortness of breath, cough, upper abdominal pain, and progressive back pain for one week. Her past medical history included hypertension, chronic obstructive pulmonary disease (COPD), type 2 diabetes, lower back pain, hyperlipidemia, mild hyponatremia, umbilical hernia, and a splenectomy. The patient had intolerance to codeine. Her daily home medications included losartan 100 milligrams (mg) daily, simvastatin 40 mg daily, fluticasone/salmeterol 250/50 one inhalation twice daily, metformin 500 mg daily, albuterol inhaler 90 microgram (mcg) every 4 hours as needed, indapamide 2.5 mg daily, tiotropium 18 mcg one inhalation daily, pantoprazole 40 mg daily, and vitamin D 400 units daily. Objective findings on admission include height =168 centimeters (cm), weight = 90 kilograms (kg), respiratory rate =25 breathes per minute, oxygen saturation =94 percent on room air, blood pressure =147/74 mmHg, heart rate =106 beats per minute, distant S1 and S2, INR=0.92, and serum creatinine =0.8 mg/dL. All other laboratory values were within normal limits. Cardiology was consulted and the electrocardiogram showed a normal sinus rhythm at 94 beats per minute.

The patient was initially diagnosed with a COPD exacerbation but her stay became complicated on the fifth day by a new diagnosis of paroxysmal atrial fibrillation. She was admitted to telemetry where she received nebulized albuterol and atrovent respiratory treatments as needed, azithromycin 500 mg intravenously (IV) daily, and methylprednisolone 60 mg IV every 8 hours for 48 hours. A tabulated $CHADS_2$ score of two in this patient supported aggressive risk factor modifications and the initiation of warfarin based on current American College of Chest Physicians clinical practice guidelines.[5] Enoxaparin 90 mg (1 mg/kg) subcutaneously every 12 hours was started, and oral warfarin 5 mg was initiated three days later. Within an hour of the first dose of warfarin, the patient developed dermatitis with intense pruritis and generalized erythema on her left arm. There was no IV-site in that arm. Subsequently, she received diphenhydramine 50 mg IV and famotidine 40 mg orally following the reaction and her rash, pruritic, and erythema improved. Per physician request, the patient was re-challenged with warfarin 2.5 mg (not one-half of 5 mg tablet) three days later. A rapid and extensive generalized dermatitis developed on her arms, hands, chest, neck, and face. Again, she was given diphenhydramine 50 mg IV, and warfarin was discontinued. The dermatitis resolved within hours leaving signs of cutaneous hemorrhage and these ecchymotic regions faded over the next two days. Due to unknown reason(s), dermatology was never consulted and no other definitive diagnostic examinations were performed. This patient was later discharged on dabigatran 150 mg oral twice daily for new paroxysmal atrial fibrillation, and warfarin was added to her allergy list.

DISCUSSION

To our knowledge, this is the first case of immediate generalized dermatitis following the administration of warfarin 5 mg tablet. A more severe dermatitis developed upon re-challenge using the 2.5 mg tablet, and subsequently, warfarin was discontinued indefinitely. The mild symptoms that occurred following the first warfarin dose were potentially a result of IV methylprednisolone administered on that morning, attenuating the overall dermatological reaction. On the day of warfarin re-challenge, the steroids had been tapered off which might explain a more severe reaction. Using the Naranjo Adverse Drug Reaction Probability Scale, it was calculated as a score of eight, which indicated the occurrence of an adverse drug reaction to be probable (Table 1).[6]

Table 1. Naranjo Adverse Drug Reaction Probability Scale[6]

Question	Yes	No	?
1.) Are there previous conclusive reports on this reaction?	+1	0	0
2.) Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3.) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4.) Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
5.) Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6.) Did the reaction reappear when a placebo was given?	-1	+1	0
7.) Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8.) Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9.) Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10.) Was the adverse event confirmed by any objective evidence?	+1	0	0

Greater than 9 = definite adverse drug reaction (ADR), 5-8 = probable ADR, 1-4 = possible ADR, 0 = doubtful ADR

Dermatologic reactions to warfarin have been rarely reported. In 1959, Sheps and Gifford first reported transient urticaria that occurred forty minutes after an oral administration of 50 mg of warfarin sodium in a thirty year old man.[7] In a 2010 report by Bogart et al, the use of warfarin 5 mg, one-half of a white warfarin 10 mg tablet, allowed successful anticoagulation in a patient with new onset atrial fibrillation who previously experienced an immediate urticaria with the warfarin 5 mg tablet.[8] The authors suggested that the dye contained in warfarin tablets should be considered before switching a patient's regimen. However, titrating and maintaining therapeutic levels using fractions of a 10 mg tablet would be extremely challenging, and lack of precision could lead to inconsistent drug absorption and effect. In our case, the patient's home medications were continued using the hospital supply, which included other colored tablets: losartan 100 mg (light green), simvastatin 40 mg (brick red), and pantoprazole 40 mg (yellow). Therefore, it was unlikely that the dermatological reaction reported in our case was due to dye, suggesting a true hypersensitivity reaction to warfarin. Lastly, in 1960, Adams and Pass reported pruritic, maculopapular eruptions that developed after 27 days of warfarin therapy.[9] Although treatment was discontinued in this report, a re-challenge after ten weeks from the first reaction resulted in the development of pruritus and a recurrence of oral and superficial cutaneous lesions. In all three case reports mentioned, the adverse reactions resolved once warfarin was discontinued.[7-9]

The exact cause of warfarin hypersensitivity remains undefined, and potential mechanisms were not identified or explained in past case reports.[7-9] Improved manufacturing process of warfarin over time cannot be excluded. Immunologic drug reactions are typically divided into four categories using the universal system proposed by Gell and Coombs in 1963 (Table 2).[10] The extensive dermatitis described in this case seemed to display qualities of both Type I IgE and Type IV delayed T cell hypersensitivity. The generalized dermatitis occurred rapidly, suggesting the immediate release of vasoactive substances like histamine. Also, reactions involving T cells usually manifest with prominent skin findings because the skin is a repository for T-cells.[11] Because a dermatology consult and further diagnostics were not performed, it was difficult to categorize the type of hypersensitivity reaction in our patient.

Table 2. Immunologic Reaction Classification – Derived from Gell and Coombs[10]

Type	Description	Mechanism	Clinical Features
I	Immediate reaction (within one hour)	Antigen (drug) exposure causes IgE-mediated activation of mast cells and basophil. Release of histamine, prostaglandins, and leukotrienes	Anaphylaxis Angioedema Bronchospasm Hives
II	Antibody dependent	Antigen associated with cell binds to antibody leading to cell or tissue destruction	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex	Formation of antigen-antibody complexes that deposit in vessels or tissue. Tissue destruction results from activation of compliment system	Serum sickness
IV	Cell mediated or delayed hypersensitivity	Antigen exposure stimulates T cells, which then mediate tissue injury. Subtypes IVa-IVd, depending on type of cells involved	Contact dermatitis Exfoliative Dermatoses

Dermatologic adverse reactions following warfarin therapy are rare but very serious because alternative therapies for life-long anticoagulation in patients with atrial fibrillation are limited. Because no other vitamin K antagonists are currently available in the United States, a novel oral direct thrombin inhibitor, dabigatran etexilate (Pradaxa®), can be used in atrial fibrillation patients with a documented warfarin allergy.[12] Anticoagulation with low molecular weight heparins or factor Xa inhibitors is another therapeutic option for the prevention of thromboembolic events, but subcutaneous administration makes these agents undesirable for long-term use. Anticoagulation with aspirin alone is not recommended for the prevention of thromboembolism in patients with a $CHAD_2$ score of one or above. Jantoven is the crystallization of warfarin sodium and lacks the impurities of amorphous warfarin; therefore, the risk of cross-sensitivity is reduced.[13] However, physicians still remain weary of its use in patients with warfarin allergies, and its retail availability is limited.

Generalized dermatitis following warfarin therapy is rare but responds well to intravenous steroids, diphenhydramine, histamine receptor antagonists, and warfarin discontinuation. Low molecular weight heparins, new direct oral anticoagulants, and crystallized warfarin sodium are possible alternative agents for the prevention of thrombosis in patients with nonvalvular atrial fibrillation, and each option must be explored in the case of warfarin allergy.

REFERENCES

1. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e44S-88S. doi: 10.1378/chest.11-2292. [PMID 22315269]
2. Coumadin [package insert]. Bristol-Myers Squibb Pharma Company, Princeton, NJ; October 2011. Available at http://packageinserts.bms.com/pi/pi_coumadin.pdf [accessed on 3/13/2013].
3. The Joint Commission Hospital National Patient Safety Goals website. Available at: http://www.jointcommission.org/assets/1/18/NPSG_Chapter_Jan2013_HAP.pdf [accessed on 3/13/2013].
4. Warkentin AE, Donadini MP, Spencer FA, Lim W, Crowther M. Bleeding risk in randomized controlled trials comparing warfarin and aspirin: a systemic review and meta-analysis. *J Thromb Haemost*. 2012;10(4):512-20. doi: 10.1111/j.1538-7836.2012.04635.x. [PMID 22257078]
5. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e531S-75S. doi: 10.1378/chest.11-2304. [PMID 22315271]
6. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Robets EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–45. [PMID 7249508]
7. Sheps SG, Gifford RW Jr. Urticaria after administration of warfarin sodium. *Am J Cardiol*. 1959;3(1):118-20. [PMID 13606072]
8. Bogart MA, Cheema A, Wooten JM, Bogart DB. Warfarin Allergy: An Easy Solution. *Clin Cardiol*. 2010;33(3):E31-2. doi: 10.1002/clc.20554. [PMID 20112234]
9. Adams CW, Pass BJ. Extensive dermatitis due to warfarin sodium (Coumadin). *Circulation*. 1960;22:947-48. [PMID 13681359]
10. Gell PGH, Coombs RRA, eds. Clinical Aspects of Immunology. 1st ed. Oxford, England: Blackwell; 1963.
11. Clark RA, Chong B, Mirchandani N, Brinster NK, Yamanaka K, Dowgiert RK, Kupper TS. The vast majority of CLA+ T cells are resident in normal skin. *J Immunol*. 2006;176(7):4431-9. [PMID 16547281]
12. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Poque J, et al. Dabigatran versus Warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-51. doi: 10.1056/NEJMoa0905561. Epub 2009 Aug 30. [PMID 19717844]
13. Jantoven [package insert]. Upsher-Smith Laboratories, Inc., Minneapolis, MN, October 2011. Available at http://www.upsher-smith.com/wp-content/uploads/LA-107442-01-WarfarinSodium-Tablet-Insert.pdf [accessed on 3/13/2013]