Case Report

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A Case Report on Warfarin Induced Skin Necrosis: Drug-drug Interaction or Inappropriate Therapy

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Abstract

Introduction: Warfarin is one of the most frequently prescribed oral anticoagulant. Necrosis and/or gangrene of skin and other tissues is an uncommon but serious risk associated with warfarin. The incidence of warfarin induced tissue necrosis is about 0.01 % to 0.1%.

Case description: A 62-year-old male presented to emergency with a complaint of skin discoloration and edema on left lower limb diagnosed as warfarin induced skin necrosis. He had an episode of hemiparesis 20 days back for which he was started on oral warfarin along with other medications. On diagnosis warfarin was stopped and fresh frozen plasma (FFP) was given along with vitamin K. Due to progressing tissue necrosis, above knee limb amputation was done. We assume that an interaction between rosuvastatin and warfarin or possibly lack of adequate bridge therapy with heparin resulted in this complication.

Conclusion: Warfarin induced skin necrosis is a known early complication of the therapy. Though late onset appearance of this event is rare but not unknown. Bridging therapy with heparin and avoiding use of interacting drugs concomitantly could prevent many such reactions.

Keywords: Warfarin, Skin necrosis, warfarin adverse effects, late onset warfarin-induced skin necrosis

Abbreviations: FFP: Fresh Frozen Plasma; INR: International normalized ratio; ICU: Intensive Care Unit; PROS1: Protein S Coding gene; S.C.: Subcutaneously; ECG: Electrocardiography

Introduction

Warfarin is one of the most commonly prescribed medication right from its inception. The indications for warfarin are in the prophylaxis and/or treatment of venous thrombosis, pulmonary embolism, prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement. It reduces the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction [1]. Necrosis and/or gangrene of skin and

other tissues is an uncommon but serious risk associated with warfarin. The incidence of warfarin induced tissue necrosis is about 0.01 % to 0.1% [2,3]. A large body of literature reported occurrence of this serious adverse event within ten days of commencement of the therapy in a warfarin naïve patient [4,5].

Case Report

The present case, a 62-year-old male with hypertension, diabetes and diffuse coronary artery disease receiving treatment for his clinical conditions presented to

emergency with a complaints of skin discoloration and edema on left lower limb for last three days. On the day of his visit to emergency, he complained of hematuria since morning. On presentation he was conscious, oriented, with blood pressure of 90/60 mm of Hg, pulse rate of 84/min and SpO2 99%. There was a color change in the left foot and left leg with edema, shiny skin with normal local temperature. There was a reduced power in left lower limbs and loss of power in left upper limb. He had an episode of hemiparesis 20 days back with a right middle carotid artery territory infarct followed by which he was started on oral warfarin 5 mg/day along with other medications like rosuvastatin, aspirin, nitrates, glipizide, metformin, amlodipine and metoprolol. History of follow up subsequent to warfarin therapy was lacking. The INR on presentation was 2.13. A diagnosis of warfarin induced skin necrosis was made and decision was taken to stop warfarin immediately. Two units of fresh frozen plasma (FFP) was given along with vitamin K. Arterial doppler study showed an echogenic plaque in lumen of left common femoral artery which was not causing any significant velocity changes. The echocardiography showed an ejection fraction of 45% with mild mitral regurgitation. Necrotic area of the wound was debrided under general anaesthesia (Figure 1). A neurology and cardiology opinion was sought, based on which oral antidiabetics were withheld and insulin was initiated. Subsequently, rosuvastatin, aspirin and other medications were started.

Figure 1: Skin necrosis followed by warfarin therapy.

Daily dressing was done along with supportive therapy and antimicrobials (meropenem, linezolid, colistin etc.) followed by a second debridement of the necrosed tissue. Despite all efforts, the condition of the patient kept deteriorating exemplified by hypotension and low

O₂ saturation. He was sent to intensive care unit where ECG showed poor R wave progression and T wave depression in V4, V5, V6 with low voltage complexes. The hypotension was managed and SpO2 got improved. Next day he complained of chest pain and ECG showed ST depression in V3, V4, V5, V6 leads with positive troponin I. Inj. enoxaparin was added 0.6 ml S.C. twice daily. The necrosis gradually increased, and above knee limb amputation was done with adequate antimicrobial cover and inj. heparin 5000 IU, intravenous 6 hourly was started along with other medications. The patient had uneventful recovery with satisfactory healing of the amputated limb. Patient was discharged and asked to come for follow up after 10 days.

Discussion

Skin necrosis associated with warfarin is a rare occurrence (0.01 % to 0.1%) yet a known complication of warfarin therapy [2,3]. Typically, it occurs in middle aged, obese women with deep vein thrombosis or a pulmonary embolism on treatment with warfarin and usually occurs in the areas where there is store of subcutaneous fats like breast, buttocks, and limbs but can also occur in the other areas. The complication usually present within few days of initiation of therapy with first symptoms occurring within 10 days and peak between 3 and 6 days [4,5]. We considered the cited case worth reporting as skin necrosis onset was little late than usual. Although, late onset skin necrosis has been reported but is relatively rare [6-8].

The pathogenesis of the warfarin-induced cutaneous necrosis is supposed to be due to the pro-coagulant effects of the drug. Warfarin inhibits vitamin K dependent clotting factors II, VII, IX and X but their half-life is long (20 to 60 hours). Whereas, warfarin also inhibits anticoagulant proteins C and S, which have a short half-life leading to sharp fall in their concentrations. This culminate into a anticoagulant- procoagulant mismatch leading to a transient procoagulant state leading to thrombotic occlusion of the microvasculature, resulting into cutaneous lesions [9]. Patients with positive lupus anticoagulant, protein C and S, antithrombin and factor VII deficiency are more susceptible to this grave complication. The congenital form of Protein S deficiency is determined by mutations in the gene PROS1 (3q11-q11.2), with autosomal dominant inheritance. The homozygous individuals manifest the disease within infancy, but heterozygous individuals are found to be asymptomatic until their adulthood. At present in our setup we are not doing genetic analysis, we cannot comment on the possibility of genetic susceptibility in this patient. There

are reports that warfarin directly causes toxic vasculitis at the junction of the precapillary and arterial capillary of the dermovascular loop. The damaged capillaries dilate and rupture leading to petechial rash whereas, veins distal to the damaged capillaries thrombose culminating into tissue necrosis [10].

The interaction by unknown mechanism between rosuvastatin and warfarin (started after stroke episode) could have led to the intensified pharmacodynamic action of warfarin resulting in skin necrosis in this case. Moreover, in acute thrombotic events, there is required an overlap of low molecular weight heparin or unfractionated heparin and warfarin for 4-5 days to avoid worsening or development of any new thrombosis [11]. Therefore, adequate bridge therapy reduces the likelihood of development of a procoagulant state and this life-threatening condition but information on concomitant heparin therapy was lacking in this case as it was referred from other hospital. However, we could not confidently rule out the absence of initial concomitant heparin with warfarin therapy; may be due to improper documentation of treatment history. Therefore, possibility of absence of bridge therapy could not be completely ruled out in causation of skin necrosis.

Early recognition and treatment with intravenous vitamin K, FFP, and continued wound care are essential to prevent further complications. Considering all the factors of this adverse event was possibly related to the suspected drug (As per WHO Causality Scale). The adverse event has been notified to the National Coordinating Center (NCC) for Pharmacovigilance Programme of India (PvPI).

Conclusion

Warfarin is in clinical use since ages and skin necrosis is a known early complication of the therapy for multiple reasons as cited in the text. Though late onset appearance of this event is rare but not unknown. Moreover, the possibility of drug interaction should always be kept in mind. Bridging therapy with heparin at the inception of warfarin therapy could prevent many such reactions.

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