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Elevation in International Normalized Ratio due to Administration of Cefoperazone in Valvular Patients on Warfarin Therapy: Series of Two Case Reports

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Abstract

Warfarin is an oral anticoagulant, which is commonly prescribed in hospital settings in various thrombotic conditions. It is known to have had a broad range of interactions with other medicinal gents widely used during clinical settings, particularly antibiotics, resulting in altered coagulation parameters and bleeding in such patients. In this study, we intend to describe two such cases that developed excessive hypoprothombinemic response due to cefoperazone and improved after substituting cefoperazone with alternative antibiotic. While there is no conclusive proof of warfarin-cefaperazone interactions, it is recommended that healthcare providers explore alternate antibiotic use in warfarin therapy patients and allow careful surveillance of the coagulation profile for all those patients receiving warfarin and antibiotics in combination with warfarin dosage modification.

Keywords: Warfarin • Valve replacement surgery • Major bleeding • Cefoperazone

Introduction

Warfarin is the world's most frequently used oral anticoagulant is generally used for thromboembolism diagnosis and prevention, in patients with deep vein thrombosis, pulmonary embolism, atrial fibrillation, and artificial heart valves [1]. Warfarin has a narrow therapeutic spectrum and needs regular testing to reduce life-threatening effects due to under coagulation and over coagulation both [2]. International Normalized Ratio (INR) is the laboratory metric used to monitor the treatment of warfarin. The American Heart Association offers recommendations for the correct anticoagulation level in patients following valve replacement surgery based on the type of valve: mechanical or biological, and advises the use of warfarin to reach an INR of 2.0-3.0 after replacement of aortic valves with mechanical prostheses, while INR levels of 2.5-3.5 after replacement of mitral valves [3].

Wide ranges of drugs have been associated with increased risk of major bleeding in warfarin users [4]. Concomitant use of antibiotics is particularly common among warfarin users and is associated with a high risk of over anticoagulation. The basic mechanism through which antibiotic prescription drugs interact with warfarin to raise the risk of major bleeding is disruptions in the intestinal flora that synthesize vitamin K2 and inhibitions of cytochrome p450 isozymes that metabolize warfarin [5]. Interactions among warfarin and specific antibiotic agents were increasingly investigated, mainly through case reports; case series studies [6-8]. Here, we will report two cases of warfarin and cefoperazone drug interaction in patients reported with coagulopathy in a cardiac hospital setting in Pakistan, who were taking warfarin due to a history of valve replacement surgery.

Case Description

A 60 years old female patient on warfarin therapy 5mg had undergone Aortic Valve Replacement (AVR) surgery due to a history of Aortic Stenosis (AS) in a cardiac hospital in Pakistan, Rawalpindi. At the time of discharge, the patient was also prescribed sildenafil 25 mg OD and captopril 6.25 mg BID for pulmonary arterial hypertension and left ventricular dysfunction respectively, as evident from her echocardiogram report. One week after discharge, the patient was reported with the complication of bronchospasm and shortness of breath therefore, the patient was referred to a surgical ward for admission where she was nebulized immediately. On examination, patient was vitally stable, afebrile, and normotensive. Chest examination showed right lung crepitations and therefore, furosemide 20 mg Intravenously (IV) at 6 hours interval was initiated.

Two-dimensional echocardiography was done and the interpretation of results showed dilated aortic root, moderate concentric left ventricular hypertrophy, fair left ventricular systolic function with

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ejection fraction 55%.

Lab investigations showed hypoalbuminemia i.e. 29 g/liter, leukocytosis having white blood cell count of 19 × 109 cells per liter, and hyperuricemia with serum uric acid levels of 8 mg/dl. Hemoglobin levels and alkaline phosphatase levels were under normal range. Patient INR was under normal limits of 3.1 at the time of admission. To treat any underlying sternal wound infection, cefoperazone 1 gm IV at 12 hours interval was initiated and on the very next day, her INR raised to 6.67. Therefore, warfarin was withheld and cefoperazone was stopped. Cephradine 500 mg oral 6 hourly was initiated, and vitamin K IV 10 mg was administered to reverse the coagulopathy until INR levels were normalized back within the range (Figure 1).

Figure 1. Administration of Cefoperazone.

Case Report 2

A 40 years old female patient on warfarin therapy 5 mg had undergone Mitral Valve Replacement (MVR) surgery due to a history of mitral valve stenosis in a cardiac hospital setting in Pakistan, Rawalpindi. After two weeks of discharge, the patient was presented with warfarin- induced coagulopathy in emergency with hematuria and epistaxis, since she mistakenly did self-medication with 6 tablets of warfarin per day. The lab investigation showed INR result with fail to clot, warfarin was withheld and she was admitted in the surgical ward. Treatment was initiated with 6 fresh frozen plasmas along with vitamin K 10 mg IV to reverse the effect of warfarin- induced coagulopathy. Patient INR dropped to 2.18 on the next day, and warfarin 5 mg was restarted. Cefoperazone 2 g at 12 hours interval was also initiated to treat any underlying sternal wound infection. Patient INR was raised again to a value of 12.97 on the next day of cefoperazone initiation. Cefoperazone was stopped and FFPs were administered again to reverse the coagulopathy. Other medications prescribed were bisoprolol 2.5 mg OD and spironolactone 20 mg OD for underlying complications and shown to have no interaction with warfarin.

Discussion

Cefoperazone is a third-generation beta-lactam cephalosporin, having a broad spectrum of activity. Only a few adverse effects have been described in clinical scenarios with this agent, and it is given in combination with beta-lactamase inhibitor sulbactam, in a variety of respiratory, skin, and urinary tract infections. Cefoperazone acts by inhibiting the synthesis of the cell wall of various gram-positive and gram-negative bacteria [9].

The chemical structure of cefoperazone revealed that it has a methyl thiotetrazole side chain which on metabolism forms free N-methylthiotetrazole (NMTT). The free NMTT inhibits hepatic vitamin K epoxide reductase, and carboxylation of II, VII, IX, and X clothing factors can be inhibited, thereby, contributing to bleeding and hypoprothrombinemia. In addition, it disrupts vitamin K2 producing intestinal flora, hence aggravating the problem [10].

Isolated prolongation of prothrombin duration after administration of cefoperazone and fast reversal upon treatment of vitamin K is indicative of coagulopathy caused by cefoperazone. Patients with healthy amounts of vitamin K do not experience coagulopathy due to cefoperazone alone, while there is a high chance of coagulopathy due to drug administration in vitamin K deficient patients and patients on warfarin therapy [11].

Warfarin also acts by competitively inhibiting the Vitamin K Epoxide Reductase Complex 1 (VKERC1), an important enzyme present in the body for activating the vitamin K. By this process, warfarin can deplete functional reservoirs of vitamin K; thereby decrease the formation of active clotting factors. The presence of vitamin K is required for hepatic synthesis of coagulation factors II, VII, IX, and X as well as for coagulation regulatory factors protein C and protein S. Vitamin K is an important cofactor for all these vitamin K-dependent clotting factors to be synthesized [12,13]. Warfarin patients receiving multiple medications at the same time may increase the risk of hypoprothrombinemia further. However, in both cases, there is no evidence of drug-drug interactions between warfarin and concomitant medications prescribed to these patients. Nevertheless, in the first case age factor, low albumin, with leukocytosis might increase the risk of over anticoagulation in the presence of cefoperazone and warfarin [14].

Very few reports involving coagulopathy secondary to the administration of Cefoperazone are reported. A recent study by Z Cai et al., analyzed the literature (PubMed), and found that there were only around 30 publications that listed hypoprothrombinemia and hemorrhage caused by cefoperazone [15-18]. Here, we describe that co-administration of warfarin and cefoperazone have a synergistic effect and may cause fatal coagulopathy in patients taking these two drugs together. Therefore, alternative selection of antibiotics in patients on warfarin therapy must be considered in such cases.

Conclusion

Concomitant use of warfarin and cefoperazone should be avoided and use of alternative, safe antibiotics is recommended in patients using warfarin. Further, close monitoring of INR while initiating new antibiotics is necessary in patients on warfarin therapy. To examine the occurrence of coagulopathy and bleeding following cefoperazone administration, further studies are needed, however.

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