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Enhanced anticoagulant effect of warfarin in a patient treated with cloxacillin

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Key words

warfarin – cloxacillin – interaction – coagulopathy

Abstract. Objective: To present the case of warfarin-cloxacillin interaction that resulted in an increased international normalized ratio (INR). **Case summary:** A 70-year-old man had been treated with warfarin for atrial fibrillation. He was hospitalized because of superficial thrombophlebitis of the left median cubital vein, which developed after venipuncture. An antibiotic therapy with cloxacillin was initiated immediately after the admission. Two days later, INR value increased from baseline 1.9 to 4.6. Anticoagulation therapy was discontinued and INR value was measured daily. His INR remained high for the entire duration of antibiotic therapy. Three days after the cloxacillin therapy was discontinued, the INR decreased to the baseline value. **Discussion:** In the presented case, the temporal relationship between the administration of cloxacillin and increased INR suggests that the cloxacillin was responsible for the enhanced warfarin activity. According to the Drug Interaction Probability Scale, a causal relationship between the warfarin-cloxacillin interaction and increased INR value was rated “probable”. **Conclusion:** Interactions between warfarin and cloxacillin can result in serious adverse reactions. INR value should be closely monitored when patients are prescribed this combination of drugs.

Introduction

Warfarin is known for having numerous drug and dietary interactions, which can lead to life threatening adverse reactions [1]. However, it is the most commonly used oral anticoagulant with established efficacy for the treatment and prevention of thromboembolic events [2]. We present a case of warfarin-cloxacillin interaction that resulted in an increased international normalized ratio (INR).

Case report

A 70-year-old man was hospitalized in October 2010 because of superficial thrombophlebitis that developed after venipuncture of the left median cubital vein. He had been treated with nebivolol and warfarin for atrial fibrillation since 2006. A target INR value had been maintained between 2.0 and 3.0, with warfarin dose of 3 mg and 4.5 mg on alternate days. Drug compliance was established through the review of patient’s medical records from his general practitioner and patient interview.

On admission, the patient presented with fever and redness and tenderness over the left median cubital vein. Doppler ultrasound showed no signs of deep vein thrombosis. Laboratory investigations revealed increased erythrocyte sedimentation rate (130 mm/h), C-reactive protein (220 mg/l), and fibrinogen (6.9 g/l) values. Hemoglobin concentration and white blood cell and platelet counts were normal as were prothrombin time and partial thromboplastin time, serum total protein, albumin and globulin concentrations, kidney and liver function tests.

Therapy with nebivolol and warfarin was continued. An empiric i.v. antibiotic therapy with cloxacillin was initiated immediately after three blood samples for culture had been taken. A cloxacillin-sensitive *Staphylococcus aureus* was isolated from the cultures after 24 h. Three days after the initiation of antibiotic therapy, the patient’s clinical condition improved with regression of signs and symptoms of thrombophlebitis. Thus, i.v. antibiotic therapy was substituted with oral cloxacillin. Antibiotic therapy was discontinued after 10 days of hospitalization.

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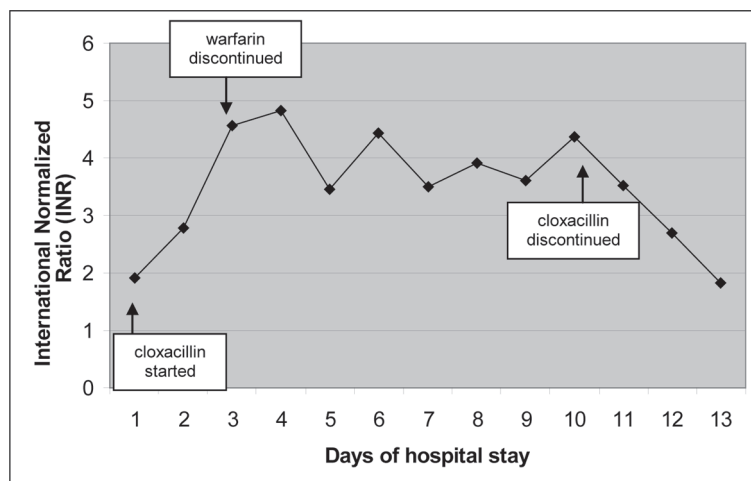


Figure 1. Changes in the international normalized ratio (INR) during cloxacillin therapy.

Two days after the cloxacillin therapy was introduced, the INR value increased from the baseline 1.9 to 4.6. Since there were no signs of hemorrhage, fresh frozen plasma and vitamin K were not administered [3]. Anticoagulation therapy was discontinued and INR value was measured daily. The INR values remained high for the entire duration of antibiotic therapy (Figure 1). Three days after the cloxacillin therapy had been discontinued, the INR decreased to 1.8. The patient was restarted on warfarin 3 mg daily. During the 6-month follow-up, the therapeutic INR range of 2.0 – 3.0 was maintained with a daily warfarin dose of 4.5 mg.

Discussion

The literature does not provide strong evidence of the clinically significant interaction between warfarin and penicillinase-resistant penicillins. Several reports document warfarin-resistance in patients treated with dicloxacillin, nafcillin, and flucloxacillin [4, 5, 6, 7, 8, 9, 10, 11]. This drug-induced warfarin-resistance often develops within 7 days of starting antibiotic therapy. The suggested reason is an increase in the warfarin metabolism induced by the antibiotics [12]. The warfarin-cloxacillin interaction causing a decrease in INR has been described in a single report [13]. The report presented warfarin-resistance in a patient with endocarditis during cloxacillin therapy. Induction of warfarin metabolism was the proposed mechanism of

interaction, the same as with other penicillinase-resistant penicillins [13]. No case reports have described warfarin-cloxacillin interaction that resulted in an increased INR.

In the presented case, the temporal relationship between the administration of cloxacillin and increase in the INR suggests that the cloxacillin was responsible for the increased warfarin activity. Other possible causes of changes in INR values were excluded on the basis of diagnostic test results and clinical course of the disease. Infection as a possible cause of increased INR was excluded because it was limited to the vein and subcutaneous tissue, and there was no evidence of systemic inflammatory response or disseminated intravascular coagulation. There were no changes in the patient's therapy or diet, which could have enhanced warfarin activity during his hospital stay. Compliance was controlled by health care personnel. According to the drug interaction probability scale, a causal relationship between the warfarin-cloxacillin interaction and increased INR value was rated "probable" [14].

Increased warfarin effect in patients treated with antibiotics is thought to be due to the reduced intestinal flora, especially the vitamin K-producing bacteria, which in turn leads to the reduced vitamin K absorption and vitamin K deficiency [15]. The onset of coagulopathy can be quite variable, ranging between 7 days after starting antibiotics to 4 weeks after their discontinuation. It depends on many factors, such as vitamin K intake and liver stores of vitamin K [16]. This mechanism of increased warfarin activity was unlikely in the presented case, because the INR increased 2 days after cloxacillin had been started and returned to the pretreatment value soon after the antibiotic had been discontinued. Such a fast change in the INR value suggests a pharmacokinetic interaction between warfarin and cloxacillin.

Previous reports suggested that penicillinase-resistant penicillins can induce cytochrome P450 isoenzymes involved in warfarin metabolism and lead to warfarin-resistance [4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. Cloxacillin-induced changes in warfarin metabolism cannot explain the increased anticoagulation activity in this case. We suggest that warfarin activity in our patient was increased due to plasma protein binding displacement. Both warfarin

and cloxacillin are highly protein-bound and, therefore, susceptible to displacement from protein binding sites when given concomitantly with other agents with a high affinity for protein binding [17, 18]. The drug displacement caused by cloxacillin could have increased the concentration of unbound warfarin, leading to an increase in INR. Although many investigators consider changes in plasma protein binding to have little or no clinical relevance, in case of warfarin and other drugs with low clearance and low therapeutic index such interactions might be clinically significant [18, 19].

The case demonstrates difficulties in predicting the clinical significance of interaction between warfarin and cloxacillin. Both drugs are commonly prescribed agents. Frequent INR monitoring and warfarin dose titration are necessary to avoid life-threatening complications resulting from drug-drug interaction.

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