Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2973-19
Intern Med 58: 3251-3253, 2019
http://internmed.jp

【 CASE REPORT 】

# Extreme Elevation of the Prothrombin Time-International Normalized Ratio due to a Probable Interaction between Warfarin and Flutamide

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**Abstract:**
Flutamide, a chemotherapeutic agent for prostate cancer, is known to enhance warfarin anticoagulation. However, not much is known about its pharmaceutical interaction. We herein report the case of a patient with an implanted pacemaker for atrial fibrillation with bradycardia who was on warfarin. This patient presented with deterioration of hematuria, gingival, ear, and subcutaneous bleeding. The prothrombin time-international normalized ratio was extremely elevated after starting flutamide to treat progression of prostate cancer. Fatal bleeding complications were able to be prevented by the immediate administration of prothrombin complex concentrate, but the effect of flutamide on warfarin was prolonged for about two more weeks after the withdrawal of flutamide.

**Key words:** warfarin, flutamide, prothrombin complex concentrate

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## Introduction

Some anticancer agents are known to affect warfarin-induced anticoagulation (1-6). Therefore, in patients on warfarin, it is important to confirm its interactions with drugs at the initiation of cancer chemotherapy. Some drugs are known to affect warfarin metabolism, such as its binding to plasma proteins, drug-metabolizing enzymes, including cytochrome P450 2C9 (CYP2C9), and Vitamin K. Flutamide is known to enhance the anticoagulation effects of warfarin, although the mechanisms underlying the interaction between these two agents is not understood.

We recently treated a patient who had undergone mitral valve replacement (MVR) by bioprosthesis for mitral regurgitation and had a pacemaker implanted for atrial fibrillation with bradycardia and needed warfarin for anticoagulation. This patient presented with deterioration of hematuria and gingival, ear, and subcutaneous bleeding. The prothrombin time-international normalized ratio (PT-INR) in this patient was remarkably elevated to 17.14 after starting treatment with flutamide for the progression of prostate cancer.

## Case Report

The patient was an 86-year-old man who had undergone MVR with bioprosthesis for severe mitral regurgitation 2 years earlier. He had had a pacemaker implanted for atrial fibrillation (AF) with bradycardia and was on 2.0-2.5 mg of warfarin per day. The PT-INR was controlled to within the therapeutic range of 2.5 to 3.0. He had also been diagnosed with cT2aN0M0 prostate cancer four years earlier and undergone photoselective vaporization of the prostate (PVP) and external beam radiation therapy (76 Gy). Luteinizing hormone-releasing hormone (LH-RH) agonist therapy (Leupropreline acetate) had been started one year ago following lymph node metastasis to multiple sites. Bicalutamide, an anti-androgenic agent, was added to manage the increase in levels of prostate-specific antigen (PSA). However, since the levels of PSA continued to increase, bicalutamide had been replaced with flutamide (375 mg/day), another anti-androgenic agent, 2 months ago. His PT-INR, which had been 2.26 a month ago, remained stable at 2.36 when measured 21 days ago. Warfarin was continued through this pe-

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Received: March 6, 2019; Accepted: May 22, 2019; Advance Publication by J-STAGE: July 10, 2019
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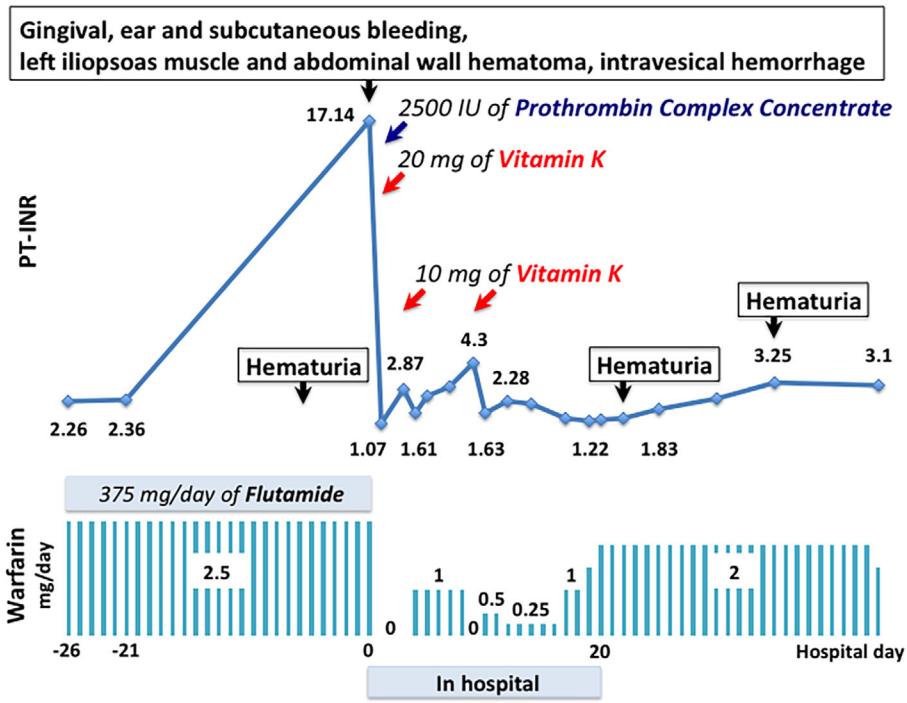


**Figure.** **The clinical course of PT-INR and daily dose of warfarin. The upper line graph shows the transition of the PT-INR value. The horizontal axis shows the hospital days. The lower bar chart represents the daily dose of warfarin. The vertical arrowhead shows each event, and the oblique arrowhead shows the drug administration. PT-INR: prothrombin time-international normalized ratio**

riod at 2.5 mg/day. Following vesicostomy surgery, he suffered recurrent macroscopic hematuria several times, and warfarin was continued at the same dose.

He returned to our clinic with macroscopic hematuria 8 days ago, and PT-INR was not measured at that time. He then presented with deterioration of hematuria along with gingival, ear, and subcutaneous bleeding, at which time the PT-INR was found to be extremely elevated at 17.14.

Computed tomography revealed left iliopsoas muscle hematoma, intravesical hemorrhaging, and abdominal wall hematoma but no intracranial hemorrhaging. He was admitted to our hospital immediately. Because of acute and potentially fatal bleeding, we decided to administer 2,500 IU (50 IU/kg) of prothrombin complex concentrate (PCC, Kcentra®; CSL Behring, King of Prussia, USA) with 20 mg of Vitamin K. The gingival and ear bleeding stopped within 30 minutes after the administration of PCC. The speedy administration of PCC helped avoid hemorrhagic complications and other serious adverse reactions of thromboembolic events, such as stroke, pulmonary embolism, and deep vein thrombosis. The PT-INR decreased from 17.14 to 1.07 at 1 day after administration of PCC and admission, however, it was increased to 2.87 at 2 days after admission without administration of warfarin. PT-INR then decreased to 1.61 at 3 days after admission. Although warfarin was readministered at 1 mg/day, the PT-INR increased to 4.3 at 4 days after admission. Following the administration of Vitamin K, warfarin was readministered at 0.25 to 0.5 mg/day for a week.

The effect of flutamide on warfarin was prolonged for two more weeks after the withdrawal of flutamide. It took about three weeks for the warfarin dose to be returned to normal. Figure shows the clinical course of PT-INR and the daily dose of warfarin.

## Discussion

Patients with cancer are at an increased risk for thromboembolic events and require anticoagulant therapy (7, 8). AF is common in elderly patients, which requires anticoagulation therapy (9). Some anticancer agents, such as etoposide, carboplatin, capecitabine, fluorouracil, and paclitaxel, are known to interact with warfarin, a commonly used anticoagulant (1-6). Several studies have reported the extreme elevation of PT-INR due to such anticancer agents (1, 2, 4, 5). Therefore, close attention should be paid to the interactions between warfarin and anticancer agents.

The mechanisms that underlie these interactions include displacement of plasma protein binding, drug-metabolizing enzymes, and Vitamin K. Bicalutamide, an anti-androgenic agent that belongs to the same group of drugs as flutamide, also enhances the anticoagulation effects of warfarin. Bicalutamide is reported to displace warfarin from the plasma protein binding sites. However, Asakawa et al. reported flutamide to have no effect on the binding of warfarin to plasma proteins in rats (10). While the mechanisms underlying the interaction between warfarin and flutamide remain unclear, we cannot deny the likely interaction between these agents as the cause of the extreme elevation of PT-INR in

the present case.

Direct oral anticoagulants (DOACs), such as dabigatran, direct thrombin inhibitor, and direct factor Xa inhibitors, such as rivaroxaban, apixaban, and edoxaban, have become widely used in anticoagulation therapy for AF in recent years. DOACs do not require PT-INR monitoring and can achieve effective anticoagulation in patients in whom anticoagulation is uncontrollable with warfarin alone. In Japan, however, DOACs are also approved for the treatment of non-valvular AF. It was difficult to switch the anticoagulation agent for this patient from warfarin to DOACs because his mitral valve had been replaced with a bioprosthesis two years earlier.

Warfarin competes with Vitamin K and reduces the production of the Vitamin K-dependent coagulation factors II, VII, IX, and X, thereby achieving an anticoagulant effect. Patients receiving warfarin anticoagulation therapy often fall into an abnormal anticoagulant state that takes several hours to reverse by the administration of vitamin K. Rapid reversal of an acute anticoagulant state is critical for patients with acute, potentially fatal bleeding, such as intracranial hemorrhaging. The European guideline recommends PCC for the treatment of Vitamin K antagonist-associated major acute bleeding (11). PCC consists of Vitamin K-dependent coagulation factors (II, VII, IX, X), Proteins C and S, and antithrombin III (12). In the present case, bleeding complications, including thromboembolic events, were immediately averted by the administration of PCC. Therefore, in cases of potentially fatal bleeding, patients receiving warfarin should be administered PCC immediately without hesitation.

The mechanism of interaction between warfarin and anticancer agents and the subsequent effects are complicated and difficult to predict. Heparinization instead of warfarin anticoagulation or close monitoring of the PT-INR is recommended for all patients receiving warfarin along with anticancer agents, especially in the initial phase of cancer chemotherapy.

The present patient had end-stage prostate cancer with multiple bone metastasis. As a treatment for prostate cancer, only leuprorelin, a gonadotrophin-releasing hormone (GnRH) analogue, was continued after stopping flutamide. Recently, enzalutamide and abiraterone, which are novel hormone therapeutics with strong antiandrogenic action, have become available for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Although enzalutamide is a substrate of CYP2c9 and may reduce the effects of warfarin, abiraterone is a substrate of CYP3A4 and may not influence the effects of warfarin anticoagulation.

## Conclusion

We encountered a case of remarkable interaction between warfarin and flutamide. We were able to stop the complications from bleeding from becoming serious by the immediate administration of PCC in addition to Vitamin K. The effect of flutamide on warfarin was prolonged for about two more weeks after the withdrawal of flutamide. The interaction between warfarin and anticancer agents varies among patients and is unpredictable. Substitution of warfarin anticoagulation with heparinization or close monitoring of the PT-INR is recommended for all patients receiving warfarin with anticancer agents, especially in the initial stages of chemotherapy.

**The authors state that they have no Conflict of Interest (COI).**

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