

Case Report

Two Cases of Different Bleeding Performance Caused By the Application of Warfarin Sodium and Antibiotics

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Abstract

Warfarin is commonly used for the prophylaxis and treatment of intravascular thrombosis or thromboembolic disease [1]. However, warfarin-induced bleeding may occur in patients who are receiving a combination of warfarin and other drug types, whereby the degree of hemorrhage varies on drug combinations. In addition, the risk of bleeding could be easily ignored due to the deficiency of standard care. In this study, we report an in-depth study of two cases of bleeding induced by the combination of warfarin and antibiotics treatment. We also describe a rational guide for the clinical management of warfarin-induced hemorrhage.

Case 1

A 68-year-old woman patient was admitted to the emergency department and presented with symptoms of right lower abdominal pain and cough. On August 17, 2019, the patient was admitted to the hospital for coughing. The patient did not show a fever upon hospital admission. The patient was receiving long-term warfarin therapy after an Aortic Valve Replacement (AVR) to treat her Valvular Heart Disease (VHD) 10 years ago. A prothrombin time/International Normalized Ratio (INR) was regularly checked and maintained at around 2.0. To manage the pulmonary infection, an intravenous infusion of 1 g Ceftriaxone every 24 hours and 2 capsules of oral methoxyphenamine (Asmeton) every 8 hours were given as the regimen. On August 23, 2019, the patient developed a lower right abdominal pain without a recent history of trauma.

Images of the abdominal Computed Tomography (CT) suggested the presence of hematoma in the right lower abdominal wall that was about 8x6x5cm in diameter (Figure 1). The patient also experienced a spontaneous skin hematoma in the abdomen. Laboratory examinations revealed a leukocyte count of 14×10^9 / L and an INR level of 6.2. Immediately after, warfarin was discontinued and 10 mg of Vitamin K was given. After 24 hours, the patient's INR dropped to 1.15. We gradually introduced warfarin starting at 1.5mg until 3mg depending on the INR results, which were maintained at around 1.5 INR. The patient's abdominal wall hematoma was slightly reduced compared with the previous one

while the cough symptom had significantly improved before the patient was discharged. Cefuroxime 0.25g every 12 hours was prescribed to the patient after hospital discharge.



Figure 1: Massive hematoma in the right abdominal wall.

Case 2

An 66-year-old male patient was admitted to the emergency department and presented with symptoms of hemoptysis and cough. The patient was receiving warfarin therapy after an cerebral infarction half year ago. A prothrombin time/International Normalized Ratio (INR) was regularly checked and maintained at around 2.0. On August 26, 2019, To manage the pulmonary

infection, an intravenous infusion of 4.5 g piperacillin sodium and tazobactam sodium every 12 hours was given as the regimen. On August 29, 2019, the patient developed a hemoptysis without a recent history of trauma. Laboratory examinations revealed an INR level of 8.2. Immediately after, warfarin was discontinued and 10 mg of Vitamin K was given. After 24 hours, the patient's INR dropped to 2.0. The patient did not have hemoptysis again.

Discussion

Warfarin is an oral anticoagulant commonly used to prevent arterial and venous thromboembolism events. The mode of action of warfarin is achieved by reducing the amount of vitamin K required for the activation of clotting factors II, VII, IX, and X [2]. The anticoagulant response is highly variable and is affected by genetic polymorphism of the enzyme involved in drug metabolism, the amount of vitamin K taken with diet, various drugs, food, and herbal treatments. The most important side effect of warfarin treatment is bleeding. Bleeding occurs more frequently in the intracerebral, skin, gastrointestinal tract, genitourinary organs, adrenal glands, epidural space, peritoneal cavity, and subconjunctival region [3]. Factors affecting the anticoagulant effect of warfarin may include the patient's intrinsic factors, drugs, and diet [4].

The effects of combined drugs on the anticoagulant effect of warfarin mainly involve the following two aspects: ① Pharmacokinetic interactions that affect the absorption, distribution, metabolism, and excretion of warfarin; ② Pharmacodynamic interactions that interfere with coagulation by affecting vitamin K in warfarin anticoagulant mechanisms [5]. The effect of antibiotics on warfarin is currently thought to be related to its influence on the intestinal flora and thus affecting the absorption of vitamin K. Studies have also shown that upper respiratory tract infections increase the risk of warfarin bleeding. The reason is that the Upper Respiratory Tract (URT) infection typically causes a fever that affects the activity of the enzyme in the body thereby disturbing the metabolism of warfarin. URT infection also affects the appetite of the patient and thus reduces the intake of vitamin K, which may increase the risk of warfarin bleeding.

A study found that patients with a body temperature above 38°C were twice as likely to have a follow-up INR of 5.0 or more compared with those with a temperature of 38°C or less [6]. In this report, we described two patients who are presented with cough, no fever, and poor appetite upon disease onset. Both patients were taking warfarin as a maintenance medicine. The dosage of antibiotics given was within the recommended level, suggesting that regular doses of antibiotics would also enhance the efficacy of warfarin and could enhance the risk of bleeding. We found that the risk of bleeding may not be associated with the period of warfarin medication. Patient No. 1 took warfarin for more than 10 years and

the dose of warfarin was maintained at around 3 mg.

Abdominal wall hematoma occurred 1 week after the administration of antibiotics for upper respiratory tract infection. Patient No.2 was taking warfarin for half a year. Hemoptysis occurred 3 days after taking antibiotics along with warfarin. The two cases suggest that the application of antibiotics affects warfarin not in a slow process but rather in a relatively fast manner. Intravenous (IV) antibiotics may have a greater effect on warfarin metabolism since both patients showed an elevated INR after IV antibiotics. The hospital discharged patients given with oral antibiotics did not show an increased INR upon regular check-up, suggesting that IV antibiotics could be responsible for high INR values. One plausible reason is that the liver first-pass effect of oral drugs weakens the effect of antibiotics on warfarin.

In the case of Patient No. 2, the INR was higher than in Patient No.1 and the cough was also more severe. Of note, both patients have similar age but Patient No.2 has a history of comorbidity (hypertension). Patient No. 2 showed only hemoptysis, while Patient No. 1 showed a huge abdominal wall hematoma. Further study found that the chest X-ray of Patient No. 1 showed better lung condition, whereas the chest CT of Patient No. 2 showed extensive lung inflammation. In the case of Patient No. 2, the pulmonary inflammation resulted in brittle small blood vessels in the lungs, possibly increasing the risk of blood vessel ruptures and hemorrhage. In Patient No. 1, the rupture of small blood vessels in the abdominal wall was attributed to the severe cough, and at the same time, an elevated the INR. Patient No. 1 exhibited a more serious condition than Patient No. 2 patient because the former belongs to the high-risk group of women who suffered from warfarin [6].

Conclusion

Patients who are taking warfarin for a long time and are presented with symptoms of respiratory infection should not only be managed according to the patient's infection but also for potential complications attributed to warfarin and antibiotics combination. When antibiotics, especially intravenous drugs, are needed, no matter how long the patient takes warfarin, physicians need to pay close attention to the patient's INR and detect abnormalities early for appropriate interventions. Therefore, when combining antibiotics with warfarin therapy, physicians should monitor INR more frequently to avoid possible serious bleeding complications.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of Interest

There are no conflicts of interest.

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