Hemoptysis due to Aspirin Treatment Alternative to Warfarin Therapy in a Patient with Atrial Fibrillation

Wei Song¹, Jia Cao², Yazhou Xu³, Zhonglin Han³, Hao Wen³ and Xuefan Cui¹

Abstract

An 80-year-old female with a history of hypertension and atrial fibrillation had been receiving warfarin anticoagulant therapy and had stably maintained an international normalized ratio (INR) within the 2.0-3.0 range. Due to dental extractions, she was prescribed aspirin (100 mg/day) as an alternative therapy to warfarin. Three days later, the patient complained of hemoptysis without obvious inducement and the INR was 3.51. The aspirin was immediately discontinued and intravenous vitamin K was administered. Hemoptysis did not reappear and the INR returned to the normal limits. According to the Drug Interaction Probability Scale, a causal relationship between aspirin and warfarin and an increased INR value is possible.

Key words: hemoptysis, interaction, aspirin alternative to warfarin

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Introduction

Warfarin is a coumarin derivative which has anticoagulant effects by inhibiting the synthesis of multiple coagulation factors. Although new anticoagulant drugs have been developed, warfarin is still the most commonly prescribed anticoagulant for cardiovascular disease as well as in primary and secondary prevention of venous thromboembolic diseases (1). Aspirin is a salicylate drug and has an antiplatelet aggregative activity by inhibiting the synthesis of prostaglandin cyclooxygenase. It is widely used for the long-term antithrombotic treatment of cardiovascular and cerebrovascular diseases (2).

Although many case reports have described the bleeding risk of oral non-steroidal anti-inflammatory (NSAIDs) treatment with warfarin (3, 4), few case reports have demonstrated a relationship between hemoptysis and aspirin prescribed as an alternative to warfarin. In these reports, the patients on long-term warfarin treatment often underwent dental procedures, surgery or other interventional treatments or examinations, and the warfarin therapy was interrupted, reduced or replaced by aspirin, a low molecular weight heparin or other drugs. However, anticoagulant therapy should not be interrupted, especially for the patients with a high risk of thrombosis. Thus, determining the correct replacement drugs for anticoagulants and the appropriately reduce dosage are crucial for avoiding bleeding or thromboembolism. In the present case, hemoptysis was caused by aspirin prescribed as an alternative to warfarin. By quickly discontinuing the anticoagulant and actively treating hemoptysis, the patient recovered and was discharged from the hospital. Therefore, clinicians should carefully monitor the half-life of warfarin, the high protein binding rate, and the interaction of other anticoagulants during invasive procedures in the long-term anticoagulant patients. Monitoring the INR value may also aid in avoiding bleeding complications in such patients.

Case Report

An 80-year-old female (height 158 cm, weight 58 kg, BMI 23.23) with a more than 10-year history of atrial fibrillation had taken warfarin 3 mg or 2.5 mg qd in alternation and maintained the international normalized ratio (INR) within the 2.0-3.0 range. The patient stopped taking warfarin...
Table: Aspirin Alternative to Warfarin and the Coagulation Function.

| Projects                                  | Community          | Emergency       | Hospitalization |
|-------------------------------------------|--------------------|-----------------|-----------------|
| Warfarin (po)                             | 3mg or 2.5mg qd,   | -               | -               |
| Warfarin in vivo                          | Completely clear in 7 days | -               | -               |
| Aspirin (po)                              | 100mg qd           | 100mg qd        | -               |
| Hemoptysis volume (mL/24h)                |                    | 100             | -               |
| INR                                       | 2.0-3.0            | 3.51            | 1.31            |
| PT (11±3s)                                |                    | 40.4            | 15.1            |
| APTT (24.5±10s)                           |                    | 127.7           | 33.5            |

Abbreviations: D1-8: day 1 to day 8, po: Per os, INR: the international normalized ratio, PT: prothrombin time, APTT: activated partial thromboplastin time, -: not tested

due to recent dental procedures and was prescribed 100 mg/day aspirin. Three days later, hemoptysis occurred, which was bright red and accompanied by blood clot, without an obvious stimulus and the volume of the blood was approximately 100 mL. The patient had no chest pain, chest tightness, dizziness or fatigue. The blood pressure was 120/79 mmHg. A blood test performed in the emergency department in the end of July, 2014 showed the following: white blood cell (WBC) count was normal, the neutrophils percentage (NE%) was 79.1% (40.0-75.0%) and there were no obvious abnormalities in the hepatic and renal function. A blood coagulation test showed an INR of 3.51↑, prothrombin time (PT) 40.40s↑ (11.00±3s), activated partial thromboplastin time (APTT) 129.70s↑ (24.5±10s), fibrinogen (Fib) 4.20 g/L↑ (2.00-4.00 g/L), and normal thrombin time 18.5sx (18.0±3s). A chest CT scan showed multiple nodules, right-lung effusion and possible infectious lesions. In the emergency department, intravenous vitamin K and carbazochrome sodium sulfonate, cefodizime, levofloxacine and ambroxol for hemostasis, empiric anti-infection, to relieve the cough and to reduce the sputum production. Hemoptysis disappeared within four days and the cough and expectoration were superior than before the treatment. The coagulation function test demonstrated the PT was 14.00s, APTT was 28.20s and the INR was 1.21. The patient was discharged in a good condition. The relationship between hemoptysis and the coagulation function when using aspirin as an alternative to warfarin is shown in Table.

**Discussion**

There may be many factors involved in hemoptysis caused by aspirin alternative to warfarin. First, the bleeding risk of warfarin is related to the anticoagulation intensity (INR). Our patient had a more than 10-year history of atrial fibrillation and had been taking oral warfarin (3 mg or 2.5 mg qd) while maintaining an INR within the 2.0-3.0 range. According to the 2010 European Society of Cardiology (ESC) guidelines for atrial fibrillation (5), the patient suffered from hypertension (1 point), age≥ 75 years (1 point) and CHADS2 score≥ 2 points, thus, the patient had an indication of long-term anticoagulation with warfarin. An INR of 2.0-3.0 is consistent with the recommended target range in the guidelines and the risks of bleeding and thromboembolism are the lowest at these values. Although elderly patients may have hepatorenal hypofunction, which could have caused the metabolism of warfarinor a decreased excretion, some studies have shown that the warfarin functions are not affected by mild or moderate hepatorenal hypofunction (3, 6). The present patient had been on long-term anticoagulation therapy with warfarin with no previous history of hemoptysis or other complications until aspirin was administered as an alternative to warfarin therapy. Therefore, the high anticoagulation intensity of warfarin should be...
When aspirin was administered alternative to warfarin therapy, the bleeding risk closely correlated with a potential drug interaction. According to some guidelines to warfarin therapy (1, 5, 6), warfarin has many adverse drug interactions. The present patient had been taking metoprolol and losartan hydrochlorothiazide daily for cardiovascular disease, which had no known adverse drug interactions with warfarin, and was not receiving anti-infective drugs before hemoptysis. The first day after discontinuing the warfarin therapy, the patient orally took one tablet of aspirin qn instead. However, the half-life of the S-type and R-type of warfarin (Marevan) according to the manufacturer's instructions is 18-35h and 20-70h, respectively. Warfarin should have completely cleared the body by approximately 5-7 days. Therefore, aspirin and the remaining warfarin may have had an adverse drug interaction in vivo. This interaction may have enhanced the anticoagulant effect and elevated the INR to 3.51, which may be the cause of hemoptysis in this patient. An evaluation using the Drug Interaction Probability Scale for aspirin treatment alternative to warfarin therapy yielded a score consistent with a possible interaction.

The risk of bleeding for aspirin treatment alternative to warfarin therapy may be related to the patient's physiological or pathological condition, disease and other factors. First, the hepatic and renal functions of the present patient were normal before hemoptysis; therefore hepatic and renal dysfunction, which could suggest reduced metabolic or excretive rates for both warfarin and aspirin in vivo, could be excluded. Second, a chest CT scan as well as negative tumor markers, tuberculosis antibodies, serum r-interferon, and Legionella antibody ruled out bronchiectasis, tumor lesions, tuberculosis, and Legionella infection, all of which could cause hemoptysis. The blood tests indicated high NE% and C-reactive protein (CRP) levels. Additionally, moist rales were heard in the lower part of the bilateral lungs and multiple nodules and plaque shadows were found in the chest CT scan. These findings indicated that the patient likely had a pulmonary infection. The patient had no symptoms of chest pain and tightness, pathologic cardiac murmur was negative, and breathing, pulse, blood pressure and heart rate were all normal. The cardiac examination report with color Doppler ultrasound showed a left ventricular internal diameter of 45 mm, a right ventricular diameter of 49 mm, an ejection fraction (EF) of 64.0%, which ruled out hemoptysis caused by heart failure. Moreover, warfarin has a high plasma protein binding rate with an oral bioavailability >90% and the unbound concentration is only between 0.5% and 3% in the enterohepatic circulation. However, the patient's serum albumin concentration was low. Thus, the unbound concentration of warfarin may have increased in vivo and enhanced the anticoagulant effect of warfarin, which may be related to hemoptysis. Undeniably, pulmonary infection can lead to hemoptysis. The INR was 3.51 in the patient with hemoptysis.

Aspirin treatment alternative to warfarin therapy with hemoptysis may have a potential drug interaction with a synergistic anticoagulation effect on the pharmacodynamics of warfarin. Warfarin has long half-life and takes approximately seven days to be completely eliminated in vivo. The patient discontinued taking warfarin and initiated aspirin treatment the following day. The remaining warfarin in the patient's body (anticoagulation effect) may have had a synergistic effect with the aspirin treatment (antiplatelet aggregative activity) thereby enhancing the intensity of the anticoagulation therapy. Recently, a study reported the bleeding risk of simultaneously taking warfarin and aspirin in the patients with atrial fibrillation and showed that using warfarin monotherapy as the reference, the hazard ratio (95% confidential interval) of aspirin for fatal and gastrointestinal bleeding were 1.37 (1.13-1.65) and 1.28 (1.17-1.41), respectively (4). Therefore, in patients with atrial fibrillation, aspirin treatment may lead to a higher risk for bleeding and may be related to hemoptysis.

Aspirin treatment alternative to warfarin therapy with hemoptysis may have a drug interaction on the pharmacokinetics. Although the protein binding rate of aspirin is low, the protein binding rate for the salicylate salt of hydrolyzed aspirin in vivo is 80-90% (7). It may competitively inhibit the binding protein of nonmetabolized or excreted warfarin in vivo and can be converted into a free fraction. Thus, the concentration in the free fraction of warfarin was increased and the anticoagulation effect of the patient was increased. This may also be an important mechanism related to hemoptysis.

Aspirin treatment alternative to warfarin therapy with long-term anticoagulant therapy requires a tooth extraction, the patient should receive drug administration according to the following guidelines: 1) patients with uninterrupted anticoagulant therapy can gargle with tranexamic acid and aminoacaproic acid during dental procedures or 2) if a non-emergency surgery, warfarin therapy should be interrupted approximately 5 days before surgery (corresponding to approximately five half-lives of warfarin), until the INR falls to 1.5 or less. If the patient requires surgery or a procedure and the INR is still more than 1.5, oral low-dose vitamin K (1-2 mg) may normalize the INR. If the patients require an acute surgery, oral low-dose vitamin K is recommended to maintain the INR in the normal range. Then, warfarin therapy should be administered after surgery.

Warfarin is constituted of optically active isomers R- and S-type at an equivalent ratio. The pharmacokinetics, pharmacodynamics, genetics, other drug usage, diet, various diseases and other factors of the patient may affect the anticoagulation effect of warfarin. For instance, aspirin and NSAIDs, by inhibiting the platelet function, can increase the risk of warfarin-related bleeding. Through the analysis of this case, we discovered that the anticoagulant effect of warfarin may overlap with aspirin if not discontinued for an appropriated amount of time. Thus, aspirin and warfarin may have potential adverse drug interactions. An increased con-
centration of the free fraction of nonmetabolized or excreted warfarin (with anticoagulant effects in vivo) and aspirin (with anti-platelet aggregations) may interact and lead to an enhanced anticoagulant effect. Another possibility is that the patient’s low serum albumin concentration may have increased the concentration of the free fraction of warfarin. The hazard ratio of aspirin for fatal and gastrointestinal bleeding is more than warfarin. These factors may cause the INR values to exceed the target range thereby causing hemoptysis. Health care providers should pay careful attention to potential drug interactions in patients on long-term anticoagulant therapy when administering alternative treatments in order to ensure the safety and well-being of these patients.

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