BILBERRY POTENTIATES WARFARIN EFFECT?

Abstract

The use of dietary supplements, including vitamins, minerals, amino acids, and herbas or other natural products, has increased steadily over the last two decades. Here, we report a patient consuming large amounts of bilberry while under warfarin treatment who admitted to the emergency service with rectal bleeding and haematuria. A 77-year-old man who had hypertension for six years, was diagnosed as atrial fibrillation, and since he had a prior stroke a year ago, warfarin was started. On the 16th day of warfarin therapy, the patient was admitted to the emergency room with rectal bleeding and dizziness. Coagulation tests revealed a prolonged prothrombin time (PT) of 110.5 s, an international normalised ratio (INR) of 15.0, and an activated partial thromboplastin time (aPTT) of 76.4 s. After infusion of 2 units of fresh frozen plasma his rectal bleeding ceased. The next day he admitted to the emergency service with severe haematuria and dizziness. His INR was 6.24, and prothrombin time (PT) was 55.7 s. Fresh frozen plasma was started and he was hospitalized in the hematology service for further evaluation of his inconsistent INR values. On his detailed history we found that he had been consuming large amounts of bilberry every day for five years. In patients undergoing anticoagulant pharmacotherapy, herbal medications may interact with cardiovascular drugs. Warfarin is the most common drug involved. Therefore, before warfarin is started the patient should be asked attentively about the dietary habits. Bleeding patients should also be asked about dietary supplements.

Key Words: Warfarin; Anticoagulants; Herb-Drug Interactions; Vaccinium Myrtillus.

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YABANMERSİNİ, WARFARİN’İN ETKİSİNİ ARTTIRMAKTA MIDIR?

ÖZ


Anahtar Sözcükler: Warfarin; Antikoagülanlar; Bitki-İlaç Etkileşimi; Vaccinium Myrtillus.
INTRODUCTION

The use of dietary supplements, including vitamins, minerals, amino acids, and herbals or other natural products, has increased steadily over the last two decades (1). In a survey conducted in 1999, about 49% of adult Americans were estimated to have used herbal products during the previous year (2).

Aside from an appraisal of product safety and effectiveness, attention should be paid to the potential for these products to interact with medication. Patients at greatest risk for interactions are those with chronic diseases, who use multiple medications, particularly those with a narrow therapeutic range, have genetic variants in drug metabolism, impaired organ function, and are at either end of the age spectrum (3). It has been documented that 61% of patients with cardiovascular disease taking supplements reported that they did not have any information about the risks, benefits, and adverse effects of their potential interactions with prescription drugs alternative medicines, or about their potential interactions with prescription drugs (4).

Bilberry (Vaccinium myrtillus) has been variously used for the treatment of diarrhea, circulatory diseases, eye conditions, inflammation and diabetes (5). Although bilberry constituents have multiple pharmacological actions, most of the research has focused on the anthocyanosides. Extracts containing anthocyanosides have been shown to possess strong antioxidant properties (6), decrease capillary permeability and fragility (7), and inhibit platelet aggregation (8). Since bilberry and its extracts have antiplatelet aggregating properties, it should be avoided to be used in patients with hemorrhagic disorders and those taking anticoagulant or antiplatelet drugs (9).

Anticoagulation is very effective for primary and secondary prevention of thromboembolic events. Warfarin and other coumarin act by inhibiting the synthesis of functional vitamin K dependant coagulation factors II, VII, IX and X. Drug interactions can critically interfere with warfarin control. Common examples of drugs that can influence the absorption or metabolic clearance of warfarin include antibiotics, amiodarone, statins and anticonvulsants (10). Some herbal medicinal are recognized as important modifiers of the anticoagulant effects of warfarin (11).

Here, we report a patient, consuming large amounts of bilberry while under warfarin treatment and presenting with rectal bleeding and haematuria in emergency service.

CASE REPORT

A 77-year-old man who has hypertension for six years, was diagnosed as atrial fibrillation, and since he had prior stroke a year ago, warfarin was begun as 5 mg once a day in the evening before the dinners after his baseline international normalized ratio (INR) value was found out as 0.91. His preceding medication was continued with the same drugs and in the same dosages which were metoprolol 50 mg, simvastatin 20 mg, ramipril 2.5 mg, vitamin B12 and tamsulosin 0.4 mg per oral and once a day. On the 16th day of warfarin therapy, patient was admitted to the emergency room with rectal bleeding and dizziness. On examination, his body temperature was 36.8°C, heart rate was 100 beats/min and irregular, and blood pressure was 160/70 mmHg in both arms. There was fresh blood on rectal examination. He had no accessory heart sounds, murmurs, or peripheral pulse deficits. His lungs were clear on auscultation. Hematological tests were as follow; hemoglobin 9.0 g/dL, hematocrit 28.9%, leukocyte count 5.45 x 10^3 /μL, platelet count 343 x 10^3 /μL. Coagulation tests revealed prothrombin time (PT) 110.5 second, INR:15.0, activated partial thromboplastin time (aPTT) 76.4 second. After infusion of 2 packs of fresh frozen plasma his rectal bleeding ceased. The patient refused to have a recto-sigmoidoscopy. On follow up his hematocrite did not decreased and his INR was found to be 2.66, PT was 28.6 second, aPTT was 45.1 second. Warfarin did not interrupted because of his atrial fibrillation, prior stroke story and ceased bleeding after fresh frozen plasma. Therefore, he was discharged from the hospital with the advice for warfarin to use half of the initial dosage which was 2.5 mg. The next day, he admitted to the emergency service with severe hematuria and dizziness. INR was found to be 6.24, prothrombin time (PT) 55.7 second, activated partial thromboplastin time (aPTT) 59.6 second. Hematological tests revealed hemoglobin 8.6 g/dL, hematocrit 26.5 %, leukocyte count 5.99 x 10^3 /μL, platelet count 373 x 10^3 /μL. Urine analysis showed 300 erythrocyte /μL. Fresh frozen plasma was commenced and he was hospitalized in hematology service for further evaluation for inconsistent INR values. On his detailed history we found out that he had been consuming large amounts of raw bilberry fruits every day for five years. First, we tried to find out a possible interaction with warfarin and his former and ongoing medication. However, there was no proven data about such an interaction between warfarin and metoprolol, simvastatin, ramipril, vitamin B12 or tamsulosin. For inconsistent INR values, attention should be paid to the potential for these products to interact with medication. Patients at greatest risk for interactions are those with chronic diseases, who use multiple medications, particularly those with a narrow therapeutic range, have genetic variants in drug metabolism, impaired organ function, and are at either end of the age spectrum. It has been documented that 61% of patients with cardiovascular disease taking supplements reported that they did not have any information about the risks, benefits, and adverse effects of their potential interactions with prescription drugs alternative medicines, or about their potential interactions with prescription drugs (4).

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were administered, the patient was symptom free and on the 3rd day of hospital stay his complete blood count revealed hemoglobin and hematocrit, 9.1 gr/dl and 25.9%, respectively. Coagulation tests were normal.

Patient was advised not to consume bilberry. His INR value was within normal limits and he had no more bleeding in his following outpatient examinations.

**Discussion**

Many drugs interact with herbs and herbal medicines in humans. These drugs include anticoagulants (warfarin, aspirin and phenprocoumon), sedatives and antidepressants (midazolam, alprazolam and amitriptyline), oral contraceptives, anti-HIV agents (indinavir, ritonavir and saquinavir), cardiovascular drug (digoxin), immunosuppressants (cyclosporine and tacrolimus) and anticancer drugs (imatinib and irinotecan) (12). Unfortunately, clinicians and patients do not always have information about interactions between herbs and prescribed drugs (13). For numerous reasons, up to 40% of patients may avoid disclosing their use of herbal and other dietary supplements to their healthcare providers (1).

In patients who are undergoing anticoagulant pharmacotherapy, herbal medications and herbs may interact with cardiovascular drugs. Warfarin is the most common drug involved (14). The therapeutic properties of bilberry are attributed to the presence of anthocyanosides. Anthocyanosides are thought to have a stabilizing effect on collagen, prevent capillary fragility, inhibit blood from clotting and improve microcirculation (15). There may be an increased risk of bleeding in those taking anthocyanidin extracts from bilberry along with blood thinners, particularly warfarin. This has not been tested scientifically, but those taking warfarin or other blood thinners, particularly warfarin, are of considerable concern due to potential for harmful adverse events, including, bleeding or thromboembolic complications (17). Therefore, before warfarin is begun the patient should be asked attentively about the dietary habits. Bleeding patients should also be asked about dietary supplements.

**References**