Turkish Journal of Geriatrics
2011; 14 (1) 79-81

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Case Report

BILBERRY POTENTIATES WARFARIN EFFECT?

Abstract

The use of dietary supplements, including vitamins, minerals, amino acids, and herbals 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 protrombin time (PT) of 110.5 seconds, an international normalised ratio (INR) of 15.0, and an activated partial thromboplastin time (aPTT) of 76.4 seconds. 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 protrombin time (PT) was 55.7 seconds. 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.

Olgu Sunumu

YABANMERSİNİ, WARFARİN'İN ETKİSİNİ ARTTIRMAKTA MIDIR?

Öz

Vitaminler, mineraller, amino asidler, bitkisel ve diğer doğal ürünleri içeren besinsel destek ürünlerin kullanımı son 20 yıldan daha fazla süreden beri artmıştır. Biz bu olguda warfarin tedavisi sırasında fazla miktarda yaban merisini tüketen ve acil servise rektal kanama ve hematüri ile başvuran hastayı sunmayı amaçladık. 6 yıldır hipertansiyon şikayeti olan bir sene önce inme geçiren ve atrial fibrilasyon tespit edilen hastaya warfarin başlanmıştır. Warfarin tedavisinin 16. gününde hasta acil servise rektal kanama ve baş dönmesi nedeniyle başvurmuştur. Yapılan koagülasyon testlerinde protrombin zamanı 110.5 sn, international normalised ratio (INR):15.0, aktive parsiyel tromboplastin zamanını (aPTT) 76.4 sn olarak tespit edildi. 2 Ünite taze donmuş plazma sonrasında rektal kanama durdu. Bir gün sonra hasta yeniden acil servise hematüri ve baş dönmesi şikayeti ile başvurdu. Koagülasyon testlerinde INR 6.24, protrombin zamanı (PT) 55.7 sn olarak tespit edildi. Hastaya taze donmuş plazma verildi ve hematoloji servisine daha ileri değerlendirme amacıyla yatırıldı. Hastanın öyküsü derinleştirildiğinde hastanın son 5 yıldan beri her gün büyük miktarlarda yabanmersini tükettiğini tespit ettik. Antikoagülan tedavisi altındaki hastalarda bitkisel ilaçlar kardiyovasküler ilaçlar ile etkileşebilir. Warfarin en sık etkilenen ilaçtır. Bu nedenle hastalara warfarin başlamadan önce bitkisel ürünleri kullanıp kullanmadıkları hakkında dikkatli bir araştırma yapmak gerekmektedir. Ayrıca kanamalı hastalarda da bitkisel ürünleri kullanıp kullanmadıkları konusunda bilgi edinilmelidir.

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

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Geliş Tarihi: 29/08/2009
(Received)

Kabul Tarihi: 29/10/2009
(Accepted)

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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 product ingredients 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 medications 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 103/uL platelet count 343 x 103 /uL. Coagulation tests revealed protrombin 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, protrombin 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 103 /µL, and platelet count 357 x 103 /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 or tendency to bleed. Biochemical tests were normal; BUN 15 mg/dL, creatinine 1.17 mg/dL, ALT (SGPT)18 U/L, AST (SGOT)23 U/L, ALP 69 U/L, LDH 442 U/L, total bilirubin 0.22 mg/dL, sodium 138 mmol/L, potassium 4.1 mmol/L, albumin 3.8 g/dL. Hematuria ceased after 2 unites of free frozen plasma and 20mg of vitamin K. After two units of packed red blood cells

were administered, the patient was symptom free and on the 3rd day of hospital stay his complete blood count revealed hemoglobin and hematocrit, 9.1gr/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 in the same class, known as anticoagulants, should be very careful if, considering use of bilberry (16). Our patient, was on coumadin treatment, admitted to emergency service with rectal bleeding and hematuria in two consecutive days. After the thorough investigation that we found out that he was taking large amounts of raw bilberry fruits. After the cessation of bilberry he had no more bleeding.

The patients do not tell the doctor about their diets, because they do not think that this may be important. Unfortunately, most of the doctors also do not ask their patients about dietary supplements. However, some of the herbs or herbal extracts may interact with some drugs by orienting or antagonizing their effect. Dietary supplement interactions with 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.

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