วารสารวิชาการสาธารณสุข
ปีที่ 25 ฉบับที่ 3 พฤษภาคม - มิถุนายน 2559

Journal of Health Science
Vol. 25 No. 3, May - June 2016

รายงานผู้ป่วย *Case Report*

Pomegranate Juice Elevated International Normalized Ratio in a Patient on Warfarin: a Case Report

Pornwalai Boonmuang, B.Pharm., B.C.P.*

Wichai Santimaleeworagun, B.Pharm., Ph.D.*

Parnrada Nulsopapon, B.Pharm., M.Pharm.**

** Faculty of Pharmacy, Silpakorn University, Nakhon Pathom*

*** Phramongkutklao Hospital, Bangkok*

Abstract The aim of this study was to evaluate and report a case of elevated international normalized ratio (INR) in a patient taking pomegranate juice. A case of one, 72- year-old Thai woman had taken warfarin due to aortic valve replacement with a tissue valve. Her underlying diseases included diabetes mellitus type II, hypertension and dyslipidemia; and medication history was comprised of aspirin, volglibose, bisoprolol, metformin, glicazide, simvastatin and digoxin. She denied smoking and alcohol drinking. In one of her regular visits on appointments for routine examination of INR. The INR from this visit was 7.58 which was elevated from previous INR of 2.99 examined 2 months ago. She had taken 1.5 mg/day for 1 month before the elevated INR. There was no clinical sign/symptom which indicated abnormal bleeding despite the elevated INR. The patient was interviewed for drug utilization and adherence including daily consumption by a pharmacist who notified daily intake of 2 glasses (about 50 ml) of pomegranate juice during the past 2 months. Drug-drug and drug-disease interactions were reviewed by medical team and found to be non relevant to the elevated INR. The mechanism of drug-herb interaction between warfarin and pomegranate juice is unclear. *In-vivo* and *in-vitro* studies indicated *Punica granatum* extract showed the inhibitory activity against CYP3A4 and had a report of decrease platelet aggregation. This case report represents that pomegranate juice may be synergistic effects to warfarin as same as previous reports. Therefore, pharmacists should advise and closely monitor the patients who use pomegranate juice with warfarin.

Key words: **warfarin, interaction, pomegranate juice, INR**

Introduction

Currently, prevention and slow progression of cardiovascular disease is being emphasized in the dietary supplement industry. One of them, pomegranate juice, is a polyphenol-rich fruit juice with high antioxidant capacity.[1] Evidence suggests that nutritional antioxidants contribute to the reduction of oxidative stress, platelet aggregation and artherogenesis.[1-3] Vitamin K antagonist (VKA) or warfarin therapy has been used for the primary and secondary prevention of sys-

temic thromboembolism, atrial fibrillation, heart valve replacement, and other causes of cardioembolism.[4] Furthermore, warfarin can be affected by various environmental factors including age, body weight, diet, alcohol intake and interacting medications.[5] There are various mechanisms of warfarin that interacts with other medications. Cytochrome P450 (CYP) isozyme 3A4 is the main hepatic enzyme which catalyzes the metabolism of warfarin, thus potential warfarin interactions with other drugs and complementary supplements.[6] Herbs or complementary supplement have documented interactions with warfarin included ginseng, green tea, coenzyme Q10, St John's wort and dong quai.[7-8] These interactions could change the warfarin effect and lead to serious adverse drug reaction. Therefore, pharmacists should be educating and checking all medication, including herb or dietary supplements with warfarin especially herbal products associated with documented interactions with warfarin. Focus on the interaction between pomegranate juice and warfarin was lacking in data. The purpose of this study was to report about the onset and pattern of interaction between pomegranate juice and warfarin.

Case Report

A 72-year-old Thai woman with a medical history including type 2 diabetes mellitus, hypertension and dyslipidemia was the subject of this study. She received aspirin, volglibose, bisoprolol, metformin, glicazide, simvastatin and digoxin. She had been taking warfarin due to aortic valve replacement with a tissue valve. The patient received long-term warfarin treatment with other medication for two weeks. She denied smoking and alcohol drinking. In this regular visit, she came to the hospital to be checked for INR. Her vital sign and physical examination were normal, but INR value changed from 2.99 to 7.58. The patient's previous INR was 2.0-3.0 and she did not have bleeding symptoms. She was taking warfarin 1.5 mg/day (10.5 mg/week). The pharmacist interviewed the patient to find out the cause of INR elevation but the elevated INR value could not be explained by other causes such as compliance, drug-drug interaction, drug-disease interaction, dosage of warfarin and diet. She started taking some pomegranate juice 2 glasses (about 50 ml) per day during the two month period. To encourage patient to discuss pomegranate juice or dietary supplement that she agreed to reduced the pomegranate juice to one glass. Thus, her warfarin dose was withheld for two days and the warfarin doses to 1.5 mg was decreased on Monday, Wednesday, Friday and Sunday (6 mg/week, total weekly dose decreased about 43 percent). The physician's appointment was the week after. One week later, her INR decreased to 1.54.

Discussion

Pomegranates are a source of polyphenols and many antioxidants have had antiatherogenic, antioxidant, antihypertensive, and anti-inflammatory effects.[1-2] This present case was a report about the interaction between pomegranate juice and warfarin. The mechanism of these interactions is unknown. One hypothesis proposed by Usia, et al. was about the effect of *Punica granatum* inhibitory activity against CYP2D6 and CYP3A4.[9-10] Unfortunately, warfarin is extensively metabolized by CYP3A4. Furthermore, pomegranate juice could inhibit platelet aggregation which is the first step of coagulation, therefore reducing the platelet aggregation may refer to increasing of pro-

longed bleeding time and risk of bleeding.[3,11] It remains unclear about pomegranate juice has an effect on warfarin and can not predicted with definitely. Thus, as other causes for elevated INR value were ruled out. This present case report showed the magnitude of the interaction between these two agents peaked about in weeks, which resulted to a 43 percent reduction in the warfarin dose and withheld of warfarin for 2 days. The previous case report described a 64-year-old woman who used warfarin with stable INR and dosage of warfarin. The patient was consuming pomegranate juice 2-3 times/week. After that, she stopped drinking the juice, her INRs came to subtherapeutic range. Physician increased the warfarin dosage, the INR were maintained to therapeutic range.[12] As with a study, one article revealed that a 37-year-old woman consumed pomegranate juice about 3 liters. She denied any alteration in medication and other herbs or dietary supplements. In the week before admission, the INR value were elevated and with a large hematoma on the left calf.[13] The data of three reports used concurrently with pomegranate juice with warfarin showed in Table 1. For the limitation of this study, it was done after the case had already passed the visit which maybe a cause for a recall bias.

In conclusion, this study reported the interaction between pomegranate juice and warfarin which lacks substantial data for reference. This case report emphasized the necessity of patient education and close monitoring when pomegranate juice was added, increased or decreased in a patient taking warfarin. Finally, Pharmacists can play a crucial role on patients taking warfarin. They should be educated on the warfarin such as compliance, drug-drug interaction, drug-herb interaction or complementary medicine and alternative medicine. Moreover, the pharmacist should ask all these points especially to patients who had out of target INR value including education on the monitoring of bleeding or ischemic stroke symptoms.

Table 1 The data of three reports used concurrently with pomegranate juice with warfarin

Case report	Gender	Age (yr)	Indication of warfarin use	Amount/duration of used of pomegranate juice on warfarin	Effect of pomegranate juice on warfarin	Management
Komperda KE[11]	Female	64	Recurrent deep vein thrombosis	2-3 times/week (not reported amount and duration)	She stopped drinking the juice, and her INRs became subtherapeutic	Increased dose of warfarin and no rechallenge pomegranate juice
Jarvis S, et al[12]	Female	37	Mitral valve replacement	3 litres/ about 1 week	INR of 14 with a large hematoma on the left calf	Not reported
Present report	Female	72	Aortic valve replacement	50 ml/2 months	INR changed from 2.99 to 7.58	Hold warfarin and decreased dose of warfarin

Acknowledgements

The authors would like to thank Miss Pairin Supsongserm and Dr. Ponwanit Charoenputtakun for their assistance with the English in the manuscripts.

References

1. Jurenka J. Therapeutic Applications of Pomegranate (*Punica granatum L.)*: a review. Alternative Medicine Review 2008;13:128-44.
2. Basu A, Penugonda K. Pomegranate juice: a heart-healthy fruit juice. Nutrition Review 2009;67:49-56.
3. Aviram M, Dornfeld L, Rosenblat M, Volkova N, Kaplan M, Coleman R, et al. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. Am J Clin Nutr 2000;71:1062-76.
4. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek E, Palareti G. Oral anticoagulant therapy. Chest 2012;141:S44-88.
5. Wadelius M, Pirmohamed M. Pharmacogenetics of warfarin: current status and future challenges. Pharmacogenomics J 2007;7:99-111.
6. Nutescu EA, Shapiro NL, Ibrahim S, Wost P. Warfarin and its interactions with foods, herbs, and other dietary supplements. Exper Opin Drug Saf 2006;5:433-51.
7. Myers SP. Interactions between complementary medicines and warfarin. Australian Prescriber 2002; 25:54-6.
8. Stenton SB, Bungard TJ, Ackman ML. Interactions between warfarin and herbal products, minerals, and vitamins: A pharmacist's guide. Can J Hosp Pharm 2001; 54:186-92.
9. Usia T. Iwata H, Hiratsuka A, Watabe T, Kadota S, Tezuka Y. CYP3A4 and CYP2D6 inhibitory activities of Indonesian medicinal plants. Phytomedicine 2006; 13:67-73.
10. Liao F, Li B. Inhibition of shear-induced platelet aggregation by Chinese herbal medicines. Clinical Hemorheology and Microcirculation 1997; 17:315-8.
11. Kim H, Yoon YJ, Shon JH, Cha IJ, Shin JG, Liu KH. Inhibitory effects of fruit juices on CYP3A activity. Drug Metabolism and Disposition 2006;34:521-3.
12. Komperda KE. Potential interaction between pomegranate juice and warfarin. Pharmacotherapy 2009; 29:1002-6.
13. Jarvis S, Li C, Boggle RG. Possible interaction between pomegranate juice and warfarin. Emerg Med J 2010;27:74-5.

บทคัดย่อ: กรณีศึกษาการใช้น้ำทับทิมสกัดร่วมกับยาวาร์ฟารินแล้วส่งผลต่อค่าไอเอ็นอาร์

พรวลัย บุญเมือง ภ.บ., ว.ภ. (เภสัชบำบัด)*; วิชัย สันติมาลีวรกุล ภ.บ., ปร.ด.*;
ปานรดา นวลโสภาภณ ภ.บ., ภ.ม.**

** คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร จังหวัดนครปฐม; ** กองเภสัชกรรม โรงพยาบาลพระมงกุฎเกล้า กรุงเทพมหานคร*

Journal of Health Science 2016;25:529-33.

การศึกษานี้มีวัตถุประสงค์เพื่อประเมินและรายงานกรณีศึกษาที่มีการใช้น้ำทับทิมสกัด ร่วมกับยาวาร์ฟารินแล้วส่งผลให้ค่าไอเอ็นอาร์เพิ่มขึ้น โดยรายงานผู้ป่วย 1 ราย เพศหญิง อายุ 72 ปี ได้รับยาวาร์ฟารินเนื่องจากมีประวัติผ่าตัดเปลี่ยนลิ้นหัวใจชนิดเนื้อเยื่อที่ตำแหน่งลิ้นหัวใจเอออร์ติก นอกจากนี้ยังมีโรคประจำตัวอื่น ๆ คือ โรคเบาหวานชนิดที่สอง โรคความดันโลหิตสูงและโรคไขมันในเลือดสูง ประวัติการใช้ยาที่ผู้ป่วยได้รับได้แก่ ยา bisoprolol ยา metformin ยา glicazide ยา simvastatin และยา digoxin ผู้ป่วยปฏิเสธการสูบบุหรี่และดื่มสุรา ครั้งนี้ผู้ป่วยมาติดตามการรักษาที่โรงพยาบาลตามปกติ ผลการตรวจทางห้องปฏิบัติการพบว่า ค่าไอเอ็นอาร์เพิ่มขึ้นจาก 2.99 เป็น 7.58 ในระยะเวลา 2 เดือน และไม่มีภาวะเลือดออกผิดปกติ (เดิมผู้ป่วยใช้ยาวาร์ฟารินขนาด 1.5 มิลลิกรัมต่อวันเป็นระยะเวลา 1 เดือน) จากการซักประวัติพบว่า ผู้ป่วยให้ความร่วมมือในการกินยาดี กินยาถูกต้อง ไม่มีอันตรกิริยาระหว่างยากับยาและยากับโรค แต่ผู้ป่วยดื่มน้ำทับทิมสกัด ปริมาณ 2 แก้วต่อวันหรือประมาณ 50 มิลลิลิตร เป็นระยะเวลา 2 เดือน ปัจจุบันกลไกการเกิดอันตรกิริยาระหว่างยาวาร์ฟารินกับน้ำทับทิมสกัดยังไม่ชัดเจน แต่มีการศึกษาพบว่าน้ำทับทิมสกัดมีฤทธิ์ยับยั้งการทำงานของเอนไซม์ CYP3A4 และลดการเกิดกระบวนการทำงานของเกร็ดเลือด ซึ่งสอดคล้องกับรายงานกรณีศึกษาที่พบว่า การใช้น้ำทับทิมสกัดจะเสริมฤทธิ์ของยาวาร์ฟาริน ดังนั้นเภสัชกรควรแนะนำและติดตามการรักษาด้วยยาวาร์ฟารินอย่างใกล้ชิดในผู้ป่วยที่ใช้ยาวาร์ฟารินร่วมกับน้ำทับทิมสกัด

คำสำคัญ: **ยาวาร์ฟาริน, อันตรกิริยาระหว่างยา, น้ำทับทิมสกัด, ไอเอ็นอาร์**