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Case Report

Interaction between warfarin and astaxanthin: A case report

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ABSTRACT

This report explains the potential interaction between warfarin and astaxanthin in a 69-year-old Thai woman with history of ischemic stroke. Before taking astaxanthin, the patient used constant doses of warfarin, atenolol, digoxin, aspirin, omeprazole, and simvastatin concomitantly for 17 days without any signs and symptoms of adverse events. One day after astaxanthin was supplemented to her treatment regimen, ecchymosis was found on the right side of her groin and thigh. On the next day, area of ecchymosis was larger. International normalized ratio (INR) values increased from 1.4 to 10.38. Warfarin and astaxanthin were withheld and vitamin K was given. Two days later, INR reduced to 1.43 and symptoms of ecchymosis were better. Causality assessment of adverse drug reaction indicated a probable relationship between bleeding symptoms and astaxanthin supplementation. Counseling the patients and caregivers as well as monitoring for potential interactions with dietary supplements should be considered as an active process in order to prevent negative outcomes to patients undergoing warfarin therapy.

<**Learning objective:** Astaxanthin, a powerful antioxidant, has been claimed to have benefits on the cardiovascular system. The populations with high risk of atherosclerotic diseases, including patients treated with warfarin may take astaxanthin for improving their disease and overall health status. Interestingly, warfarin displays clinically significant interactions with various dietary supplements and may have potential to develop unwanted anticoagulation effects when used concomitantly with astaxanthin.>

Introduction

Warfarin, the drug with narrow therapeutic index, is one of the most widely used oral anticoagulant agents. Administration of warfarin needs close monitoring of international normalized ratio (INR) in order to prevent undesirable anticoagulation effects. Drug interaction is a common cause of INR fluctuation. Various drugs, herbs, foods, and dietary supplements can interact with warfarin leading to the events of adverse reactions in patients [1].

Astaxanthin is a xanthophyll carotenoid found in microalgae, fungi, complex plants, seafood, flamingos, and quail [2,3]. Several studies, both experimental and in humans, demonstrated the potent antioxidant and anti-inflammatory properties of astaxanthin which produce potential benefits on atherosclerotic cardiovascular disease [3]. In addition, anti-diabetic, anti-lipid peroxidation, anticancer, and immunomodulation of astaxanthin were reported [2]. Use of astaxanthin as a nutritional supplement has been rapidly growing in foods, feeds, nutraceuticals, and pharmaceuticals. The supplement products are available in market in various forms such as capsule, tablet, powder, cream, energy drink, and extract. Numerous purposes of astaxanthin products are labeled including benefits for eye, joint, skin, muscle, gastrointestinal, aging, cardiovascular, and immune system [2]. These health claims may cause great demand for astaxanthin supplementation. The populations with high risk of atherosclerotic diseases, including patients treated with warfarin, may take this supplement to improve their disease and overall health status. As potential to develop clinical significant drug interactions, co-administration of warfarin with any dietary supplements including astaxanthin needs careful attention in order to avoid undesired anticoagulation outcomes.

Case report

A 69-year-old Thai woman with right hemiparesis and dysarthria was sent to emergency department of community hospital on 12 September 2016. She was transferred to the

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provincial hospital by stroke fast tract system. Her diagnosis on admission was ischemic stroke and the electrocardiogram showed persistent atrial fibrillation. The patient had history of essential hypertension for 7 years, well controlled by daily amlodipine 2.5 mg.

At the provincial hospital, the patient was treated with amiodarone 150 mg IV stat and omeprazole 40 mg IV every 12 h. Oral drugs were digoxin 0.125 mg stat then 0.0625 mg daily, atenolol 25 mg stat then 12.5 mg daily, simvastatin 40 mg daily and aspirin 300 mg daily for 3 days. Warfarin 5 mg at bedtime was started on 13 September and then reduced to 3 mg on 15 September 2016. The baseline INR and activated partial thromboplastin time (APTT) before starting warfarin were 1.06 and 18.1 s, respectively.

On 16 September the patient was sent back to the community hospital and discharged from the community hospital on that day. Her home medications were as follows: daily warfarin 3 mg, atenolol 12.5 mg, digoxin 0.0625 mg, aspirin 81 mg, omeprazole 20 mg, and simvastatin 40 mg. Her INR on discharge date was 1.4. The follow-up date for the next visit was on 11 October 2016.

After hospital discharge, the patient had good adherence with home medication regimen without any signs or symptoms of adverse events. On 2 October 2016, her husband bought astaxanthin 4 mg capsules for her in order to improve overall health status. In that evening, the patient started taking astaxanthin 2 capsules. On the next day she continued to take 2 capsules of astaxanthin in the morning and 2 capsules in the evening. On 4 October 2016, a family pharmacist working with the home care team of the community hospital visited the patient and noticed that she had ecchymosis at her right groin, thigh, and arm. Swelling and tenderness at the lesions as well as limitation of range of motion by pain were also detected. Her daughter informed that ecchymosis at right groin and thigh started to appear on 3 October 2016 in the evening but family members did not realize them as abnormal conditions. The patient had no history of any injuries before these events emerged. The family pharmacist suspected potential interaction between astaxanthin and warfarin and recommended sending the patient to the hospital. Laboratory test results showed the increase in INR and APTT value to 10.38 and 78.8 s, respectively. Warfarin as well as astaxanthin was withheld and vitamin K 5 mg IV then 2 mg per oral were given to the patient.

On 6 October 2016, a smaller area of ecchymosis at her right groin and thigh was observed with no ecchymosis at right arm. Her INR value was 1.43 and APTT was 25.3 s. The previous drug regimen was continued except the warfarin dosage which was reduced to 1.5 mg. Her INR on 11 October 2016 was 2.3 and reduced to 1.2 on 8 November 2016. Adjusting warfarin doses thereafter was done to maintain target INR range of 2.0–3.0.

Timeline of warfarin and astaxanthin administration and INR values is shown in Fig. 1.

Discussion

Interactions between warfarin and many types of dietary supplements have been increasingly reported. One of the major mechanisms of interactions is additive or synergistic pharmacological effect. Various dietary supplements affect blood hemostasis by interfering with platelet function or coagulation cascade as well as promoting fibrinolysis then may potentiate anticoagulant activity of warfarin therapy [1,4]. Although no case reports or clinical studies of interactions between warfarin and astaxanthin have been identified, the warnings of concomitant use have been mentioned in some articles. One review literature indicates that

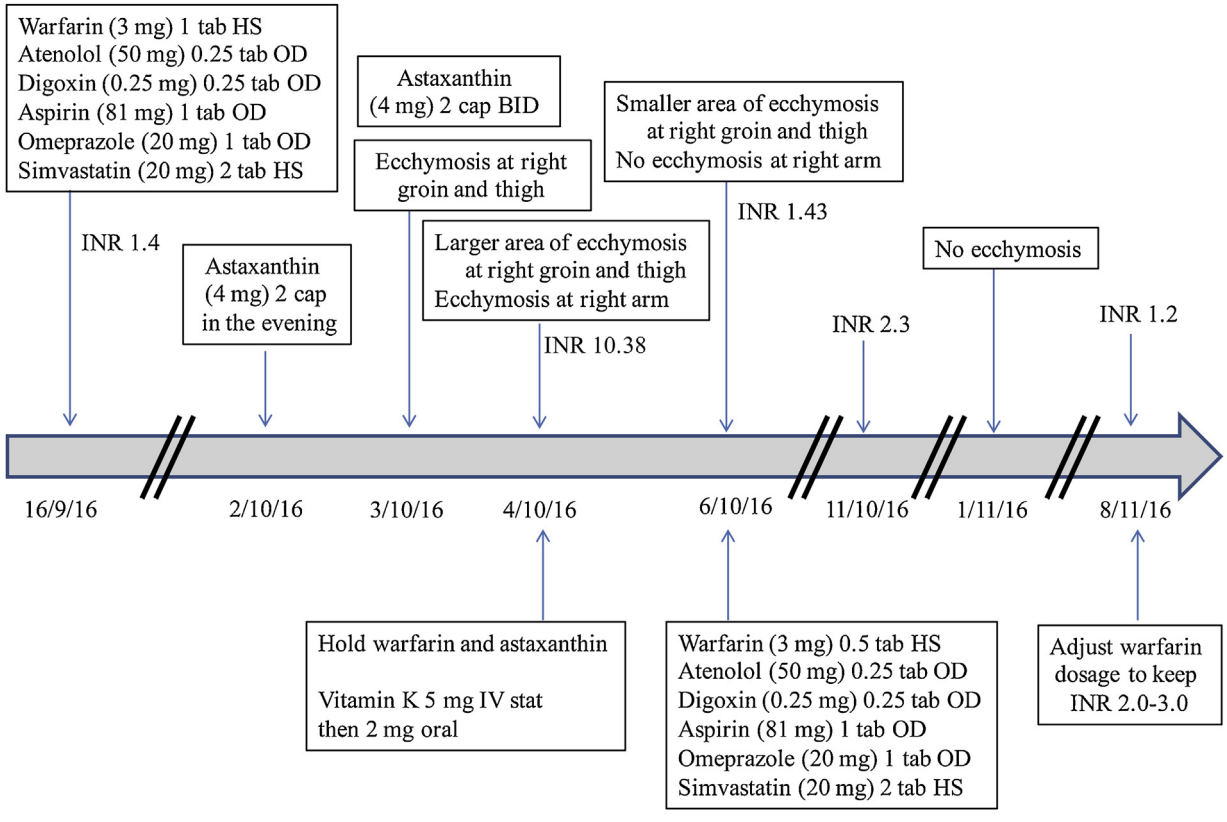

Fig. 1. Timeline of warfarin-astaxanthin interaction.
INR, international normalized ratio.

astaxanthin may affect bleeding. Patients who take other drugs that may also affect bleeding including anticoagulants should use astaxanthin with caution or make dosage adjustments [5]. Therefore, potential adverse events of bleeding complications after astaxanthin was administered along with warfarin may occur and should not be ignored.

A number of animal studies have addressed astaxanthin effects on hemostatic function. A study in hyperlipidemic rats reported that treatment with astaxanthin could inhibit coagulation, increase fibrinolytic activity, and reduce platelet aggregation. Test of coagulation parameters showed that astaxanthin increased prothrombin time and APTT. For fibrinolytic system, astaxanthin decreased expression and activity of type-1 plasminogen activator inhibitor (PAI-1) as well as increased activity of tissue-type plasminogen activator. In addition, increased PGI2 expression while relative decrease in thromboxane B2/6-keto prostaglandin F1α rates reflected its antiplatelet activity [6]. In vivo study demonstrated that astaxanthin exhibited reactive oxygen species scavenging activity, leading to an increase in bioavailability of nitric oxide (NO). Regarding the blood vessel dilatation and platelet inhibition effects of NO, this study showed antithrombotic properties of astaxanthin in cerebral vessels of stroke-prone spontaneously hypertensive rats [7]. Chan et al. showed that astaxanthin could enhance activities of natural anticoagulants, protein C, and antithrombin III, in diabetic rats. Moreover, decrease in the level of von Willebrand factor, the activity of factor VII, and the activity of PAI-1 were also demonstrated which reflected on the antiplatelet, anticoagulant, and thrombolytic properties of astaxanthin, respectively [8]. These pharmacological properties of astaxanthin on blood hemostasis can potentiate warfarin actions when used concomitantly.

Since warfarin is metabolized to inactive form by cytochrome P450 (CYP450) [1], another mechanism of interactions that might be involved in warfarin toxicity is inhibition of its metabolism by astaxanthin administration. However, astaxanthin is not reported to have a significant inhibitory effect on any isoform of CYP450 enzymes [9]. Therefore, the pharmacokinetic drug interaction during metabolism stage was not considered to be related to the interactions between warfarin and astaxanthin.

Other causes of bleeding complications in this patient had been ruled out. The patient was bedridden with good communication and co-operation. She certainly could not have had the activities that might cause change in warfarin responses such as heavy exercise, smoking, or drinking alcoholic beverages. Her vitamin K-containing diets were consistent. Before astaxanthin was administered, co-therapy of warfarin with other home medications in constant doses for 17 days did not lead to any signs or symptoms of bleeding events. Therefore, the remaining factor influencing incidence of warfarin toxicity was astaxanthin supplementation. Adverse drug reactions causality assessment by using Naranjo algorithm indicated a probable relationship between bleeding symptoms including elevated INR and astaxanthin supplement in this patient [10].

The recommended dose of astaxanthin varies depending on expected benefits, ingredients, clinical studies, expert opinions, and product labels [3,5]. This patient used astaxanthin 4 mg capsule extracted from *Haematococcus pluvialis* microalgae in the dosage of 2 capsules twice daily. The product label recommends taking 1–3 capsules daily. Therefore, the patient took more than the recommended dose. As pharmacodynamic interaction is related to pharmacological effects of both interacting agents, the undesired effects can occur in a dose-dependent manner. The higher the dose of astaxanthin that patients take, the greater the chance of affecting hemostatic activities and potentiating warfarin effects. For our patient, whether the adverse interactions lessened upon decreasing the dose of astanxanthin remains a question. However, events of ecchymosis and abnormal INR improved and finally disappeared when astaxanthin was withdrawn.

To our knowledge, this is the first case report of potential interaction between warfarin and astaxanthin. Elevated INR to more than 10.0 and bleeding complications occurred after astaxanthin was added to the patient's warfarin regimen. For patients treated with warfarin, health care professionals should play a pivotal role in monitoring of possible interactions with other drugs, foods, herbs, and dietary supplements. Patient and caregiver education on this issue should also be conducted in order to prevent dangerous adverse drug interactions to patients.

Conflict of interest

The authors declare that there is no conflict of interest.

References

[1] Nutescu EA, Shapiro NL, Ibrahim S, West P. Warfarin and its interactions with foods, herbs and other dietary supplements. Expert Opin Drug Saf 2006;5:433–51.
[2] Ambati RR, Phang SM, Ravi S, Aswathanarayana RG. Astaxanthin: sources, extraction, stability, biological activities and its commercial applications—a review. Mar Drugs 2014;12:128–52.
[3] Fassett RG, Coombes JS. Astaxanthin: a potential therapeutic agent in cardiovascular disease. Mar Drugs 2011;9:447–65.
[4] Strohecker JL, Carbajal DM, Crandall B, Day J, Lappe D, Mahapatra S, et al. Herbal and non-herbal supplement use is common in warfarin-treated patients and the majority of these agents impact warfarin safety and efficacy. J Innov Card Rhythm Manage 2012;3:611–9.
[5] Asthxanthin: a review of the literature. Available from www.naturalmedicinejournal.com/journal/2012-02/astaxanthin-review-literature. [Accessed 7 July 2018].
[6] Deng ZY, Shan WG, Wang SF, Hu MM, Chen Y. Effects of astaxanthin on blood coagulation, fibrinolysis and platelet aggregation in hyperlipidemic rats. Pharm Biol 2017;55:663–72.
[7] Sasaki Y, Kobara N, Higashino S, Giddings JC, Yamamoto J. Astaxanthin inhibits thrombosis in cerebral vessels of stroke-prone spontaneously hypertensive rats. Nutr Res 2011;31:784–9.
[8] Chan KC, Pen PJ, Yin MC. Anticoagulatory and antiinflammatory effects of astaxanthin in diabetic rats. J Food Sci 2012;77:H76–80.
[9] Zheng YF, Bae SH, Kwon MJ, Park JB, Choi HD, Shin WG, et al. Inhibitory effects of astaxanthin, β-cryptoxanthin, canthaxanthin, lutein, and zeaxanthin on cytochrome P450 enzyme activities. Food Chem Toxicol 2013;59:78–85.
[10] Naranjo CA, Shear NH, Lanctot KL. Advances in the diagnosis of adverse drug reactions. J Clin Pharmacol 1992;32:897–904.