

Critical elevation of international normalized ratio in an elderly woman using a natural health product

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Patients of Canadian family physicians commonly use natural health products (NHPs) such as herbs, vitamins, minerals, and other supplements.¹ While many of these products might be harmless aside from their out-of-pocket costs, they might sometimes interact with prescription medications or cause other harms.² While registered medications must publish harms and possible drug interactions, this is not the case for many NHPs.³

A systematic review described 80 herbs and botanicals that had clinically important interactions with prescription and over-the-counter drugs.⁴ Drugs that had antiplatelet or anticoagulant activity, such as warfarin and acetylsalicylic acid, interacted with more than 30 herbs and herbal products. In another systematic review, antiplatelet and anticoagulant agents were the most common drugs found to interact with herbal medicines.⁵ Interactions with warfarin are important to understand because warfarin has a narrow therapeutic range. When its effect is augmented it can rapidly lead to bleeding, whereas when its effect is decreased it predisposes the patient to the formation of blood clots. Older women in particular have been identified as a high-risk group for adverse interactions related to NHPs.³

We present the clinical case of an older woman taking warfarin who experienced a critically elevated international normalized ratio (INR) possibly associated with a multivitamin supplement.

Case

Ms A. is an 89-year-old female patient taking warfarin who presented for routine INR testing on December 17, 2013. Her INR was found to be critically elevated at greater than 10.0. The INR measurement was repeated that day and found to be still greater than 10.0. Her previous INR was 3.5 on December 10, 2013. The patient did not demonstrate any clinical signs or symptoms of abnormal anticoagulation. This critical result was the first substantial variation in the patient's history since warfarin was initiated in 2009 owing to a new diagnosis of atrial fibrillation.

This patient's pertinent medical history included atrial fibrillation, controlled hypertension, and a history of occasional falls in recent years. Her medications at the time of her elevated INR included warfarin (3 mg/d), 2 multivitamin tablets twice daily, and hydrochlorothiazide (25 mg/d), initiated in 2005. She was also taking 1000 IU of vitamin D and 500 mg of vitamin C daily, and had been taking these supplements consistently since 2005.

She had started taking the multivitamin, Vitalux Healthy Eyes, on December 13, 2013, on the advice of her ophthalmologist to prevent age-related macular degeneration. The patient started taking 1 tablet twice daily, and was advised to gradually increase the dose to 2 tablets twice daily. She reported diligent adherence to this regimen, as well as adherence to taking 3 mg of warfarin daily. She reported no substantial change in diet, no alcohol consumption, no tobacco or acetaminophen use, and no recent changes to her medications aside from the addition of the multivitamin. The patient was referred to hospital and treated with 5 mg of oral vitamin K and was advised to immediately discontinue taking the multivitamin and warfarin. The patient's INR decreased to 6.2 a day later (December 18, 2013) and returned to 1.7 on December 20, 2013 (**Table 1**). She restarted warfarin uneventfully and her INR remains in the therapeutic range with 3 mg of warfarin daily.

Discussion

Anticoagulant and antiplatelet agents account for a substantial and clinically important number of adverse drug events associated with NHPs. Warfarin in particular is known to interact with a long list of alternative products and medications, leading to adverse and even life-threatening events such as

EDITOR'S KEY POINTS

- A natural health product (NHP) that contains vitamin E might interact with warfarin, resulting in a critical international normalized ratio elevation.
- To assess this potential interaction, the World Health Organization criteria were used to determine adverse events related to NHP–prescription drug interactions: chronology, repetition, plausibility, exclusion of other causes, inappropriate use, and potential contamination.
- Family physicians should alert patients taking anticoagulant and antiplatelet agents of the risk of interactions and harms from concurrent use of certain NHPs. Older patients in particular should be aware of potential risks.



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Cet article se trouve aussi en français à la page 538.

Table 1. Patient INR levels

DATE IN 2013	INR	EVENT
November 26	3.0	NA
December 10	3.5	NA
December 13	NA	Patient starts taking the multivitamin
December 17	> 10.0	Community laboratory measurement
December 17	> 10.0	Hospital laboratory measurement
December 18	6.2	Measurement after taking 5 mg of oral vitamin K*
December 20	1.7	INR returns to normal and warfarin is restarted

INR—international normalized ratio, NA—not applicable.
*Multivitamin is discontinued.


dangerous bleeding from INR elevation and thromboembolic events from INR suppression.^{4,5}

Vitalux Healthy Eyes is an NHP formulated multivitamin based on the AREDS (Age-Related Eye Disease Study) and AREDS2 trials and is recommended to reduce the risk of macular degeneration in patients older than 50 years of age.^{6,7} It contains 28 micronutrients including 33.5 mg of vitamin E, a dose more than twice the Health Canada recommended daily allowance of 15 mg.^{8,9} Vitamin E has been documented to increase the anticoagulant effect of warfarin at doses 10 times the recommended daily allowance.¹⁰⁻¹³ Vitamin C, selenium, and magnesium were 3 other components of the multivitamin that have been shown to interact with warfarin, although the level of evidence for these is weaker and vitamin C has a procoagulant effect.

We argue that this patient's case fulfils the World Health Organization criteria required to establish a possible adverse event between a prescription drug and an NHP.¹⁴ These criteria include chronology, repetition, medical or pharmacologic plausibility, exclusion of other causes, inappropriate use, and potential contamination.¹⁴ The chronology of the patient's case is logical: INR was altered within 4 days and was normalized after cessation of the multivitamin. It is unlikely that this event was caused by other prescriptions or products, nonadherence, dietary changes, or diseases, as it was an isolated event and the patient denied any changes in diet, smoking, or alcohol intake, or inappropriate use of her prescriptions. Finally, pharmacologic plausibility exists as the multivitamin contains vitamin E.² Although the multivitamin contains a lower dose of vitamin E than what has been previously found to interact with warfarin,¹¹ it is important to consider the possibility that older adults, especially older women, might be particularly vulnerable to such interactions.^{3,15} In a convenience sample of adults older than age 60, for example, 31.5% of participants were at risk of having at least 1 drug-NHP interaction.¹⁶ Older women are particularly at

risk of interactions with warfarin, as they appear to require the lowest doses of warfarin to achieve therapeutic levels.¹⁷ This might be owing to several factors such as polypharmacy, shifts in metabolism, and comorbidities.¹⁸

Conclusion

Family physicians should alert patients taking anticoagulation and antiplatelet agents of the risk of interactions and harms from concurrent use of certain NHPs. Older patients in particular should be aware of these potential risks. Clinical considerations include increased monitoring of INR levels when starting NHPs or considering other forms of anticoagulation. In this case, we report a critical INR associated with a possible interaction between warfarin and a multivitamin in an older female patient, possibly related to the vitamin E content of the supplement. Vitamin K, discontinuation of the multivitamin, and temporary discontinuation of warfarin returned her INR to normal values. Restarting warfarin was uneventful. 

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Competing interests

None declared

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