Elevated International Normalized Ratio from Vitamin K Supplement Discontinuation

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OBJECTIVE: To report a case of a critically elevated international normalized ratio (INR) following discontinuation of a vitamin K supplement in a patient receiving warfarin.

CASE SUMMARY: A 64-year-old man with atrial fibrillation received warfarin for primary stroke prevention. He was initiated on low-dose vitamin K supplementation therapy secondary to a high level of INR variability. The patient was stabilized on this therapy for approximately 9 months with a mean INR of 2.02 and a warfarin dose ranging from 6.5 to 7.5 mg/week. At a visit with his primary care physician, the patient's INR was subtherapeutic at 1.5. He had not been taking his vitamin K supplement for nearly a week, but had not missed any doses of warfarin. The vitamin K supplement was discontinued and his warfarin dose was increased by 14.3%. Nearly 2 weeks later the patient presented with a critically elevated INR of 8.5, but no acute bleeding. No other factors affecting the INR could be determined. After a dose of 2.5 mg of vitamin K was administered and warfarin was withheld for 2 days, the patient's INR returned to 2.9. Low-dose vitamin K supplementation and warfarin at a lower dose of 7 mg/week were restarted. His INR remained relatively stable, with no ensuing critical INR changes or other sequelae.

DISCUSSION: Vitamin K supplement removal was believed to be a major contributor to the critically elevated INR. While the warfarin dose had been increased according to the clinic protocol (14.3% for an INR of 1.5), the timing of the INR elevation following supplement removal follows pharmacodynamic expectations of clotting factor synthesis. This case is labeled a category D error.

CONCLUSIONS: Discontinuation of vitamin K supplementation therapy might result in elevation of INR.

KEY WORDS: discontinuation, medication error, phytonadione, vitamin K supplementation, warfarin.

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Vitamin K antagonists like warfarin are a vital aspect in the pharmacotherapy of multiple conditions, including primary and secondary prevention of deep vein thrombosis and pulmonary embolism, chronic management of patients with prosthetic heart valves, as well as the prevention of systemic embolism of patients with atrial fibrillation. Multiple studies have demonstrated warfarin's ability to prevent stroke and even prolong survival for patients with atrial fibrillation; however, the variability of warfarin's anticoagulant effects are well known.[1] A patient's international normalized ratio (INR) can be affected by a myriad of factors including dietary variation, regimen adherence, drug interactions, and comorbid disease states. Due to its narrow therapeutic range, warfarin can place patients who experience significant INR variability at risk for hemorrhagic events.[2]

Vitamin K (phytonadione, phytomenadione) supplementation is a potential strategy to reduce variability in patients with unstable INRs. Multiple small studies have demonstrated that vitamin K supplementation may increase the time in goal range for patients receiving warfarin.[3-6] This has led to a recommendation from the American College of Chest Physicians that vitamin K 100-200 µg/day may be used for patients with a variable INR response that is not attributable to any of the usual known causes for instability.[1] We describe a patient who was stabilized with such therapy who presented with a critically elevated INR after his vitamin K supplement was discontinued.

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Case Report

A 64-year-old white man presented with atrial fibrillation at the age of 57 years. At that time he was rate con-

trolled and initiated on long-term anticoagulation with warfarin (Coumadin, Bristol-Myers Squibb, New York, NY) with a prescribed INR goal of 2.0-3.0. The patient also had a history of diabetes mellitus type 2, peripheral neuropathy, coronary artery disease, hyperlipidemia, spinal stenosis, osteoarthritis, and an unspecified seizure disorder, with no known seizures in the past several years. He did not smoke cigarettes or drink alcohol and weighed 108 kg (body mass index 33.6 kg/m²).

In July 2007, the patient was referred to a pharmacist-run outpatient anticoagulation clinic that operates with a predefined warfarin dosage adjustment protocol in a collaborative practice agreement with the associated clinic's internal medicine staff physicians. All INRs are checked via a CoaguCheck XS device (Roche Diagnostics, Basel, Switzerland). If INRs are greater than 5.0, a venous blood sample is obtained for confirmation. The clinic pharmacist interviews the patient at each appointment in regard to adherence to warfarin and all other medicines, changes in medications and diet, and signs and symptoms of bleeding, bruising, or embolism.

The patient initially presented to the clinic with a therapeutic INR while being maintained on a weekly warfarin dosage of 8 mg (1.5 mg twice a week and 1 mg 5 days a week). For 1 year (July 2007-July 2008) his INR remained fairly stable (mean 2.4; range 1.5-3.5) on a weekly dose reflective of his relative warfarin sensitivity (range 7-9 mg). His anticoagulation stability prior to referral to the clinic was unknown. He admitted to having a diet that was generally very low in vitamin K–containing foods (eg, green vegetables, green tea) and did not generally consume foods containing cranberry, grapefruit, mango, or soy milk.

In July 2008, the patient presented with a supratherapeutic INR of 3.6, at which point his 1-mg daily dose was decreased by 7.1% to 6.5 mg/week (Figure 1). The patient returned the following week with an INR of 4.8, despite the previous week's dose decrease. Another dose decrease of 15.4% was made; however, the patient returned 1 week later with yet another supratherapeutic INR of 4.4. He claimed adherence to his typical diet and all medications. He denied any medication changes, including over-the-counter medications or herbal supplements. The weekly dose was finally decreased to 5 mg/week and the patient was also started on vitamin K-1 100-µg tablets daily (Country Life Vitamins; Hauppauge, NY) to decrease INR variability. For approximately 9 months (September 2008-May 2009), the patient's INR remained fairly stable (mean 2.02; range 1.6-3.6) while he took that supplementation. A summary of dosing during the time of vitamin K supplement initiation as well as further dosage titration is outlined in Table 1.

The patient presented with an INR of 1.5 during a maintenance visit with one of the clinic's physicians in June 2009. A discussion with the patient revealed that he had not been taking his vitamin K supplementation for nearly 1 week, as he had not had time to return to the health foods store where he purchased it. Despite the patient's nonadherence to his vitamin K supplement, his INR was still subtherapeutic. He denied any recent missed doses of warfarin or other medications in the past month since his last INR; only that of his vitamin K supplement. He had not changed his diet from baseline. At that time, his physician recommended that vitamin K supplementation be discontinued due to the subtherapeutic INR and increased the warfarin dose by 14.3% to 8 mg/week, as suggested by the clinic's dosage adjustment protocol (clinic protocol recommendation for INR <1.6: increase 10-20% for goal INR 2.0-3.0). The patient returned 1 week later to the anticoagulation clinic with an INR of 2.4 and was told by the clinic pharmacist to continue taking the same dose of warfarin. During a follow-up clinic visit almost 2 weeks after the supplement was discontinued, the patient's INR was found to be 8.5 by venous sample. A summary of dosing and INRs at the time of the vitamin K supplement discontinuation is listed in Table 2. The patient had reported no recent changes in the intake of vitamin K–containing foods, cranberry, mango, grapefruit, soy milk, or green tea. In fact, no other medication (including over-the-counter products and herbal medications) or dietary changes had been reported

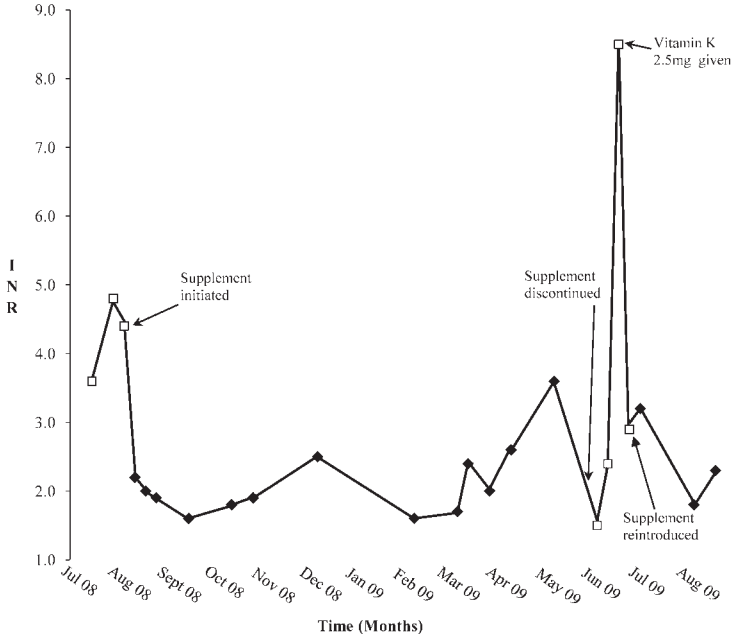

Figure 1. International normalized ratio (INR) trend throughout Vitamin K supplementation, removal, and reintroduction. ♦ = INR on vitamin K supplement; □ = INR off of vitamin K supplement.

in the past 8 weeks. The patient had not admitted to any missed or extra doses of his other medications. All of the patient's medications at the time are listed in Table 3. No other factors known to affect the INR or warfarin metabolism could be readily identified. The patient had no signs of active bleeding.

In response to this critically elevated INR value, the patient was instructed to take 2.5 mg of vitamin K orally and hold 2 days of warfarin. Two days later, an INR of 2.9 was achieved. There were no sequelae of this episode other than a small bruise at the site of the venous sample draw. The patient was instructed to take warfarin 1 mg daily and resume his 100-µg vitamin K supplementation. Over the next month, his INR remained relatively stable (mean 2.43; range 1.8-3.2). No critically elevated INRs have since been observed.

Table 1. INRs and Warfarin Doses at Time of Vitamin K Supplementation

Date	Current Warfarin Dose	INR	New Warfarin Dose	Notes
July 23, 2008	7 mg/week (1 mg daily)	3.6	6.5 mg/week (0.5 mg Thursday; 1 mg all other days)	↓ 7.1%
August 1	6.5 mg/week (0.5 mg Thursday; 1 mg all other days)	4.8	5.5 mg/week (0.5 mg Saturday, Monday, Wednesday; 1 mg all other days)	↓ 15.4%
August 8	5.5 mg/week (0.5 mg Saturday, Monday, Wednesday; 1 mg all other days)	4.4	5 mg/week (1 mg Monday, Wednesday, Friday; 0.5 mg all other days)	↓ 9.1%; Vitamin K supplement initiated
August 15	5 mg/week (1 mg Monday, Wednesday, Friday; 0.5 mg all other days)	2.2	5 mg/week (1 mg Monday, Wednesday, Friday; 0.5 mg all other days)	
August 22	5 mg/week (1 mg Monday, Wednesday, Friday; 0.5 mg all other days)	2.0	5 mg/week (1 mg Monday, Wednesday, Friday; 0.5 mg all other days)	
August 29	5 mg/week (1 mg Monday, Wednesday, Friday; 0.5 mg all other days)	1.9	5.5 mg/week (0.5 mg Monday, Wednesday, Friday; 1 mg all other days)	↑ 10%
September 17	5.5 mg/week (0.5 mg Monday, Wednesday, Friday; 1 mg all other days)	1.6	6.5 mg/week (0.5 mg Friday; 1 mg all other days)	↑ 18.1%
October 15	6.5 mg/week (0.5 mg Friday; 1 mg all other days)	1.8	7 mg/week (1 mg daily)	↑ 7.7%
October 29	7 mg/week (1 mg daily)	1.9	7 mg/week (1 mg daily)	
December 12	7 mg/week (1 mg daily)	2.5	7 mg/week (1 mg daily)	
February 11, 2009	7 mg/week (1 mg daily)	1.6	7.5 mg/week (1.5 mg Thursday; 1 mg all other days)	↑ 7.1%
March 11	7 mg/week (1 mg daily)	1.7	7.5 mg/week (1.5 mg Thursday; 1 mg all other days)	Pt. took wrong dose (↑ 7.1%)
March 18	7.5 mg/week (1.5 mg Thursday; 1 mg all other days)	2.4	7.5 mg/week (1.5 mg Thursday; 1 mg all other days)	
April 1	7.5 mg/week (1.5 mg Thursday; 1 mg all other days)	2.0	7.5 mg/week (1.5 mg Thursday; 1 mg all other days)	
April 15	7.5 mg/week (1.5 mg Thursday; 1 mg all other days)	2.6	7.5 mg/week (1.5 mg Thursday; 1 mg all other days)	

INR = international normalized ratio.

Discussion

It is very difficult to objectively assess this particular case as an adverse drug reaction. The main obstacle in doing so is that this event was likely caused by discontinuation of a medication. Commonly used probability scales, such as the Naranjo algorithm, were designed to help assess a given drug's likelihood of having caused an adverse reaction when it had been administered, not when it had been removed.[7] When considering vitamin K antagonist therapy, medication discontinuation is often as clinically relevant as initiation because the INR may fluctuate in either circumstance. Unfortunately, very little attention has been given in the medical literature to the possible adverse effects of medication discontinuation.[8] So, while it may not be possible to appropriately apply the Naranjo algorithm to this case, it may certainly be considered a medication error.

Medication errors associated with warfarin are relatively common and are variable in their causes.[9] Given the narrow therapeutic index of the drug, these errors can easily become severe adverse events. The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health-care professional, patient, or consumer."[10] While medication errors are typically thought to be due to system problems or health-care provider errors, the role of a patient must be considered as well, as is appropriate in this case.

Using definitions from the NCC MERP, this would be considered a category D error since it did not cause harm to the patient, but did require intervention and additional INR monitoring.[11] Many problems may have contributed to this event. Analysis of the case reveals that specific patient factors, provider factors, and system problems could all be contributors.

First, the patient was not adherent to the recommended regimen of vitamin K supplementation. Had the patient never mentioned that he was not taking the vitamin K supplement, this event might have occurred "naturally" over time as was described in a report by Kurnik et al.[12] In this series, patients initiated and discontinued multivitamin preparations (containing 25 µg of vitamin K) without consulting their physician. One patient experienced a critically elevated INR upon discontinuation of a multivitamin and subcapsular hematoma of the kidney. Much like our patient, this occurred approximately 2 weeks after discontinuation. Additionally, our patient's anticoagulation was relatively well maintained over several months on 6.5-7.5 mg/week with vitamin K supplementation, making the subtherapeutic INR on June 12, 2009, unexpected. Since no other changes were made, other than nonadherence to the vitamin K supplement, one might suspect that the patient was not forthcoming with recent omitted doses of warfarin. However, this is a somewhat difficult presumption given that the patient readily admitted nonadherence to his vitamin K supplement. The patient was questioned at every appointment about adherence and had never admitted to missing a dose of warfarin in the proceeding 8 weeks. It is possible that he was simply not cognizant of a missed dose in the week immediately prior to June 12, 2009.

Table 2. INRs and Doses at Time of Vitamin K Supplement Discontinuation and Reinitiation

Date	Current Warfarin Dose	INR	New Warfarin Dose	Notes
May 13, 2009	7.5 mg/week (1.5 mg Thursday; 1 mg all other days)	3.6	7 mg/week (1 mg daily)	↓ 6.7%; Adherent to vitamin K supplement
June 12	7 mg/week (1 mg daily)	1.5	8 mg/week (1.5 mg Saturday, Monday; 1 mg all other days)	↑ 14.3%; Vitamin K supplement discontinued
June 19	8 mg/week (1.5 mg Saturday, Monday; 1 mg all other days)	2.4	8 mg/week (1.5 mg Saturday, Monday; 1 mg all other days)	
June 24	8 mg/week (1.5 mg Saturday, Monday; 1 mg all other days)	8.5	Held warfarin for 2 days	1 Dose of vitamin K 2.5 mg
June 26	Held warfarin for 2 days and took 1 dose of vitamin K 2.5 mg	2.9	7 mg/week (1 mg daily)	Vitamin K supplement reinitiated
July 6	7 mg/week (1 mg daily)	3.2	6.5 mg/week (0.5 mg Thursday; 1 mg all other days)	↓ 7.1%; Adherent to vitamin K supplement
August 12	6.5 mg/week (0.5 mg Thursday; 1 mg all other days)	1.8	7 mg/week (1 mg daily)	↑ 7.7%; Adherent to vitamin K supplement
August 25	7 mg/week (1 mg daily)	2.3	7 mg/week (1 mg daily)	Adherent to vitamin K supplement

INR = international normalized ratio.

The clinic physician's recommendation to discontinue the vitamin K supplementation may have been an issue of knowledge of the therapy. At the time of the event, the patient was 1 of only 2 patients seen in this large, pharmacist-run anticoagulation service who were receiving vitamin K supplementation therapy. The American College of Chest Physicians recommendations regarding this therapy had, however, been in publication for a year at this point.[1] The decision to discontinue the vitamin K supplement therapy might have been a plausible regimen modification given the subtherapeutic INR at the time, but such an alteration should have been made on its own without also increasing the warfarin maintenance dose. Pharmacodynamic changes affecting the synthesis of vitamin K–dependent clotting factors often take 15 or more days to recognize.[13] Since the patient had stopped using the supplement for approximately 5-7 days at the time of his appointment with his physician, the full effects of this change would not have been seen. This patient had been off vitamin K supplementation for approximately 18-20 days at the time of the INR elevation. It appears that the dual modulation of therapy (removal of the supplement plus increasing the warfarin maintenance dose by 14.3%) may have resulted in a delayed synergistic effect. Without specific knowledge of the complex pharmacokinetic and pharmacodynamic properties of warfarin, the possible impact on the patient's INR may not have been recognized by the physician.

There were systems problems at play in this error. At the patient's first follow-up appointment after discontinuation of the supplement, his INR was within therapeutic range (2.4) and the dosing protocol may have discouraged the pharmacist from making therapy modification at that time. Additionally, at the time of the error, this clinic was using an exclusive paper charting system that required both the physician and the clinical pharmacist to sign an anticoagulation progress note. The appropriate anticoagulation note was used at this physician appointment; however, it did not reach the pharmacist for review until later in the week. Since the time of this case, the clinic has moved to an electronic progress note system that allows for instant review and cosignature.

The Joint Commission's 2010 National Patient Safety Goal 03.05.01 is to "reduce the likelihood of patient harm associated with the use of anticoagulant therapy."[14] This goal applies to hospital, ambulatory care, and long-term care settings. We believe that this case has relevance not only to the ambulatory care setting in which it occurred, but also to the hospital and long-term care settings. Most hospital pharmacies do not

carry alternative therapy products on their formulary, including low-dose vitamin K supplement tablets. Patients stabilized on warfarin with vitamin K supplementation may, therefore, be inadvertently placed in harm's way when admitted to a hospital if this supplement cannot be continued due to formulary restrictions, especially with longer hospitalizations. It appears from our case that patients may experience a delayed destabilization when a vitamin K supplement is removed. Thus, patients may not even experience INRs out of range until sometime beyond discharge. Patients are also at risk for errors occurring during transitions of care. This may be seen in the transition to the long-term care setting where medication changes and omissions are particularly problematic.[8] Many providers may consider any vitamin supplement to be of little consequence, which may lead to discontinuation during transitions of care. Regardless of the location, this case also highlights the need for in-depth counseling for patients started on warfarin. This should certainly include the role of vitamin K in therapy and, as mentioned by the Joint Commission, compliance.[14]

There are no previous reports of the effects of vitamin K supplementation discontinuation for a patient previously receiving such therapy to augment anticoagulation stability. Rombouts et al.[6] monitored for such an effect for patients on phenprocoumon who had been stabilized with vitamin K 100 µg for 24 weeks.They monitored for this effect for 4 weeks following patient removal from the vitamin K supplement, and no such adverse events were reported in their publication.

Table 3. Medication Profile at the Time of Critically Elevated INR

Medications	Initiated or Last Change
Digoxin 0.125 mg, 1 tablet daily	Prior to January 2007
Potassium chloride 20 mEq extended-release, 2 tablets daily	Prior to January 2007
Insulin glargine 12 units daily	Prior to January 2007
Losartan potassium 25 mg, 1 tablet daily	Started April 2007
Sulindac 200 mg, 1 tablet twice daily	Started March 2007
Esomeprazole magnesium 20 mg, 1 capsule daily	Started April 2007
Rosuvastatin calcium 10 mg, 1 tablet daily	Started March 2007
Furosemide 40 mg, 1 tablet twice daily	Prior to January 2007
Topiramate 50 mg, 1 tablet in the morning, 1½ tablets at night	Dose increased February 2007 (from 25 mg in the morning)
Gabapentin 400 mg, 2 capsules at night	Dose increased May 2008 (from 600 mg at night)
Warfarin sodium 1 mg, 1½ tablets on Saturday and Monday, 1 tablet on Tuesday, Wednesday, Thursday, Friday, and Sunday	Dose increased June 12, 2009 (from 1 mg daily)

INR = international normalized ratio.

Our case does have limitations. This patient had a very low warfarin requirement compared to the general population. Even a 1-mg/week dosage change could have a surprisingly large effect on the INR. Such patients could be at higher risk for variability, especially after dosage changes. While this patient did have significant variability prior to the addition of vitamin K, he had never experienced any critical INR prior to this incident. Also the subtherapeutic INR (1.5) may raise questions of adherence despite the patient's denial of omitted warfarin doses. Obviously, any change in warfarin dose must be made under careful scrutiny of adherence. Increasing the patient's maintenance warfarin dose in the face of recently omitted doses would certainly set the patient up for a supratherapeutic INR. Additionally in this case, the vitamin K supplement was stopped around the same time that a dosage increase was made, making a temporal association with the effect more difficult. We feel that a critical INR of 8.5 could not have been reached without the removal of the vitamin K supplement. Anticoagulation had been maintained in the preceding months with vitamin K supplementation and a warfarin dose slightly lower than this dose (7.5 mg/week vs 8 mg/week at time of the critical value) with no critical values (Table 1). This difference in dosage rarely elicits such a dramatic increase in the INR (from 1.5 to 8.5 in 12 days) on its own. While the warfarin dosage change probably played an added role, it is an unlikely stand-alone cause. The INR stabilization following the reintroduction of vitamin K reinforces this hypothesis. We believe that this misadventure would have been abated by the simple continuation of the vitamin K supplement and adjustment of the warfarin dose rather than the dual modification of therapy.

Removal of a vitamin K supplement used for stabilization of the INR of a patient on warfarin resulted in a critically elevated INR. Other patients receiving such therapy should be monitored closely over the ensuing 2-3 weeks if their supplementation is discontinued. Patients on warfarin should also be counseled to not abruptly stop vitamin K supplementation without consulting those that manage their anticoagulation.

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