Vitamin K Supplementation in a Patient Taking Warfarin

M. Shawn McFarland, PharmD; Ashley Yost, PharmD; and Jeff Tunney, PharmD

This patient's anticoagulation control fluctuated, despite appropriate changes in warfarin therapy, until vitamin K supplementation was added to his daily regimen.

The vitamin K antagonist warfarin is the most frequently prescribed oral anticoagulant in the world. Yet some patients receiving warfarin therapy have unpredictable and uncontrollable fluctuations in their international normalized ratio (INR), despite aggressive management by anticoagulation clinics and dedicated practitioners. In fact, up to half of all patients taking warfarin fail to maintain an INR within their target therapeutic range.[1,2] Such INR fluctuations have been attributed to a host of factors, including concurrent medications, comorbidities, noncompliance with drug regimen, patient variability, physical activity, illness, alcohol consumption, smoking, and genetic polymorphisms. But often, the INR response to warfarin can be erratic with no discernable change in any of these factors.

Dietary vitamin K intake—a variable that often is overlooked—can play a major role in influencing a patient's anticoagulant response to warfarin.[3] Although recent studies have demonstrated that oral vitamin K supplementation can stabilize INR fluctuations in patients in whom all other varying factors have been accounted for, many anticoagulation practitioners are unaware of this valuable tool. We report a patient who required daily vitamin K supplementation to stabilize his warfarin therapy and maintain a therapeutic INR.

Dr. McFarland is a clinical pharmacy specialist in primary care at the Tennessee Valley Healthcare System (TVHS), Alvin C. York campus, Murfreesboro. At the time of this writing, **Dr. Yost** and **Dr. Tunney** were both postgraduate year-1 pharmacy residents at the TVHS, Alvin C. York and Nashville campuses.

PATIENT HISTORY AND EXAMINATION

The patient, a 44-year-old white male, had been receiving anticoagulation therapy for stroke prophylaxis for 33 years, secondary to receiving an aortic heart valve transplant with a Bjork-Shiley mechanical heart valve after developing rheumatic fever at the age of 11 years. The patient was enrolled in our anticoagulation clinic in January 2004. For the next 24 months (January 2004 to January 2006), his INR fluctuated between the lower and upper limits of his therapeutic range (2.5 to 3.5). No hemorrhage or thrombosis was evident during the fluctuations. The patient's INRs were achieved with a warfarin regimen of 60 mg to 70 mg per week.

The patient led a relatively healthy and active lifestyle, with moderate social alcohol consumption, no smoking, and no herbal or dietary supplementation. His medical history was unremarkable with the exception of the rheumatic fever during childhood. He received no drug therapy in addition to warfarin. To our knowledge, he had no known drug allergies or genetic abnormalities with cytochrome P-450 isoenzymes that would inhibit or induce metabolism of warfarin (although the latter had not been tested).

Between January 2006 and February 2007, the patient continued to follow up in the anticoagulation clinic, returning a total of 21 times. His INR was within therapeutic range only 26% of the time during this period. Despite appropriate changes in anticoagulation therapy—including warfarin dosage adjustments and continued education of factors known to affect the stability of anticoagulation while on warfarin—the patient's INR did not remain within therapeutic range for any 2 consecutive visits. Most of his visits resulted in a notation of "no known reason for INR fluctuation" in his medical record.

The patient's provider estimated that his dietary intake of vitamin K generally remained consistent, with the exception of 1 week prior to a follow-up visit when his dietary intake decreased, leading to an increase in his INR to 4.0. Additional reports

of changes in vitamin K intake were minimal and did not coincide with changes in his INR.

Counseling was provided to the patient during each clinic visit regarding the risks associated with subtherapeutic INRs, supratherapeutic INRs, and medication changes. The patient also was informed on the importance of consistent vitamin K intake, medication compliance, and consistency in alcohol consumption.

TREATMENT COURSE

In February 2007, the patient's INR was supratherapeutic at 5.5. At this time, daily vitamin K supplementation was discussed with the patient and vitamin K 100 mcg/day was added to his regimen in an attempt to stabilize INR fluctuation. He returned for follow-up 1 week later and his INR was within therapeutic range at 3.2. At his next 2 clinic visits, in April and May 2007, his INR was therapeutic at 2.8 and 3.4, respectively—the first time his INR remained within therapeutic range for 2 consecutive visits.

The patient continued the regimen of warfarin 10 mg/day along with oral vitamin K 100 mcg/day, and his INR remained within therapeutic range for 3 consecutive months. At his visit in June 2007, however, his INR was 2.2; this decrease was attributed to a missed dose of warfarin the day prior to the appointment. The warfarin and vitamin K regimen was continued and, 2 weeks later, his INR returned to within therapeutic range at 2.6. Overall, after initiation of daily oral vitamin K, his INR remained within therapeutic range 85% of the time (6 of 7 visits).

DISCUSSION

Although warfarin offers significant protection and treatment for thromboembolic events, it also can lead to serious, life-threatening complications. Fortunately, when warfarin therapy is managed properly, such complications may decrease by as much as 85%.[4]

It has been demonstrated that fluctuations in dietary vitamin K intake can produce variability in INR response to warfarin.[3] Therefore, patients are advised to maintain a steady intake of vitamin K-containing foods while receiving warfarin therapy. In addition, some patients with unstable anticoagulant response to warfarin have been shown to consume lower amounts of vitamin K than do their stable counterparts, suggesting that a higher (and steadier) intake of vitamin K leads to larger body stores of the vitamin and more reliable anticoagulation control.[5] Lower daily vitamin K intake can result in rapid depletion of body stores and can lead to variable active clotting factor production and fluctuating anticoagulation control.

Increasing vitamin K stores in the body can stabilize INR fluctuations, particularly in patients who have accounted for all other possible factors.[6] Ford and colleagues showed that supplementation of vitamin K 100 mcg/day significantly reduced INR SD ($P < .05$) and increased the proportion of patients within their target range by an absolute 25% (relative 76% increase).[7] Similarly, Reese and colleagues showed an increase in the percentage of INRs within therapeutic range in response to daily supplementation of vitamin K 100 mcg.[8]

For these reasons, recently published American College of Chest Physicians practice guidelines (recommendation 2B) call for daily oral vitamin K (100 mcg to 200 mcg) in patients with variable INRs in whom all other routine measures have been adjusted.[4]

A recent prospective study observed patients with unstable anticoagulation control—as defined by an SD greater than 0.5 with at least 3 warfarin dosage changes in the previous 6 months.[1] Seventy patients consented to participate in the study and were randomly assigned to receive either vitamin K 150 mcg/day or placebo for 6 months. Stability of INR control was compared with the previous 6 months before randomization and was evaluated for a change in the SD of INR fluctuation and the percentage of time INR remained within therapeutic range.

Compared with placebo, vitamin K supplementation resulted in a significant decrease in SD of INR fluctuation (–0.24 ± 0.14 vs –0.11 ± 0.18, respectively; $P < .001$) and a significant increase of time in therapeutic range (15% ± 20% vs 26% ± 20%, respectively; $P < .01$). Overall, anticoagulation control improved in 33 of 35 patients who received vitamin K supplementation. Anticoagulation control in the placebo group also improved, but not as significantly as in the vitamin K supplementation group. Daily warfarin dosage requirements in patients who received vitamin K supplementation increased by 16% 1 week after the study began.

IN SUMMARY

We present a case in which adding vitamin K 100 mcg/day to the warfarin regimen of a patient with unstable INRs yielded significant improvement in anticoagulation control. By increasing vitamin K stores in the body, anticoagulation control can be improved in patients whose low vitamin K intake has been associated with unstable INRs. Addition of vitamin K supplementation to anticoagulation therapy should be monitored closely as the patient's INR can decrease within 7 days, requiring an average warfarin dosage increase of 16%.

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Acknowledgment

We would like to acknowledge Dr. Gale Hamann for his review and critique of this report.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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REFERENCES

1. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. *Blood.* 2007;109(6):2419–2423.
2. Farnett LE, Bussey HI, Patel B. The use of low dose vitamin K to stabilize INR fluctuation during warfarin therapy. In: *Pharmacotherapy.* 2000;20(3):347. Abstract 52.
3. Khan T, Wynne HA, Wood P, et al. Dietary vitamin K influences intra-individual variability in anticoagulation response to warfarin. *Br J Haematol.* 2004;124(3):348–354.
4. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; for American College of Chest Surgeons. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(suppl 6):160S–198S.
5. Sconce EA, Khan TI, Mason J, Noble F, Wynne HA, Kamali F. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation [communication]. *Br J Clin Pharmacol.* 2005;59(5):624.
6. Schurgers LJ, Shearer MJ, Hamulyak K, Stöcklin E, Vermeer C. Effect of vitamin K intake on the stability of oral anticoagulant treatment: Dose response relationships in healthy subjects. *Blood.* 2004;104(9):2682–2689.
7. Ford SK, Misita CP, Shilliday BB, Malone RM, Moll S. Use of daily vitamin K supplementation in patients on warfarin with a history of frequent dose changes or variable INRs. *Thromb Thrombolysis.* 2008;25(1):94.
8. Reese AM, Farnett LE, Lyons RM, Patel B, Morgan L, Bussey HI. Low-dose vitamin K to augment anticoagulation control. *Pharmacotherapy.* 2005;25(12):1746–1751.