Low-Dose Vitamin K to Augment Anticoagulation Control

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Study Objective. To determine the effect of daily low-dose oral vitamin K supplementation on reducing variations in the international normalized ratios (INRs) in patients taking warfarin.

Design. Retrospective analysis.

Setting. Anticoagulation clinic in a large, private-practice hematology group.

Patients. Eight motivated patients (three men, five women), aged 45–79 years, receiving anticoagulant therapy with warfarin, whose INRs had been fluctuating for reasons not associated with identifiable changes in diet, warfarin dosage, activity level, illness, or changes in drug therapy.

Intervention. Daily supplementation with oral vitamin K, starting with 100 µg/day.

Measurements and Main Results. Anticoagulation providers monitored INR responses; all documented INR values were included in the analysis, even those intentionally allowed outside the therapeutic range when dosages were adjusted for procedures. After dietary vitamin K supplementation, INR fluctuations diminished in nearly all patients. Overall, a significant decrease was noted in the INR standard deviation ($p<0.05$), and more INRs were in the therapeutic range after the start of supplementation. Allowing for small fluctuations on either side of the target range, the number of INRs within 0.2 units of the target range increased from 32% to 57% (relative increase 76%). Time in range also increased by a similar degree.

Conclusion. Supplementation with daily low-dose oral vitamin K significantly increased the number of INRs in range as well as the time in range, and decreased INR fluctuation in this small series of selected patients.

Key Words: warfarin, anticoagulants, vitamin K.

(Pharmacotherapy 2005;25(12):1746–1751)

Although warfarin is used routinely for long-term anticoagulant therapy, it is perhaps the most dangerous drug prescribed on a long-term, outpatient basis. Complications of long-term anticoagulant therapy include major bleeding events, such as intracranial hemorrhage. When carefully managed, however, the complications of anticoagulation may be decreased up to approximately 85%.[1] For this reason, patients receiving warfarin for anticoagulation should be monitored closely and the dosage carefully adjusted.

A very small percentage of patients receiving warfarin for anticoagulation continue to have unpredictable and uncontrollable fluctuations in their international normalized ratios (INRs) despite careful follow-up and dosage adjustments.[2] This variability in degree of anticoagulation has been associated with complications of

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Presented in part at the American College of Clinical Pharmacy Spring Practice and Research Forum, Monterey, California, April 8, 2000.

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therapy.[3] Therefore, one can expect that interventions to reduce INR variability and thereby improve INR stability would also substantially reduce the serious bleeding complications associated with warfarin therapy.

Several factors, such as alcohol consumption, smoking, concurrent illness, interacting drugs, and changes in physical activity, may alter the stability of anticoagulation. In addition, changes in vitamin K intake (e.g., dietary or antibiotic therapy) are well recognized as a significant cause of INR fluctuation.

A tenuous balance exists between the amount of vitamin K present and the amount of warfarin needed to produce a consistent INR. Warfarin interferes with production of functional vitamin-K–dependent clotting factors in the liver. At therapeutic dosages of warfarin, clotting factor activity is reduced to approximately 20–40% of usual levels.[4]

It is generally accepted that a patient's vitamin K intake must be consistent in order to have a consistent warfarin effect. Although many dietary sources of vitamin K exist, the primary food source of vitamin K in the United States is green leafy vegetables, most commonly lettuce, spinach, collards, and broccoli.[5] The average recommended daily allowance of vitamin K is 80 µg.[6] Patients are often educated to avoid foods high in vitamin K altogether. Aside from being generally unhealthy, a deficiency of vitamin K may result in greater sensitivity to any changes in intake and proportionally greater fluctuation in the INR.

The objective of this study was to determine the potential INR stabilization effect of low-dose oral vitamin K in eight selected patients in whom wide fluctuations in the INR could not otherwise be alleviated.

Methods

The concept of dietary vitamin K supplementation was discussed with nine patients whose INRs had been fluctuating for reasons not associated with identifiable changes in diet, warfarin dosage, activity level, illness, or drug therapy (including over-the-counter and herbal products). These highly motivated patients were concerned about their therapy and generally distressed by their lack of INR control. All nine elected, on their own, to attempt dietary supplementation with 100-µg vitamin K tablets they purchased at a health food store (General Nutrition Centers, Inc., Pittsburgh, PA) at a retail cost of approximately $4/100 tablets.

The patients started taking the vitamin K with their anticoagulation provider's knowledge, but only when their INR was elevated or not substantially below their target INR. Close follow-up was provided through visits at the anticoagulation clinic. The service typically involved an in-house laboratory with rapid turnaround time and convenient face-to-face interactions with the clinician responsible for dosage modifications. Written dosing instructions were provided to each patient, and the next visit was scheduled before the patient left the clinic. These measures were designed to reduce confusion about the proper warfarin dosing schedule and to minimize nonadherence with follow-up visits. To the extent possible, each patient was consistently seen by the same clinician. All patients were followed on an outpatient basis in this manner throughout the evaluation period.

Vitamin K was started at 100 µg/day because this dosage is close to the recommended daily allowance of 80 µg[6] and approximates the usual vitamin K daily intake of 60–90 µg in the United States.[5]

The standard deviation of the INR values from each period was used to compare INR variability before and after vitamin K supplementation. The standard deviations were compared using a 2-sided Wilcoxon signed rank test (JMP 5.1; SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered to indicate a statistically significant difference. In addition, the number and proportion of INRs in the therapeutic range were evaluated before and after the start of vitamin K supplementation.

The investigators, who also were the health care providers for the patients, did not seek approval of an outside institutional review board for the following reasons. First, the study was a retrospective analysis of how patients responded to a longstanding routine practice in a large, private-practice hematology group. Patients were neither assigned to a treatment nor prescribed vitamin K; rather, they were given the option to start taking vitamin K as a dietary supplement if they chose. The rationale for this maneuver was explained to the patients before they made their decision, and they were advised that vitamin K had not been approved by the United States Food and Drug Administration for this purpose. Also, the study did not require any additional procedures or collection of additional data; it was very similar to the type of study known as a drug

utilization review.

Because this intervention was reserved for only those patients for whom all other attempts at INR stabilization failed, our small number of study patients were accrued over a prolonged period before data analysis was contemplated. One of the authors (HIB) was approached by investigators at another institution about collaborating on a randomized prospective trial of this practice. Such a study would, of course, require informed consent and full approval of an institutional review board.

Results

Patients

The eight patients were three men and five women aged 45–79 years (mean 65 yrs). All eight had been receiving warfarin therapy for 5–40 months (mean 21.7 mo); four had experienced a previous thromboembolic event. The patients had a variety of indications for anticoagulation (Table 1). Three had hypercoagulable states. Two had anticardiolipin antibodies—one with a previous stroke; the other had peripheral arterial occlusive disease and had required an amputation above the knee due to complications of thrombosis.

Table 1. Characteristics of the Eight Study Patients

Characteristic	No. of Patients
M/F	3/5
Indication for chronic anticoagulation	
Prosthetic valve replacement	3
Aortic valve only	2[a]
Aortic and mitral valves	1
Coronary artery disease	1
Atrial fibrillation	1
Venous thrombosis	2
Arterial thrombosis	3
Peripheral arterial occlusive disease	1[b]
Stroke	1
Transient ischemic attacks	1

[a]One patient with a prosthetic aortic valve replacement also had a history of transient ischemic attacks.
[b]One patient with a history of arterial thrombosis (peripheral arterial occlusive disease) also had anticardiolipin antibodies.

Anticoagulation Control

Data were available for eight patients; one of the nine patients originally identified was excluded from analysis because no postsupplementation INR values were available to determine the effectiveness of vitamin K supplementation. This patient elected to discontinue the vitamin K after experiencing a self-reported transient ischemic attack 1 week after starting supplementation (INR 3.2 at the time of the event). Given the short time the patient took vitamin K, and the INR at the time of and before the event, the patient's anticoagulation providers determined that this potential event was coincidental.

Fluctuations in INR decreased in almost all patients after the start of vitamin K supplementation (Table 2). As expected, given the small number of data points, a statistical difference was found between INRs in only two patients (patient no. 2 [p=0.031], patient no. 4 [p=0.047]) before and after the start of vitamin K supplementation. When the standard deviation of the INR was compared for all patients, a statistically

Table 2. International Normalized Ratios in the Therapeutic Range for Eight Patients Before and After the Start of Supplementation with Oral Vitamin K 100 µg/Day

Patient No.	No. (%) of International Normalized Ratios			
	In Range		In Range ± 0.2	
	Before	After	Before	After
1	7/13 (54)	18/30 (60)	9/13 (69)	23/30 (77)
2	0/9 (0)	9/22 (41)	3/9 (33)	12/22 (55)
3	1/14 (7)	9/17 (53)	5/14 (36)	13/17 (76)
4	2/23 (9)	3/17 (18)	4/23 (17)	8/17 (47)
		0/6 (0)[a]		1/6 (17)[a]
5	1/12 (8)	5/13 (38)	4/12 (33)	6/13 (46)
6	7/19 (37)	4/11 (36)	7/19 (37)	4/11 (36)
7	0/14 (0)	3/3 (100)	0/14 (0)	3/3 (100)
8	3/11 (27)	4/13 (30)	5/11 (45)	5/13 (38)
Overall	21/115 (18)	55/132 (42)	37/115 (32)	75/132 (57)
	Absolute increase 23%		Absolute increase 25%	
	Relative increase 128%		Relative increase 76%	

[a]Vitamin K was increased to 200 µg/day after 18 wks; values represent the INRs after the increase.

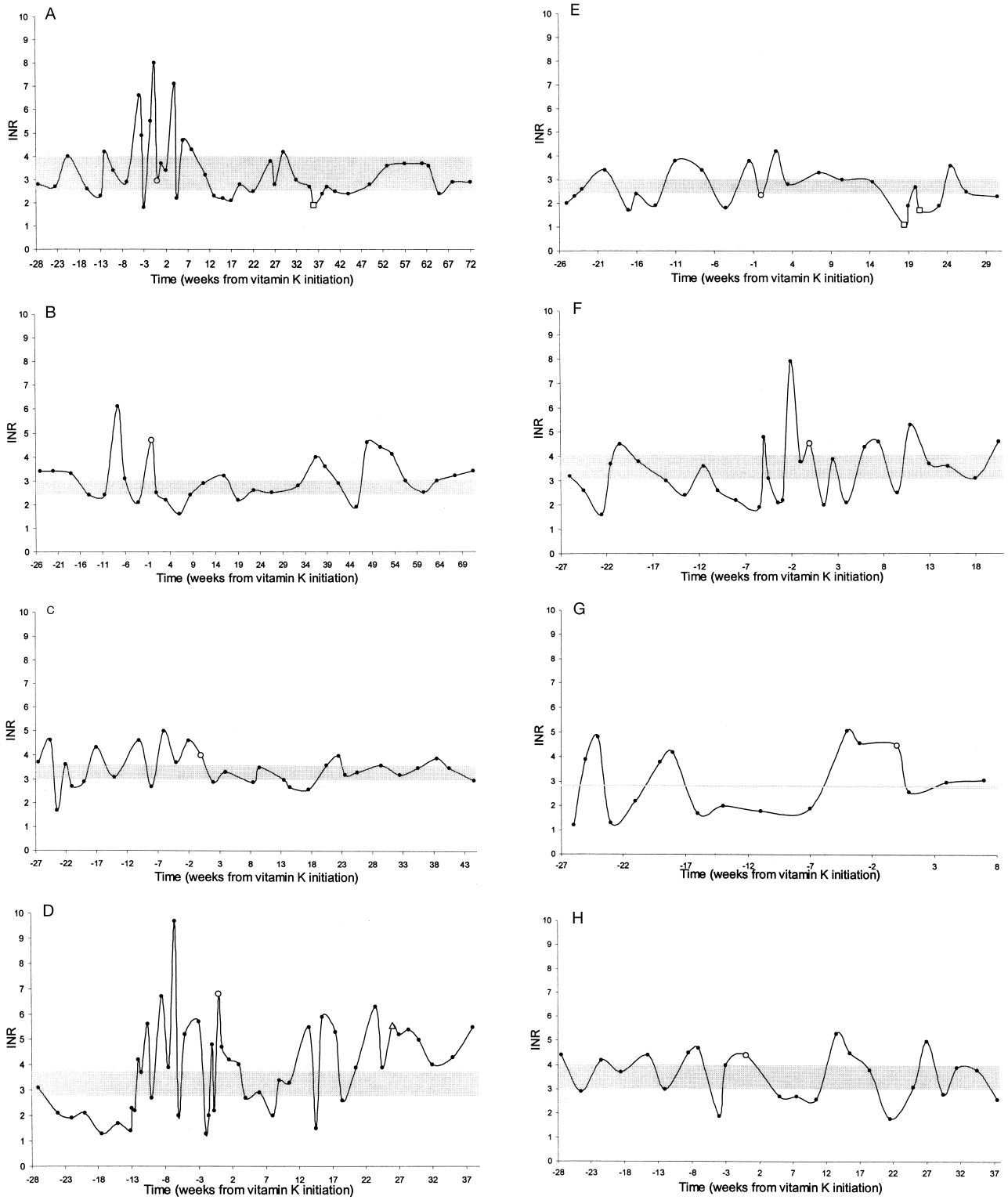

Figure 1. Anticoagulation control achieved before and after the start of oral vitamin K supplementation in the eight patients (A–H). The shaded area designates the patient's target INR range. Closed circles = measured INR values; open circles = INR values at the start of vitamin K 100 µg/day; open squares = intentionally low INR values for elective procedures; open triangle = INR at time of dosage increase to vitamin K 200 µg/day. Respective target INR ranges, and mean ± SD INRs before and after the start of vitamin K supplementation for each patient were as follows: (A) patient no. 1: 2.5–4.0, 3.8 ± 1.78, and 3.2 ± 1.03; (B) patient no. 2: 2.5–3.0, 3.4 ± 1.26, and 3.0 ± 0.79; (C) patient no. 3: 3.0–3.5, 3.7 ± 0.94, and 3.3 ± 0.40; (D) patient no. 4: 2.8–3.8, 3.5 ± 2.17, and 4.2 ± 1.31; (E) patient no. 5: 2.5–3.0, 2.6 ± 0.78, and 2.6 ± 0.84; (F) patient no. 6: 3.0–4.0, 3.3 ± 1.45, and 3.6 ± 1.09; (G) patient no. 7: INR target value of 2.8, 3.1 ± 1.45, and 2.9 ± 0.26; (H) patient no. 8: 3.0–4.0, 3.8 ± 0.87, and 3.4 ± 1.05.

Table 3. Variability of International Normalized Ratios Measured Using the Standard Deviation Before and After the Start of Supplementation with Oral Vitamin K 100 µg/Day

Patient No.	Standard Deviation[a]	
	Before Supplementation	After Supplementation
1	1.78	1.03
2	1.26	0.79
3	0.94	0.40
4	2.17	1.31
5	0.78	0.84
6	1.45	1.09
7	1.45	0.26
8	0.87	1.05

[a]Statistical comparison of the standard deviations before and after the start of oral vitamin K supplementation demonstrated a significant difference (p=0.039).

significant decrease was found (p=0.039; Table 3).

More INRs were in the designated therapeutic range after than before vitamin K supplementation (Figure 1). After supplementation, only one patient had fewer INRs in range, and one patient had all INRs in range. Overall, the absolute number of INRs in range increased from 18% to 42%—an absolute increase of 23% or a relative increase of 128% of the INRs in range. Allowing for small fluctuations on either side of the target INR range, the number of INRs within 0.2 INR units above or below the range increased from 32% to 57%—an absolute difference of 25% or a relative increase of 76% more INRs in range.

Discussion

The role of dietary vitamin K in the achievement of appropriate anticoagulation levels has been established. In one study, an increased intake of dietary vitamin K was associated with subtherapeutic anticoagulation, and a reduction was associated with elevated INRs.[7] Although this study used foodstuffs as the source of dietary vitamin K, another study used multivitamin supplementation and found that starting with a small daily dose of vitamin K 25 µg substantially affected INR control in three otherwise stable patients.[8]

In this case series, we report the effects of starting vitamin K supplementation in a small number of patients whose oral anticoagulation was unstable for unidentifiable reasons. The patients were carefully selected, highly motivated, and adherent and may not reflect the typical patient receiving anticoagulant therapy. In addition, due to numerous risk factors for thromboembolism, the target INR range for most of the patients was higher than usual, and our primary concern was avoidance of low INRs. The patients were seen in a specialized clinic setting, with face-to-face office visits (primarily with the same anticoagulation provider) and availability of a controlled, in-house laboratory with rapid turnaround time. Identifiable possible reasons for INR fluctuations were carefully excluded before vitamin K supplementation was considered.

We did not always have the same number of INR data points after the start of vitamin K supplementation that we had before. Therefore, the number of INRs in range may have been influenced by the number of INRs obtained. For example, if the INR is measured weekly rather than monthly, and all INRs are in range, then the weekly method will show 4 times as many INRs in range as the monthly method. Understanding this mathematical phenomenon, we examined the data in several ways. Both the number and percentage of INRs in range increased with dietary supplementation of vitamin K. The standard deviation, which decreased with the start of supplementation, should not have been as substantially affected by the number of INRs determined. In addition, once the patient reached stability with vitamin K, the frequency of INR measurement was actually lower than before the start of supplementation.

Of note, to mimic real-life scenarios, all data points were included in the calculations, even dosage adjustments before and after surgeries and procedures. Four INRs in patients nos. 1, 5, and 6 after the start of vitamin K were intentionally lower than the designated therapeutic range because their warfarin dosage was adjusted for a surgical procedure. Removing the data points around the time of procedures substantially increased the number of INRs in range further, and decreased the standard deviation of the INRs measured after vitamin K was started. Even with the small number of patients, and leaving in these data points, the improvement in anticoagulation control was statistically significant ($p<0.05$). Overall, we were impressed that statistical significance at any level was achieved considering the small number of patients evaluated.

Most patients demonstrated improved anticoagulation control with the addition of vitamin K. However, patient no. 6 had neither a decrease in the standard deviation of the INR nor

an increase in the number of INRs in range. This patient had lupus anticoagulant, which interferes with INR determinations. Another possibility for this patient's lack of response may be the relatively low dose of vitamin K used. Some sources cite a daily vitamin K intake as high as 300–500 µg in North America.[9] Furthermore, patient no. 6 was later found to have a hyperfunctioning thyroid nodule, which also may have contributed to the unstable anticoagulation control.

The vitamin K dosage was increased for patient no. 4 due to lack of response. This patient had a cerebral venous sinus thrombosis at age 45 years. Although a hypercoagulable state clinically was suspected, all her test results were negative. Before the evaluation period, she had extension of the thrombosis and a new thrombus, with an INR of 1.4 (target range 2.8–3.8) at the time of this event. Because of this history, the patient often required bridge therapy with low-molecular-weight heparin due to INR fluctuations below the lower limit of the target range before the start of vitamin K. Initially, supplementation with vitamin K 100 µg/day minimized the number of INRs that were well below the lower limit of the range and decreased the magnitude, but not the frequency, of the fluctuations. After 18 weeks of vitamin K 100 µg/day, the dosage was increased to 200 µg/day. At this point, the patient's INR fluctuations substantially diminished. The increased dosage did not immediately result in more INRs in the therapeutic range, but it resulted in the avoidance of low INRs while the warfarin dosage was cautiously decreased.

Based on the fact that most patients in this retrospective analysis showed INR stabilization after the start of daily supplementation with oral vitamin K, we believe this is a worthwhile strategy to improve the management and control of anticoagulation in selected clinical scenarios. However, because vitamin K supplementation can substantially reduce the INR within the first 1–2 weeks, this therapy should be introduced only when the INR is elevated. Furthermore, close follow-up and careful warfarin dosage adjustment are required.

Conclusion

Dietary supplementation with daily low-dose oral vitamin K in a selected group of motivated patients significantly increased the number of INRs in range as well as the time in range, and decreased INR fluctuation. Clinical end points were not part of this study; nevertheless, the correlation between INR control and serious complications is well established, and it is logical to expect that improved INR control will result in fewer complications.

Although this study must be viewed as preliminary, it lays the groundwork for a more thorough prospective evaluation of oral vitamin K supplementation for stabilization of INRs and for improvement of anticoagulation control in outpatients.

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