

Vitamin K Intake and Sensitivity to Warfarin in Patients Consuming Regular Diets

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Summary

The effect of dietary vitamin K intake on warfarin sensitivity is known only from case reports and few small clinical studies. We followed 50 patients commencing warfarin and consuming their regular diets (for 8 weeks) to study this relationship. A one-week recall dietary questionnaire was completed at weeks 2 and 8. Daily intake of nutrients and vitamin K was calculated from standard tables. Warfarin sensitivity index (WSI) was defined as final INR/final warfarin dose (mg/day/m^2 of body surface area) (week 8).

Vitamin K intake was 17-974 (median: 179) μg/day. Median WSI was 0.82 (0.31-4.47). A WSI value of 1.1 significantly separated excess (≥250 μg/day) from normal (<250 μg/day) vitamin K consumers (16/18 vs. 15/32, respectively, $p < 0.01$). The former had lower day 5 INR (median: 1.9 vs. 3.0, $p < 0.001$), needed more warfarin to achieve INR ≥2.0 (32.0 ± 9.2 mg vs. 25.4 ± 6.4 mg, $p = 0.009$) and required a higher maintenance steady state warfarin dose (5.7 ± 1.7 mg/day vs. 3.5 ± 1.0 mg/day, $p < 0.001$).

We conclude that in 32% (16/50) of anticoagulated patients under usual dietary conditions sensitivity to warfarin is decreased by vitamin K intake ≥250 μg/day.

Introduction

Anticoagulation therapy with warfarin is characterized by considerable inter- and intra-individual variation in dose requirements (1). Multiple factors are known to affect warfarin doses, among them dietary intake of vitamin K (2, 3). The effect of diet on warfarin anticoagulation is known mainly from case reports (4-9) and a few short-term experimental studies (10, 11). To date there has been no systematic study on the effect of daily vitamin K consumption on warfarin anticoagulation in patients consuming normal diets over a relatively long period of time.

The goal of our study was to test the effect of dietary intake of vitamin K on warfarin dose requirements in a cohort of patients consuming their usual habitual diet, at the beginning of anticoagulant therapy. Our hypothesis was that increased vitamin K intake would be associated with relative warfarin resistance resulting in increased warfarin dose requirements to maintain therapeutic INR levels.

Methods

Patients

Consecutive patients referred to our outpatient anticoagulation clinic after hospitalization (mainly in the internal medicine wards, coronary care and cardiac surgery services) were eligible for the study, and were followed for at least 8 weeks (for study purposes, and further on as required, as regular outpatients) on a weekly basis. At each visit the history of changes in warfarin dosage, compliance with prescribed doses, changes in types or dosage of additional drugs taken, changes in disease symptoms as well as signs and symptoms related to bleeding were recorded. The INR was determined within 1 h from venepuncture and patients received dose instructions and were scheduled for the next visit. Warfarin doses were adjusted by the study physician to achieve the target INR (low intensity: 2.0-3.0 or moderate intensity: 2.5-3.5) by the clinical indication for anticoagulation.

Dietary Information

The study dietitian (E.D.S) conducted a dietary interview at visits 2 (no less than 2 weeks from initiation of treatment) and 8, and was blinded with respect to the details of the patients warfarin treatment. Dietary intake was determined using a questionnaire previously applied in epidemiological studies in Israel (12). This questionnaire was based on a one-week recall of food frequencies and amounts of 260 food items commonly eaten in Israel. Computerized analysis of the data was used to calculate the intake of dietary nutrients provided by each item (taken from standard tables), and to summarize the complete dietary composition per individual. All patients were offered a personalized health promoting dietary consultation at the last outpatient visit (week 8), and none were adhering to a specific diet plan (e.g. weight reduction) during the study.

Warfarin Sensitivity and other Related Parameters

For each patient, warfarin sensitivity was calculated as the ratio of the final (week 8) INR to the final warfarin dose, and expressed as the warfarin sensitivity index (WSI):

$$\text{WSI} = \frac{\text{Last INR value}}{\text{Final warfarin dose (mg/day/m}^2\text{ BSA)}}$$

Cumulative warfarin dose to INR ≥2.0 was calculated as the total amount of warfarin required at the beginning of therapy, to raise the INR ≥2.0.

Statistical Analysis

The associations of warfarin dose requirements, INR achieved, intake of dietary components, the WSI as well as the sensitivity and specificity of the WSI for high vitamin K intake, were analyzed by standard techniques. Means were compared by the Student's t-test or the equivalent non-parametric method, and rates and proportions by the Chi-square test utilizing the GB-STAT™ statistical software. All data are presented as mean ± SD. A p value ≤0.05 was considered significant. The study was approved by the hospital institutional review board.

Results

Patients

Of 75 suitable patients 20 chose to continue follow-up in community clinics before their second visit and in 5 anticoagulant treatment was stopped due to lack of clinical indication, leaving 50 patients in the

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Table 1 Patient characteristics

	Men	Women	p
N	28	22	
Age (yrs)	56.4 ± 16.1	64.6 ± 9.9	0.045
Weight (kg)	74.5 ± 11.2	70.4 ± 11.4	NS
BSA (m^2)	1.86 ± 0.16	1.74 ± 0.14	0.01
WSI	1.04 ± 0.51	0.98 ± 0.48	NS
Cumulative dose to INR ≥ 2.0	29.5 ± 10.2	29.4 ± 6.3	NS
Warfarin steady state daily dose	4.94 ± 2.2	4.58 ± 1.7	NS

NS – non significant, BSA – body surface area.

Table 2 Dietary data

	Questionnaire 1 (week 2)	Questionnaire 2 (week 8)
Energy (Kcal/day)	1914±83	1978±592
Protein(gr/day)	94.3±37.5	101.7 ±34
Total fat(gr/day)	73.2±28.1	77.4±34.4
Carbohydrates(gr/day)	200±76	224±76
Vitamin K(μg/day)	182 (26-974)	172 (17-745)

There was no significant statistical difference between the two questionnaires with respect to all the dietary components. No difference was found when the data was reanalyzed according to target INR or WSI values above and under the median value. Vitamin K values are median (range).

study. Patient characteristics are shown in Table 1. Males were younger and had higher values of body surface area (BSA) but this was not reflected in their final (steady state) warfarin doses, nor in the cumulative doses required to achieve INR ≥2.0, which were similar in males and females.

Fourteen patients were taking medications known to enhance the effect of warfarin, the most common being amiodarone, taken by 6 patients (warfarin doses were adjusted for the presence of interacting drugs only with regard to amiodarone by routine reduction of warfarin doses by 30%). There were no patients receiving drugs known to diminish warfarin effects. There was no smoking nor regular consumption of alcohol among our patients. Indications for anticoagulant therapy were prosthetic heart valve in 17 patients (5 biologic and 12 mechanical), deep vein thrombosis (11 patients) and atrial fibrillation (9 patients). Heart disease, recurrent transient ischemic attacks, peripheral arterial embolism and pulmonary embolism accounted for the remaining 13 patients. Twelve patients received moderate intensity and 38 low intensity anticoagulant therapy. The former were younger (50.9 ± 18.2 vs. 62.1 ± 12.5 years), consumed the same daily amount of vitamin K (153 vs. 185 mg/day), required the same cumulative warfarin dose to INR ≥2.0 (29.6 ± 9.6 mg vs. 29.6 ± 5.0 mg), as well as similar steady state daily warfarin doses (4.8 ± 2.0 vs. 5.1 ± 2.0 mg/day) as the low intensity group.

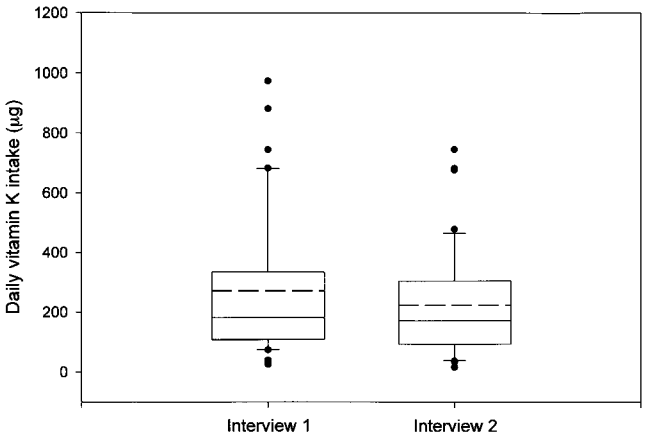

Fig. 1 Daily vitamin K intake at visit 2 (interview 1) and at visit 8 (interview 2). Boxes represent 25th, median and 75th percentiles. 95th percentiles are represented by whiskers with extreme patients as data points. Dashed line represents mean vitamin K values

Anticoagulation Control

Twenty-six patients received 10 mg/day of warfarin as loading doses while 20 other patients received daily doses of 5 and 7.5 mg (10 patients for each dose) as loading. These doses were administered during the first 2 treatment days. From day 3 onward doses were adjusted according to INR. Accordingly, follow-up at the anticoagulation clinic was started on days 2-5 after initiation of treatment. The first 5 days of treatment were considered the loading period, by the end of which 25/50 patients had reached their target INR range.

Most patients (38/50) required daily doses of 2.5-7.5 mg/day (group mean of 4.78 ± 2.03 mg/day) of warfarin as steady state maintenance doses and exhibited a stable dose requirement (about 70% of patients were maintained on a steady state dose in the range of ± 1.0 mg compared to their day 5 dose). In addition, 80% of the INR values were within the target range through week 8 of the study.

Dietary Information

Dietary data is summarized in Table 2. Dietary intake did not change during the 8-week study period as reflected by similar daily consumption of total energy, protein, fat and carbohydrates. Daily vitamin K consumption was 17-974 μg (mean 248.3 ± 205 μg/day) with a median of 179 μg/day. The majority of patients (75%) consumed less than 300 mg vitamin K daily (Fig. 1). Median vitamin K consumption was similar (182 vs. 172 μg/day) at weeks 2 and 8, above and below the median WSI value (163 vs. 258 μg/day, respectively) and was not influenced by treatment intensity (185 μg/day vs. 153 μg/day for the low and moderate intensities, respectively). High vitamin K intake (defined as intake of 250 μg/day and above) was observed in 18 patients (36%) and was related to consumption of increased amounts of green leafy vegetables (lettuce, cabbage, broccoli and spinach). These patients consumed 505 ± 181 μg/day of vitamin K (vs. 133 ± 50 μg/day in the low consumption patients, $p < 0.001$) and required higher daily steady state maintenance warfarin dose (5.8 ± 1.8 mg vs. 4.4 ± 1.3 mg, $p = 0.033$). However, they did not differ in consumption of energy, fat or other food constituents such as meat, milk or fruit.

Warfarin Sensitivity

The range of WSI values was 0.34-4.47 (mean 1.14 ± 0.81) with a median of 0.82. Two patients had extreme WSI values (4.10 and 4.47, the first with an INR of 6.3 on a daily dose of 3.2 mg and the second with an INR of 2.27 on a daily dose of 1 mg). Dietary composition and vitamin K consumption were not different from the entire group in these two patients. There was no significant difference in WSI values between males and females (median of 0.89 vs. 0.82 respectively) nor was there a difference between the low and moderate intensity treatment groups (0.82 vs. 0.87, respectively). WSI values tended to increase with age, but this was not statistically significant. Calculating sensitivity and specificity indicated the WSI of 1.1 to be optimal (sensitivity 0.89, specificity 0.53) for detecting patients consuming excess vitamin K (≥250 μg/day) in their diets. Patients with low

WSI values (≤1.1) required significantly more warfarin to reach an INR value ≥2.0 (cumulative doses 32.0 ± 9.2 mg vs. 25.4 ± 6.4 mg, p = 0.009), after 5 days of warfarin (loading) treatment their INR values were significantly lower (median, interquartile range: 1.9, 1.8-2.2 vs. 3.0, 2.6-3.7, respectively, p <0.001) and they required higher maintenance steady state doses (5.7 ± 1.7 mg/day vs. 3.5 ± 1.0 mg/day, p <0.001).

Of the 18/50 patients (36%) with daily vitamin K intake ≥250 mg, 16 (88.9%) had WSI values ≤1.1, whereas of the 32 patients who consumed < 250 mg of vitamin K daily only 15 (46.8%) had WSI values ≤1.1, (p = 0.008) (Fig. 2). Overall in 16/50 patients (32%) excess vitamin K intake was associated with decreased warfarin sensitivity. The relationship between vitamin K intake and warfarin sensitivity remained significant when patients on amiodarone were excluded from the analysis.

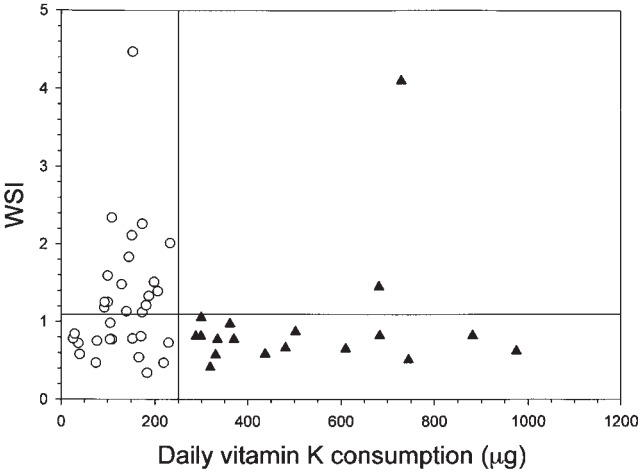

Fig. 2 Distribution of WSI values according to vitamin K daily intake. Excess vitamin K (≥250 μg/day, vertical line) consumers (▲) and ordinary vitamin K consumers (○) are separated by horizontal line representing WSI of 1.1

Discussion

The effect of diet on anticoagulation with warfarin is known mainly from case reports. These mostly relate to increased warfarin dose requirements (warfarin resistance) usually presenting as suboptimal INR levels in a previously well anticoagulated patient. This occurs usually during periods of increased vitamin K intake, mainly due to consumption of green leafy vegetables (9) in weight reduction diets (6), after resuming normal dietary habits following hospitalization or due to enteral feeding (7, 8). Some authors have reported on cases of severe clinical complications of unintended vitamin K ingestion, including myocardial infarction (5) and prosthetic valve thrombosis (4) in such patients. Conversely, vitamin K depleted diets can increase warfarin sensitivity, ending occasionally in episodes of unexpected bleeding (4). The few experimental studies on this issue have shown that vitamin K supplementation (for a few days) in the range of 250-1000 μg /day may induce a state of temporary warfarin resistance (10, 11) and that vitamin K depleted diets (delivering less than 40 μg/day of vitamin K) may decrease prothrombin activation, although not to a clinically significant extent (13). Based on these observations it has been recommended that patients on warfarin should not alter their vitamin K intake by more than 250-500 μg/day in order to maintain stable and safe anticoagulation regimens. More recently, defined diets have been proposed (3) to deliver the standard required daily allowance (RDA) for vitamin K on a regular basis (to maintain stability of anticoagulation).

In our observational study ambulatory patients on stable anticoagulation, observed over an 8-week period, were consuming an ordinary Western diet based on nutrient profiles obtained at weeks 2 and 8. Their daily intake of vitamin K (range 17-974 μg/day) was similar to that observed in other studies (3), and was stable over the observation period. Their median intake of vitamin K (179 μg/day) was twice the required daily allowance (1 μg/kg/day). Under these conditions vitamin K intake greater than 250 μg/day (consumed as 50 g of spinach, 100 g broccoli, 200 g lettuce or cabbage per day), was found in 18/50 (36%) of our patients and was associated with relative warfarin resistance in 16/50 (32%). This state of resistance was present even during the early phase of warfarin treatment (expressed as significantly higher warfarin doses needed to reach INR levels ≥2.0 and lower day-5 INR values) but was also evident as higher mean steady state doses required for proper anticoagulation. We assume that due to the short-term hospitalization in our hospital (median of 3.0 days) the effect of in-hospital diet was negligible and that even the early (week 2, post discharge) dietary interview reflects the habitual daily diet of our patients.

Warfarin resistance was ranked by the WSI value. This index is equivalent to the reciprocal relationship between steady state INR level and warfarin maintenance dose, shown to be reasonably accurate in a recent study (14). Low WSI values indicate a state of relative warfarin resistance which characterized our patients with increased vitamin K intake (≥250 μg/day). We found our WSI to have a good sensitivity and lower specificity. This high sensitivity may be of some advantage since low WSI values can draw the attention of the treating physician to a possible interaction problem in patient management (due to dietary, drug or any other problem) and can practically rule out such a problem when WSI values are normal.

Our study has several limitations. First, the use of one-week food frequency interviews to document intake of nutrients may pose a question of accuracy. This method has been shown to be comparable to an interviewer administered diet history in epidemiological studies (15), and to be accurate for its routine use. Secondly, direct measurement of vitamin K content in the various foods consumed by our patients was not done, nor was vitamin K blood level measured. Although this may raise a doubt about the true vitamin K intake, a reasonable correlation was found between total daily intake of the vitamin (as assessed by questionnaires and tables of vitamin K content in food ingredients) and the actual vitamin K plasma levels in volunteers (13, 16) using a method that enables reliable and accurate assessment of vitamin K levels in plasma and other biological samples (17). Thus, we feel confident that vitamin K intake, as estimated by our food frequency interviews reflects the true vitamin K content of the various food products consumed.

Our study followed dietary habits and vitamin K consumption for 8 weeks. This emphasizes the importance of obtaining a careful dietary history in patients on anticoagulants on a seemingly regular home diet, particularly patients who become warfarin-resistant during follow-up (a state that was found in 32% of our patients). We believe that our data are applicable to many patients under follow-up at other anticoagulation clinics due to the similarity in dietary habits. Understanding the problems caused by unintended prolonged high intake of vitamin K, may thus prevent unnecessary exposure to subtherapeutic INR values and risk of thrombosis.

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Received May 15, 1998 Accepted after resubmission November 10, 1998