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Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin

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Patients receiving warfarin who have unstable control of anticoagulation have a significantly lower intake of dietary vitamin K compared with their stable counterparts. We hypothesized that supplementation with oral vitamin K would improve stability in patients with previously unstable control of anticoagulation. Seventy warfarin-treated patients with unstable anticoagulation control were randomly assigned in a double-blinded fashion to receive a daily amount of 150 μg oral vitamin K or placebo orally for 6 months. Measures of stability of anticoagulation control in the 6-month study period were compared with those in the 6 months immediately prior to it. Vitamin K supplementation resulted in a significantly greater decrease in standard deviation of international normalized ratio (INR) compared with placebo (−0.24 ± 0.14 vs −0.11 ± 0.18; $P < .001$) and a significantly greater increase in percentage time within target INR range (28% ± 20% vs 15% ± 20%; $P < .01$). Anticoagulation control improved in 33 of 35 patients receiving vitamin K supplementation; of these, 19 fulfilled our criteria for having stable control of anticoagulation. However, only 24 of 33 patients receiving placebo demonstrated some degree of improvement, with only 7 patients fulfilling the criteria for having stable control. Concomitant supplementation of vitamin K, perhaps through reducing the relative day-to-day variability in dietary vitamin K intake, can significantly improve anticoagulation control in patients with unexplained instability of response to warfarin. (Blood. 2007;109:2419-2423)

Introduction

Up to half of all patients who receive warfarin to control coagulation fail to stabilize within their target range, with resultant increased risk of thromboembolism and the drug's adverse effect of bleeding.[1,2] While changes in concurrent medications, comorbidity, and patient adherence to therapy affect anticoagulation in a predictable way, a large part of the intraindividual variability in response to warfarin is unexplained.

Vitamin K is essential for the production of active clotting factors II, VII, IX, and X. In humans, vitamin K is obtained primarily from the diet in the form of phylloquinones, which are found in greatest concentration in green leafy vegetables.[3] There is little storage of vitamin K in the body because it is metabolized by the liver; in the absence of a dietary source, the vitamin K pool is therefore rapidly depleted.[4] Warfarin is an effective anticoagulant because it inhibits the regeneration of vitamin K hydroquinone from vitamin K epoxide by inhibiting the reductase enzymes in the vitamin K cycle.[5] Dietary changes in vitamin K intake influence anticoagulation response to warfarin; even a brief period of reduced intake of vitamin K has been demonstrated to cause warfarin sensitivity, while increased intake of vitamin K–containing foods can reduce anticoagulation, which can last for several days thereafter.[6] We have recently demonstrated that patients with unstable control of anticoagulation have a consistently and significantly lower intake of vitamin K than their matched stable counterparts.[7] This led us to hypothesize that supplementation with oral vitamin K, by increasing and stabilizing the body stores of the vitamin and reducing the relative variability in the daily dietary intake, could increase stability of anticoagulation control. We therefore investigated this in a cohort of patients taking warfarin who had unstable control of anticoagulation in a double-blinded placebo-controlled parallel design study.

Patients and methods

Ethical approval for the study was obtained from the Joint University of Newcastle and Health Authority Ethics Committee. Patients were recruited from the anticoagulation monitoring clinics at the Freeman Hospital and Royal Victoria Infirmary, Newcastle upon Tyne Hospitals National Health Service (NHS) Trust. All participants gave fully informed written consent to taking part in the study.

Patient selection

Patients with atrial fibrillation anticoagulated with warfarin for thromboembolic prophylaxis who had a target international normalized ratio (INR) range of 2.0 to 3.0, had been taking warfarin for at least 9 months, and were defined as having unstable control were eligible to take part. Based on our clinic databases, and excluding the initial 3-month induction period, the median standard deviation (SD) of INR values over 6 months is 0.3, with the 25% of the patients with the most unstable control of anticoagulation having a SD of greater than 0.5. We classified a patient as unstable if the SD of his/her INR values was greater than 0.5 and he/she had had at least 3 warfarin dose changes in the previous 6 months. Those patients whose instability was deemed to be due to poor adherence to warfarin therapy, changes in concurrent medication, comorbidity, or irregular and excessive

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alcohol consumption were excluded. Patients' motivation and likely adherence were assessed using a validated structured questionnaire about dosing history before recruiting them into the trial.[8]

Sample size

Based on our clinic database, for those patients with a target INR range of 2.0 to 3.0, 25% will have a SD of INR greater than 0.5 in the previous 6 months, and such SDs are distributed with a mean of 0.83 and SD of 0.48. Based on the assumption that this is true for the control group and assuming approximate normality for the mean SD, 35 patients in the vitamin K group and 35 patients in the placebo group were required to detect a difference of 0.32 U in the SD of INR with 80% power and at the 5% significance level.

Vitamin K and matching placebo formulation

Vitamin K (phytomenadione) (in 20:80 ethanol–deionized water solution) and matching placebo (20:80 ethanol–deionized water solution) were prepared as an oral solution at a concentration of 30 μg/mL by the Pharmacy Department at the Royal Victoria Infirmary (Newcastle upon Tyne, United Kingdom). Stability and quality control checks were performed on each batch of solution before dispensation. Both formulations were dispensed to patients in a 200 mL dark-brown glass bottle (vitamin K is light sensitive) with a 5-mL volume measuring cup every 4 weeks.

Protocol

Seventy patients were randomly allocated to 2 groups in a double-blinded fashion. One group received a once-daily supplement of 150 μg vitamin K in 5 mL solution (approximately twice the recommended daily allowance [RDA]), and the other received a 5 mL placebo with their warfarin daily dose. This dose of vitamin K was chosen as it was deemed to override any variability in dietary vitamin K intake without causing a statistically significant lowering of the INR.[9] All patients routinely attended their designated anticoagulation-monitoring service for the following 6 months, where their INR was checked and warfarin dosage adjusted if necessary using the Dawn Anticoagulation computer program (4S Information Systems, Milnthorpe, United Kingdom). This was performed independently by a pharmacist, thus preserving the study blindness. It was anticipated that the INR of some patients receiving vitamin K would fall; therefore, for safety purposes, anticoagulation status in all patients was monitored initially on a weekly basis. When each patient's INR reached and remained within target value for at least 2 visits, anticoagulation was monitored less frequently, but at intervals of no longer than 4 weeks. An overnight-fasting blood sample was taken at study entry (baseline) and at 3 further visits after 2, 4, and 6 months for the determination of plasma vitamin K concentrations. Patient compliance was assessed at each clinic visit by a warfarin tablet count and weighed measurement of the vitamin K/placebo solution remaining in bottle (this did not allow for any possible spillages).

Analyses

Capillary INR measurements were carried out by the Department of Haematology, Newcastle upon Tyne Hospitals NHS Trust. Plasma vitamin K concentrations were measured by high-performance liquid chromatography (HPLC) using postcolumn reduction and fluorimetric detection.[10] The limit of detection for extracted samples of vitamin K was 100 pg/mL, and the interday coefficient of variation for vitamin K at 1420 pg/mL was 8.6%.

The primary endpoint of the study was the SD of INR values in the 6-month study period compared with the same measurement in the 6 months immediately prior to the study. Secondary endpoints were the percentage of time at which the target INR value within 0.5 U was attained in each patient determined by the method of Azar et al,[11] the number of warfarin dose changes, and the number of patients who achieved an improved control of anticoagulation during the study compared with in the previous 6 months. Any adverse events, including the number and type of bleeding episodes and thromboembolic episodes including stroke, were recorded.

Statistic analysis

Minitab version 14 (Minitab, Coventry, England) was used to carry out all statistic analyses. The difference in measures of variability of anticoagulation (ie, SD of INR, percentage time in range, and number of warfarin dosage changes) between the 6-month period prior to the study and the 6-month intervention period were calculated. Parametric tests were used to compare the changes in SD of INR values and percentage time in range within each group, as these values fit a normal distribution. Plasma vitamin K concentrations showed a skewed distribution; these data were thus log-transformed and were then approximately normally distributed. Two sample *t* tests were carried out to compare the mean change in measures of stability of anticoagulation (SD of INR and percentage time in range during the study period) and log vitamin K concentrations in patients in the active (vitamin K) and placebo groups. The Mann-Whitney test was used to compare the difference in median number of warfarin dose changes between the active and placebo groups. In both patient cohorts, the INR and change in warfarin dose results for the first week of the intervention period were omitted from the statistic analysis; this was due to an initial decrease in the INR of those patients who received vitamin K supplementation that then necessitated an increase in warfarin dose. A small number of INR values were omitted from calculations of the measures of anticoagulation variability (n = 6 [< 1%] in the placebo group, n = 4 [< 1%] in the vitamin K group); the data omitted related to occasions when a patient stopped warfarin therapy for a period of time or commenced a course of medication known to have an established pronounced effect on the pharmacologic activity of warfarin. Results are presented as means ± SD unless stated otherwise. A *P* value below .05 was taken as being statistically significant.

Results

Patient characteristics

Seventy patients with unstable control of anticoagulation consented to take part in the study. Of these, 2 patients failed to complete it; 1 withdrew because of intervening illness, and the other died before completing the study. Neither case was related to the study. Both patients were later identified as having received placebo, and their results were not included in the final statistic analysis. There were no other reported adverse events during the study period in either group of patients. Demographics of the patients are shown in Table 1.

Daily warfarin dose requirements in patients receiving vitamin K supplementation increased by 16% ± 15% (from 3.8 ± 1.6 mg at day 0 to 4.4 ± 1.8 mg at day 7) 1 week after the study started. In the placebo group, daily warfarin dose requirements increased by 1.5% ± 8.3% (from 3.3 ± 1.5 mg at day 0 to 3.4 ± 1.5 mg at day 7) 1 week after the study started.

Anticoagulation control

There were no significant differences in measures of anticoagulation control (ie, SD of INR, percentage time in range, and number

Table 1. Patient characteristics

Variable	Vitamin K group	Placebo group
Sex, no. (%)		
Male	17 (49)	18 (51)
Female	18 (51)	17 (49)
Median age, y (range)		
Men	76 (58-82)	72.5 (62-85)
Women	73 (58-83)	76 (45-86)
White, no. (%)	35 (100)	35 (100)
Primary reason for anticoagulation, no. (%)		
Atrial fibrillation	35 (100)	35 (100)

of warfarin dosage changes) in the 6 months prior to the study between the 2 patient cohorts. While anticoagulation control was significantly improved in both cohorts in the 6-month study period compared with the previous 6 months, vitamin K supplementation resulted in a significantly greater improvement in the stability of anticoagulation (more than a 2-fold decrease in SD of INR and a nearly 2-fold increase in percentage time in range) compared with placebo. The median number of warfarin dosage changes was also significantly lower in the group receiving vitamin K supplementation than in the placebo group [Table 2].

Anticoagulation control improved in 33 of 35 patients on vitamin K supplementation; of these, 19 had a SD of INR values lower than 0.5, and thus were among the 75% of the clinic population with the most stable control of anticoagulation. However, only 24 of 33 patients receiving placebo demonstrated some degree of improvement, with only 7 of these classifiable as having stable control.

Plasma vitamin K concentrations

Fasting plasma vitamin K concentrations at baseline were not significantly different between the active (598 ± 340 pg/mL) and the placebo (694 ± 293 pg/mL) groups. Average plasma vitamin K concentrations in the 6-month study period in the patients receiving vitamin K supplementation increased significantly compared with baseline concentrations and were significantly greater than those receiving placebo in whom no significant changes in plasma vitamin K concentrations compared with baseline were noted (1502 ± 659 pg/mL vs 619 ± 210 pg/mL; $P < .001$).

Adherence

All patients recruited into the study exhibited a probable high degree of adherence as indicated by a score of 1 or lower out of 10 in the Brief Medication Questionnaire.[8] During the 6-month study period, as established by warfarin tablet count and bottle weighing, 2 patients failed to take their warfarin and the supplement on a single occasion. This was reflected in a corresponding change in their INR result. These results were included in the final statistic analysis.

Discussion

Alterations in dietary intake of vitamin K can have a significant effect on anticoagulation response to oral anticoagulants; increases in the dietary intake of vitamin K are associated with significant reductions in anticoagulation response,[6,9,12-15] whereas the opposite causes warfarin sensitivity.[6,12] Earlier we showed that in patients with stable control of anticoagulation, for every 100-μg increase in vitamin K intake in the previous 4 days, INR falls by 0.2,[16] further exemplifying the relationships between dietary vitamin K and anticoagulation response.

While day-to-day variability in vitamin K intake is common in all patients, those with an unstable anticoagulant response to warfarin consume lower amounts of vitamin K (phylloquinone) than do their stable counterparts.[7] This suggests that higher intake and thus greater body stores of phylloquinone allows for steady clotting factor activation and stable control of anticoagulation. On the contrary, a lower daily vitamin K intake can lead to rapid depletion of body stores. Subsequently, even small changes in dietary vitamin K intake translate, at the physiologic level, to large variations in active clotting factor production, rendering a patient liable to become unstable. We hypothesize that alterations in dietary intake of vitamin K have a greater effect on anticoagulation response in patients with low vitamin K status than in those with a normal vitamin K status. This is supported by the observation that in vitamin K–depleted patients a daily dose of only 25 μg of vitamin K for 4 weeks significantly reduces INR, which necessitates an increase in warfarin dose, but has no effect upon the INR of patients with a normal vitamin K status.[17]

The recognition that dietary vitamin K influences response to oral anticoagulants led to the recommendation that people should aim to consume a consistent daily dietary intake of vitamin K while taking warfarin. In a small study of 10 poorly controlled patients, a consistent vitamin K diet improved stability of anticoagulant control, but at the expense of limiting intake to 20 to 40 μg/day, which is well below the RDA of 1 μg/kg/day.[18] The design of menus to help provide a more consistent dietary intake equivalent to the RDA has recently been advocated.[19] However, these may be difficult and inconvenient for patients and those who take care of them to follow. In addition, the recommended menus are frequently misinterpreted, with many patients restricting their consumption of vitamin K–rich foods, which also reduces intake of other essential vitamins and fiber contained in such foods.

A recent small retrospective study in which a 100 μg daily oral dose of vitamin K was administered on a long-term basis to 8 patients with unstable control of anticoagulation[20] suggested that vitamin K supplementation, by increasing and stabilizing the body's stores of the vitamin, allowed for more steady activation of vitamin K–dependent clotting factors and better control of anticoagulation. To our knowledge, our study presented here is the first double-blind, randomized, placebo-controlled trial investigating the effect of vitamin K supplementation on the control of anticoagulation. Our results demonstrate that daily supplementation with 150 μg vitamin K along with warfarin therapy can lead to a more stable anticoagulation in patients, with all but 2 of the patients demonstrating improved anticoagulation control. Furthermore, more than half of these patients, according to the study selection criteria, could be reclassified as stable. As predicted, more than half of the patients

Table 2. Comparison of measures of anticoagulation control prior to and during the intervention period between the vitamin K- and placebo-treated groups of patients

	Vitamin K group			Placebo group		
Variable	Before study	Intervention period	Difference	Before study	Intervention period	Difference
SD of INR	0.72 ± 0.11	0.47 ± 0.17	−0.24 ± 0.14*	0.7 ± 0.11	0.59 ± 0.15	−0.11 ± 0.18*
Time in range, %	59 ± 20	87 ± 14	28 ± 20†	63 ± 18	78 ± 17	15 ± 20†
No. of dose changes, median (range)	5 (3-7)	2 (0-5)	−2 (−5-0)*	5 (3-8)	3 (1-8)	−1 (−3-3)*

For the vitamin K group, n = 35; for the placebo group, n = 33.
*Significant difference ($P < .001$).
†Significant difference ($P < .01$).

receiving placebo also showed some degree of improvement in their control of anticoagulation. This could be explained, at least in part, by increased patient adherence as a result of participation in the study per se and increased monitoring.[21] Also, because we had selected a study population from those within the top 25% of the SD of INR, it is likely that the SD for some patients would have been overestimated by chance. We thus expected that, during the trial, the SD of INR in the 2 groups would regress somewhat to the mean.

Inadequate and variable intake of vitamin K has important implications not only for oral anticoagulant therapy but also for the activation of Gla proteins involved in bone turnover, vascular repair, and the prevention of vascular calcification.[22] It is of theoretic concern that vitamin K supplementation, through the associated increase in warfarin dose requirements (by 16% ± 15% in response to 150 μg/day in this study), might lead to increased risk of bone fragility and osteoporotic fracture or arterial calcification.[23] However, in the absence of any experimental evidence for such risks, consideration of better anticoagulation control by vitamin K supplementation and its benefits in terms of reduction of risk of ischemic stroke and bleeding should prevail.

In order to ensure adequate patient recruitment and retention, we carefully selected patients on the basis of their motivation and long-term commitment to take part in this study. Patient adherence during the study was carefully monitored and, apart from the 2 instances highlighted earlier, adherence to the study was very high. The effect of any nonadherence was negated by using placebo. The patients recruited would therefore not have reflected the unselected anticoagulated population in which, for some, nonadherence is the root cause of their instability of anticoagulation control.[24]

Current clinical experience indicates that, if monitoring occurs monthly, only 50% to 60% of INRs measured are within target range, even in the trial situation.[25] Stability of anticoagulation is important in protecting against thromboembolic events in patients with nonvalvular atrial fibrillation (NVAF). In one study, the 52% of those anticoagulated for NVAF who achieved a 6-month period within the target range of 2 to 3 had a significantly higher mean survival and a lower rate of both thromboembolic events (0.8% vs 2.3% per patient year) and bleeds (0.4% vs 1.2% per patient year) recorded as an inpatient diagnosis than those who did not.[26] Risk of life-threatening bleeding complications, including subdural hematoma and intracranial hemorrhage, is increased in those with unstable control.[27] Anticoagulated patients with thromboembolic events and hemorrhagic complications are significantly more likely than controls to have been underanticoagulated (INR < 2.0) and overanticoagulated (INR > 3.0), respectively, at the time of their clinical event.[28] During a 2-year prospective study, the variance in INR values was significantly greater in patients who developed an ischemic stroke compared with those who did not.[29]

It will be several years yet before a suitable alternative to warfarin becomes available. Warfarin will thus remain the drug of choice for the treatment and prevention of thromboembolic disorders. Therefore, improving the safety profile of the drug is imperative. Reducing the within-patient variability in anticoagulation response to warfarin has the potential to improve the clinical effectiveness of this valuable but problematic therapy. Reducing the risk of bleeding or thromboembolic complications associated with over- and under-anticoagulation, respectively, would reduce the concern of clinicians about warfarin therapy for older patients with atrial fibrillation,[30,31] thus widening use of the drug in these patients. Improving anticoagulation control would also allow reduction in frequency of monitoring of patients with unstable control, with reductions in the associated costs of anticoagulation therapy and improved patient quality of life.[32]

In this study, we have established the potential benefit of vitamin K supplementation for patients with unstable anticoagulation response. Very few patients, however, achieve absolute stability of control over an extended period of time. Investigation of the effect of vitamin K supplementation upon anticoagulation control in a larger unselected warfarin-treated patient population is therefore warranted to demonstrate whether vitamin K supplementation leads to improved stability of anticoagulation control and subsequent reduction in the frequency of adverse events associated with warfarin therapy.

Authorship

Author contributions: E.S. was responsible for the day-to-day organization of the study. P.A. was responsible for the study design and statistic analyses of the data. H.W. and F.K. were involved in the design and initiation of the research and contributed to its progress. All 4 authors contributed to the writing of the manuscript.

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