The Effects of the Age-Related Eye Disease Study Vitamins on International Normalized Ratios in Patients Taking Warfarin

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These investigators retrospectively examined whether age-related macular degeneration patients on warfarin could benefit from the Age-Related Eye Disease Study combined vitamin therapy without significant changes in international normalized ratio levels.

Age-related macular degeneration (ARMD) is a major cause of visual impairment and blindness, affecting 1.75 million individuals in the United States.[1] By 2020, this number is expected to increase by almost 50% to about 3 million individuals.[1] Patients diagnosed with ARMD have central vision loss, which is attributed to oxidative stress of the retina and the buildup of drusen, a precursor for ARMD.[2] The prevalence of this eye disease and the cost of treatment and management of patients with vision loss have prompted many studies on risk factors for ARMD. In 2001, the Age Related Eye Disease Study (AREDS) reported that a preventive measure reduced the progression of ARMD. The study determined vision loss progression in advanced ARMD patients was reduced by 25% if the patient took a combined vitamin therapy of 25,000 IU of beta-carotene, 500 mg of vitamin C, 400 IU of vitamin E, 80 mg of zinc, and 2 mg of cupric oxide.[2-4] The antioxidants reduce the oxidative stress to prevent damage in the retina.[2-4] This research was done exclusively with Bausch and Lomb's formulation of this combined vitamin therapy, Ocuvite PreserVision.

Ophthalmologists and optometrists at the Veterans Affairs (VA) clinics are able to prescribe Ocuvite PreserVision for patients with ARMD who meet the AREDS criteria. Many of these patients are also taking an anticoagulant medication for prophylactic treatment of thromboembolic events.[5-9] The anticoagulant prescribed to these patients is warfarin.

Warfarin, a coumarin derivative, produces an anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide). Vitamin K is a cofactor for the posttranslation carboxylation of vitamin K-dependant proteins, otherwise known as coagulation factors. The vitamin K-dependant clotting factors are II, VII, IX, and X and require carboxylation for their biologic activity. Carboxylation of these factors requires the reduced form of vitamin K (vitamin KH2), molecular oxygen, and carbon dioxide and is linked to the oxidation of vitamin KH2 to vitamin K epoxide. Vitamin K epoxide is recycled to vitamin KH2 through 2 reductase steps, one of which is sensitive to vitamin K antagonists. This step reduces vitamin K epoxide to the natural food form of vitamin K, otherwise known as vitamin K1. Inhibition of this step by warfarin prevents the reformation of vitamin KH2, resulting in a decrease in vitamin KH2-dependant coagulation factors and in coagulation activity.[10,11]

Although excellent data show the clinical benefits of warfarin, it is underused because of its association with bleeding adverse events (AEs).[12] In addition, these AEs may be potentiated by the 120 documented drug-drug and drug-food interactions associated with warfarin.[5] To ensure the proper therapeutic range of warfarin, the VA has developed anticoagulation clinics to effectively manage international normalized ratio (INR) levels in patients taking warfarin. About 3,600 veterans are enrolled in anticoagulation clinics across the North Florida and South Georgia Veterans Affairs (NF/SG VA) Health Systems. These clinics monitor the patient's diet, medications, over-the-counter (OTC) supplements, alcohol intake, and recreational drug intake to ensure the therapeutic range of warfarin in the patient's blood.

Most prescription drug interac-

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tions can be identified and monitored by clinicians, but there is greater risk of interaction in patients who take OTC vitamins and supplements, for which fewer data exist. One such interaction, observed between warfarin and the antioxidant vitamins in the AREDS therapy, involves vitamins A and E. These vitamins may inhibit the oxidation necessary for the carboxylation of vitamin K-dependent coagulation factors.[10,11,13-15]

In the VA, the large number of patients on warfarin, and with ARMD, prompted the researchers to inquire whether doctors can safely prescribe Ocuvite PreserVision to patients receiving warfarin therapy, as well as determine a protocol to ensure maximum health benefits of both Ocuvite PreserVision and warfarin.

METHODS

The researchers performed a retrospective chart review for patients enrolled in anticoagulation clinics within the NF/SG VA Health System and who were taking warfarin and Ocuvite PreserVision concurrently. At the time of this study, this health system encompassed 2 medical centers, 2 outpatient clinics, and 7 community-based outpatient clinics. A review of patients on both medications, who met the inclusion/exclusion criteria, was conducted.

The inclusion criterion was as follows: Stable patients were defined as having therapeutic INR levels (between 2.0 to 3.0) on the last 2 out of 3 visits and were deemed eligible for the study if no other exclusionary factors applied. The exclusion criteria were as follows: (1) Presence of supratherapeutic INR goals (above 2.0 to 3.0); (2) Hospitalization 2 weeks before or after beginning Ocuvite PreserVision therapy; (3) Patient's use of fish oil, nonsteroidal antiinflammatory drugs, and all other OTC medications known to increase INR as defined by *Thomson Reuters Micromedex*, including agrimony, alfalfa (*Medicago sativa*), angelica, anise (aniseed), arnica (wolfsbane), asafetida, black cohosh (*Cimicifuga racemosa*), remifemin, bladderwrack (fucus, kelp), bogbean, cassia, celery (seed/extract), chamomile (*Matricaria recutita*) (German/Roman), chondroitin, clove, coenzyme Q10 (ubiquinone), dandelion, danshen, dehydroepiandrosterone (DHEA), dong quai (*Angelica sinensis*), and various forms of echinacea; and (4) Concurrent use of medications that began when the use of Ocuvite PreserVision began.

The following data were collected: Age, gender, indication for warfarin, last 3 INR levels, patient-specific therapeutic INR range, OTC/antibiotics, hospitalization within 2 weeks of follow-up INR levels, dietary consistency, vision at Ocuvite PreserVision initiation, INR levels after initiation of Ocuvite PreserVision, the passage of time (in days) since Ocuvite PreserVision initiation, adjustments in warfarin regimen after the initiation of Ocuvite PreserVision, INR at second visit after initiation of Ocuvite PreserVision, and the passage of time (in days) since Ocuvite PreserVision initiation.

STATISTICAL ANALYSIS

The results are shown as a standard deviation (SD) unless otherwise indicated. Statistical analysis was performed using Minitab software. A P value < .05 was considered statistically significant. The mean of the INR values before and after the initiation of Ocuvite PreserVision was compared with the SDs using the Wilcoxon signed-rank test.

STATISTICAL RESULTS

Between October 1, 2004, and October 1, 2009, 155 patients were enrolled in anticoagulation clinics within the NF/SG VA Health System and concurrently began taking Ocuvite PreserVision. Of these subjects, 14 met the inclusion/exclusion criteria of the present study. The average age of patients who met the criteria was about 69.9 years. All 14 patients were male and were prescribed warfarin for stroke prophylaxis secondary to atrial fibrillation (INR goal 2.0 to 3.0). The mean INR prior to initiation of Ocuvite PreserVision was 2.286 (SD = .258), which followed a normal distribution (Figure 1). After initiation of Ocuvite PreserVision, the mean INR was 2.629 (SD = .750), which did not follow a normal distribution. The mean difference in INR was −0.343, with a SD = .733. The Wilcoxon signed-rank test resulted in a P value of .0574, which was not statistically significant. Sixty-eight patients would have been needed to achieve a statistical power of 80%. Retrospective review of the patient charts resulted in 14 patients for a statistical power of 28%.

DISCUSSION

The purpose of the present study was to determine whether there was a significant change in INR levels after the initiation of Ocuvite PreserVision in patients taking warfarin concurrently. Although the sample size and statistical power were insufficient to confirm statistical significance for the study, the analysis of raw data per patient showed that the differences in INRs for each subject before and after the initiation of Ocuvite PreserVision were not statistically significant. The INR levels remained within the therapeutic range after initiation, and these findings indicate no clinically significant change and no adjustments to warfarin dosage.

Our study was limited by retrospective data, which showed the 14

patients did not have dietary changes. However, unreported dietary factors could have influenced the INR levels found in each patient. For example, when the AREDS combined vitamin therapy is recommended for a patient with ARMD, it is often suggested the patient increase the consumption of green leafy vegetables rich in vitamin K, which helps to prevent progression of the eye disease. Given that health care providers typically offer this advice, a patient's failure to report an actual increase in the intake of these vitamin K-rich vegetables could affect the results of a study. Regarding the present findings, it is possible that the effects of vitamin K in these types of vegetables could have counterbalanced the effect of Ocuvite PreserVision and thereby produced results showing no statistical difference between INR levels before and after. Future prospective studies would need to thoroughly document dietary changes.

Many eye care professionals consider the interaction between the AREDS combined vitamin therapy and warfarin to be a serious contraindication and therefore abstain from prescribing the vitamin therapy.[16-18] This trend is suggested by the observation that of 3,600 patients in the anticoagulation clinics, only 155 were prescribed Ocuvite PreserVision while on warfarin. However, lack of uniformity in patient chart documentation also limited the researchers' ability to account for those patients diagnosed with ARMD but who had not been prescribed Ocuvite PreserVision. The implication is that future prospective studies should ascertain whether a patient diagnosed with ARMD could benefit from the AREDS combined vitamin therapy.

If Ocuvite PreserVision is taken as suggested, the patient would receive a total of 400 IU of vitamin E. Previous studies show that vitamin E dosages of up to 400 units daily do not appear to greatly affect prothrombin time.[15] However, recent studies provide conflicting evidence that suggests prothrombin time is adversely affected by the combination of vitamin E and warfarin.[19]

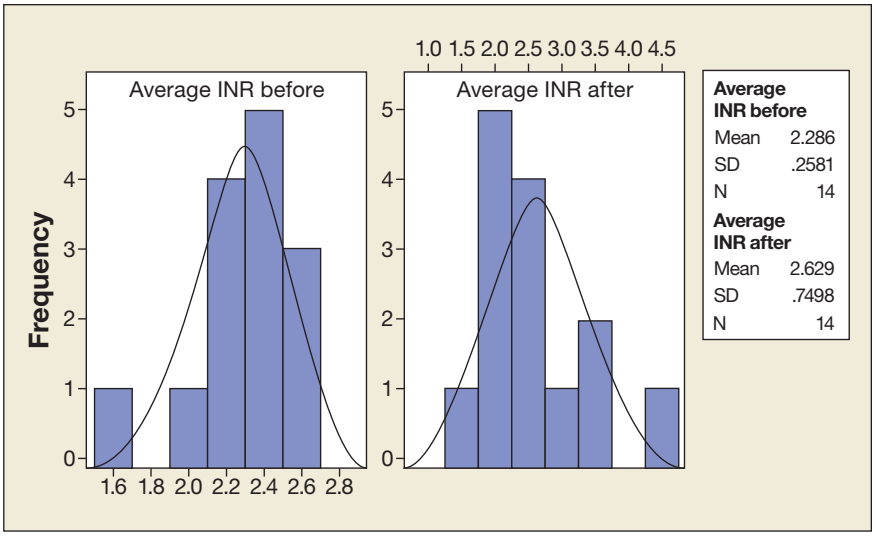

Figure 1. Average INR levels before and after initiation of Ocuvite PreserVision.

Although the present study does not refute that an interaction exists between the two, it does suggest the AREDS combined vitamin therapy should not be withheld from ARMD patients solely because the patient is on warfarin. Based on the results of our study, the authors suggest that the potential benefit of the AREDS combined vitamin therapy likely outweighs the possible risk of the drug interaction with warfarin. To mitigate the risk of interaction between the 2 therapies, we suggest the development of a protocol for prescribing the AREDS combined vitamin therapy to warfarin patients. Patients who are monitored by the VA's anticoagulation clinics are in the ideal setting to be managed once the eye care professional initiates the combined AREDS vitamin therapy.

The ideal follow-up time, after the initiation of Ocuvite PreserVision therapy, is still undetermined. The retrospective data did not provide uniform documentation about the date of initiation and the date of INR follow-up. However, based on the coagulation factor II's half-life of 96 hours (4 days), which is the longest half-life of all the vitamin K-dependant coagulation factors, it is reasonable to suggest a follow-up of 1 week after initiation of Ocuvite PreserVision.[10,19]

CONCLUSION

Relevant studies have shown that vitamins A and E have interactions with warfarin, but over time the findings have challenged the amount of each vitamin that could cause AEs in the average patient. The present study was limited by its retrospective design and by a small sample size, resulting in an underpowered study. Future prospective studies are recommended to establish statistical significance. However, the results showed clinical significance for each subject included in the study. Based on raw data obtained from each patient, it

is suggested that an ARMD patient on warfarin could benefit from Ocuvite PreserVision without significant changes in INR levels and that treatment should be managed through collaboration among doctors and include a 1-week follow-up in a VA anticoagulation clinic.

Author disclosures

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

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