A Survey of Oral Vitamin K Use by Anticoagulation Clinics

Edward N. Libby, MD; David A. Garcia, MD

Background: Despite published reports of its safety and efficacy, oral vitamin K (phytonadione) may not be widely used for patients with warfarin-associated coagulopathy. We tested the hypothesis that recommendations for phytonadione use from the American College of Chest Physicians (ACCP) Fifth Consensus Conference on Antithrombotic Therapy are not routinely incorporated into the clinical practice of many anticoagulation clinics.

Methods: Surveys were mailed to 100 separate clinics in the southwestern region of the United States that are members of the Anticoagulation Forum, an association of anticoagulation clinic personnel and medical directors in the United States and Canada. Respondents were presented with 4 scenarios involving asymptomatic patients taking warfarin whose international normalized ratio is supratherapeutic. In each scenario, the respondents were told the patient's international normalized ratio and whether the patient was at "high" risk for bleeding.

Results: Of 53 respondents, 13 (25%) indicated that their clinics never use oral phytonadione. Eighteen (34%) indicated that their clinics use subcutaneous phytonadione, despite the absence of a recommendation for this in the ACCP guidelines published in 1998. For each scenario, we made a judgment as to whether the respondent's management was consistent with guidelines found in the ACCP Fifth Consensus Conference on Antithrombotic Therapy. Overall, only 17 respondents (32%) provided all 4 answers consistent with the ACCP recommendations.

Conclusion: For patients with supratherapeutic international normalized ratio values, our survey suggests that a substantial number of anticoagulation clinics underutilize oral phytonadione.

Arch Intern Med. 2002;162:1893-1896

Two to three million patients in the United States are receiving long-term anticoagulant therapy with warfarin. Therapy with warfarin carries the benefit of prevention of thrombosis and the risk of hemorrhage. Published reports of annual bleeding risk have reported episodes of major bleeding to be as low as 1.3% per year in large, international trials of warfarin use to prevent stroke in atrial fibrillation. In many of these trials, patient selection and use of anticoagulation clinics with strict protocols and highly trained staff probably influenced the outcomes favorably. Much higher rates of major bleeding in patients receiving anticoagulation of 3% to 7% per year have been reported in studies that examined more "real world" examples of clinical care. These data suggest that there are 26000 to 210000 major bleeding episodes related to warfarin use per year in the United States.

The risk of hemorrhage is related to a number of factors, including increases in the international normalized ratio (INR), age, history of bleeding, renal insufficiency, and history of peptic ulcer disease. Bleeding risk increases dramatically as the INR rises above 4 to 5. Even brief episodes of time with elevated INRs pose a significant risk of bleeding for patients. Recent reports show that patients in typical outpatient practices are above or below the therapeutic range 50% of the time. In addition, these studies have suggested that the amount of time spent within the therapeutic INR range is directly related to therapeutic efficacy and inversely related to the risk of hemorrhage. Therefore, strategies that allow the practitioner to keep patients taking anticoagulants within or close to their therapeutic range while minimizing the amount of time spent with an elevated INR should decrease the incidence of major hemorrhage related to warfarin use.

Vitamin K (phytonadione) has been recognized for decades as a treatment for excessive anticoagulation. Recently, sev-
eral studies have documented the efficacy of oral phytonadione in returning elevated INRs to therapeutic or near-therapeutic levels within 24 to 48 hours. Published experience also suggests that use of oral phytonadione does not cause clinically significant overcorrection of the INR.

The 1998 and 2001 American College of Chest Physicians (ACCP) Consensus Conferences on Antithrombotic Therapy give identical recommendations on the use of vitamin K to manage excessive anticoagulation (Table 1). The American Heart Association, the American College of Cardiology, and the Anticoagulation Forum all endorse these recommendations for management of excessive anticoagulation.

Despite these widely available recommendations, there is great variation among anticoagulation clinics in the management of excessive anticoagulation in patients without significant bleeding. To test the hypothesis that many anticoagulation clinics do not follow the ACCP guidelines with respect to oral phytonadione use, we mailed a survey to 100 anticoagulation clinics in the southwestern United States.

### METHODS

#### IDENTIFICATION OF ANTICOAGULATION CLINICS FOR STUDY

We mailed surveys to all of the 100 clinics listed in the southwest region (New Mexico, Arizona, Louisiana, Arkansas, Texas, and Oklahoma) of the Anticoagulation Forum, an international organization of clinics providing care and management services to patients taking oral anticoagulants. A letter accompanied the survey asking that a senior member of the clinic team (nurse, pharmacist, or physician) who was familiar with the policies of the clinic answer the survey and return the form. We did not categorize the survey answers by the type (nurse, pharmacist, or physician) of respondent. Participants were offered a $10 payment for completing and returning the survey. Three months after the initial mailing, a follow-up letter was sent to those clinics that had not responded.

The institutional review board of the University of New Mexico Health Sciences Center, Albuquerque, approved the research protocol for this observational study. Informed consent was not obtained from the respondents.

### SURVEY CONTENT AND STRUCTURE

First, respondents were asked if their clinic ever used oral and/or subcutaneous phytonadione. Respondents were then presented with 4 clinical scenarios (Table 2), each describing an asymptomatic patient without active bleeding whose INR was supratherapeutic. The case presentations also offered information about each patient’s overall risk for bleeding and thrombosis. Cases were constructed so that the recommendations from the ACCP Fifth Consensus Conference regarding treatment of elevated INR values were directly applicable.

In Table 2, cases A and B each describe an asymptomatic patient without risk factors for bleeding whose INR is between 6 and 7. The ACCP states that for an INR greater than 5 but less than 9 in a patient with no significant bleeding, either of 2 management strategies is appropriate: (1) hold warfarin and recheck INR in 24 to 48 hours or (2) hold warfarin, administer low-dose oral phytonadione, and recheck INR in 24 to 48 hours.

Case C describes an asymptomatic patient with an INR of 6.3. The scenario states the patient had a recent gastrointestinal hemorrhage and is “at high risk for bleeding.” Case D describes an asymptomatic patient with an INR of 9.8. In patients with an INR greater than 5 but less than 9 with an increased risk of bleeding, the ACCP recommends the use of phytonadione (1-2.5 mg, orally). According to ACCP guidelines, patients with an INR greater than 9 and without significant bleeding should have their warfarin held and be administered phytonadione (3-5 mg, orally). In these 2 cases, an answer was considered consistent with ACCP guidelines only if it included the administration of the appropriate dose of oral phytonadione.

In each case, respondents were asked to select the management strategy that most closely reflected their clinic’s usual practice. Their choices included (1) continue warfarin at a reduced dose and recheck INR in 24 to 48 hours; (2) omit the next warfarin dose and recheck INR in 24 to 48 hours; (3) omit the next warfarin dose and administer oral phytonadione; or (4) “other” (for this choice, participants were asked to write in their response). In addition, some of the scenarios included 2 possible doses of oral phytonadione: 1 “low” (1-2.5 mg) and 1 “high” (3-5 mg).

### OUTCOME DEFINITION

We defined all respondents’ management choices as either consistent or not consistent with the recommendations of the 1998 ACCP Consensus Conference on Antithrombotic Therapy (at the time this survey was conducted, the 2001 ACCP Consensus Conference on Antithrombotic Therapy was not yet in print). For the purposes of the study, we considered nonspecific write-in strategies (eg, “call MD”) to be consistent with ACCP recommendations.

### STATISTICAL ANALYSIS

The 95% confidence interval was calculated for the proportion of respondents having answers consistent with the 1998 ACCP recommendations.

### RESULTS

Of the 100 surveys that were mailed, 14 were returned due to an incorrect address. These surveys were not counted in the study. Thirty-three clinics did not respond. Of the 86 clinics that received surveys, 53 (62%)...
responded. Of 53 respondents, 13 (25%) indicated that their clinics never used oral phytonadione. Nineteen (36%) indicated that their clinics use subcutaneous phytonadione. Thirteen clinics indicated they use both oral and subcutaneous forms of phytonadione.

In case A, more than 90% of respondents chose a strategy consistent with ACCP recommendations (Figure). Eighty-one percent chose only to omit a dose of warfarin, 11% chose to omit 1 dose and give low-dose oral phytonadione, 1% chose to continue warfarin at a lower dose, and 7% chose “other.” Most write-in responses were not consistent with ACCP guidelines because they specified that warfarin be resumed at the same dose.

In case B, a similarly large majority chose a strategy consistent with ACCP guidelines. Eighty-six percent chose only to omit a dose of warfarin, 11% chose to omit 1 dose and give low-dose oral phytonadione, 1% chose to continue warfarin at a lower dose, while 1 respondent (2%) chose “other.”

In case C, in which the patient is described as being “at high risk for bleeding,” only 55% of respondents elected to administer low-dose (1-2.5 mg) oral phytonadione. Twenty-five percent chose only to omit warfarin and recheck the INR in 24 to 48 hours, while 4% chose to give 2.5 to 5.0 mg of oral phytonadione. Sixteen percent chose “other.” Of these, 4 responses (7%) included the possibility of low-dose oral phytonadione administration. Several of the 5 write-in responses deemed inconsistent with ACCP recommendations included plans to increase dietary vitamin K intake.

In case D, describing an asymptomatic patient with an INR greater than 9, 40% chose the response consistent with ACCP recommendations (to administer 3-5 mg of oral phytonadione while withholding the next dose of warfarin). Thirty-eight percent chose only to omit warfarin and recheck the INR in 24 to 48 hours, and 11% elected to give low-dose (1-2.5 mg) oral phytonadione. Six respondents (11%) chose “other”; 4 (7%) of these write-in responses were considered consistent with ACCP recommendations. One of the 2 write-in responses that did not conform to ACCP recommendations specified subcutaneous phytonadione for this scenario.

Overall, 17 respondents (32%) answered all 4 case scenarios in a manner consistent with ACCP recommendations.

Oral phytonadione is well established to return elevated INRs (5-9) to less than 5 in 24 to 48 hours in 95% to 96% of patients without causing later difficulty in the reestablishment of anticoagulation. Although randomized controlled trials have been too small to show statistically significant decreases in bleeding rates, the natural history of untreated high INRs suggests that oral phytonadione is likely to be of benefit for many of these patients. We performed a MEDLINE search from 1964 through February 2001 using the keywords “phytonadione” and “thrombosis” and found no reports of thromboembolism associated with low-dose (1-5 mg) oral phytonadione.

The results of our survey suggest that many anticoagulation clinics do not routinely follow the recommendations of the ACCP Consensus Conference regarding the use of oral phytonadione for the management of asymptomatic patients whose anticoagulation is supratherapeutic. Thirty-five percent of clinics stated that they used subcutaneous phytonadione. This mode of therapy has not been recommended by the ACCP since 1995.12 In addition, numerous studies have documented that the absorption rate and responses of patients to subcutaneous phytonadione are erratic. Interestingly, in cases C and D (depicting the patients at highest risk for bleed-
ing) the percentage of respondents who deviated from ACCP guidelines was the highest. This is puzzling because these patients could benefit most from returning the INR to lower levels quickly. Earlier studies have confirmed that the ACCP guidelines are not adhered to but found that at very high INRs (10-20) patients were more likely to receive phytonadione.13

It is possible that the personnel managing these facilities are unaware of the recommendations, but this seems unlikely since they were identified as members of a leadership group for anticoagulation clinics. At the time we conducted the survey, the ACCP Fifth Consensus Conference recommendations had been in print for over 2 years. We speculate that many of the respondents base their management decisions on historical practice rather than on the recommendations of experts or evidence-based guidelines. Perhaps anecdotes of thrombosis associated with high doses of parenteral phytonadione have made some practitioners reluctant to follow recommendations that include the use of oral phytonadione. Finally, we acknowledge that the ACCP Consensus Conference recommendations on the management of nontherapeutic INRs are described by their authors as “grade 2C” (“very weak recommendations, other alternatives may be equally reasonable”).

The ability to generalize our results is limited by the number of clinics that failed to respond and by the fact that we mailed questionnaires to only one region. Furthermore, responses to questions about fictitious patients may not accurately reflect actual practice.

In conclusion, the results of our survey suggest that many anticoagulation clinics underuse oral phytonadione and manage elevated INR values in a manner that differs significantly from published guidelines. This is of great concern because the incidence of serious and life-threatening bleeding associated with elevated INRs is real and potentially avoidable.

Accepted for publication January 17, 2002.

This study was supported by research grants from DuPont Pharmaceuticals, Wilmington, Del, and the Department of Internal Medicine, University of New Mexico.

This study was presented at the International Society Meeting for Thrombosis and Hemostasis, Paris, France, July 10, 2001.

We are very grateful to David Schade, MD, for his critical review of the manuscript and to Tanya Morga, RN, for her assistance with this project.

Corresponding author and reprints: Edward N. Libby, MD, University of New Mexico Hospital, Department of Internal Medicine SACC, 2211 Lomas NE, Albuquerque, NM 87131 (e-mail: elibby@salud.unm.edu).

REFERENCES