Prospective Study of the Outcomes of Ambulatory Patients With Excessive Warfarin Anticoagulation

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Background: Warfarin sodium therapy is highly effective in preventing thromboembolism. Its major toxic effect is hemorrhage, the risk of which increases with the international normalized ratio (INR). Data on the rate of major hemorrhage and the rate of INR decay after an episode of excessive anticoagulation therapy would help guide management of elevated INRs in the outpatient setting.

Methods: We prospectively followed up outpatients in an anticoagulant therapy unit from April 24, 1995, through March 1, 1996. Study patients had to be taking warfarin for longer than 1 month and have an INR target range of 2.0 to 3.0. Consecutive outpatients with an INR greater than 6.0 were identified and compared with a randomly selected concurrent set of patients whose INR was in the target range. Major hemorrhage was defined as fatal, intracranial, or requiring hospitalization and transfusion of at least 2 U of blood.

Results: One hundred fourteen patients with INRs greater than 6.0 were identified and compared with 268 patients whose INRs were in the target range. None of the patients had clinically apparent bleeding at the time of the INR measurement, and none received phytonadione (vitamin K1). Patients did not differ significantly in age, sex, indication, or duration of warfarin therapy. Ten patients with an INR greater than 6.0 (8.8%; 95% confidence interval, 4.3%-15.5%) sought medical attention for abnormal bleeding, and 5 of these experienced a major hemorrhage during 14-day follow-up (4.4%; 95% confidence interval, 1.4%-9.9%) compared with none of the patients with an in-range INR (P<.001). Thirty-three percent of patients with INRs greater than 6.0 had INRs less than 4.0 within 24 hours, 55% within 48 hours, 73% within 72 hours, and nearly 90% within 96 hours of temporary discontinuation of warfarin therapy.

Conclusions: Outpatients with INRs greater than 6.0 face a significant short-term risk of major hemorrhage. Randomized trials are needed to determine the net benefit of preventive treatment with phytonadione.

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OPTIMAL management of outpatients who are receiving warfarin sodium and who have asymptomatic elevations in international normalized ratios (INRs) remains uncertain. Published recommendations from the American College of Chest Physicians Consensus Conference1 are variably adhered to in practice2 and likely reflect clinicians’ concerns about the net benefit of phytonadione (vitamin K1) therapy, the lack of prospective data on conservative management, and the practical barriers to timely administration of phytonadione in an outpatient setting. Although the relative risk of hemorrhage with elevated INRs is well documented,3-8 the absolute short-term risk of hemorrhage resulting from isolated elevations in INRs in individual patients has not been prospectively studied. In addition, there is little information on the rate of spontaneous INR decay after temporary discontinuation of warfarin therapy. Such information would help guide rational management of elevated INRs in the outpatient setting.

We assembled a large cohort of outpatients taking warfarin consecutively identified with an INR greater than 6.0 whose target INR was 2.0 to 3.0. This study builds on a previous work9 of determinants of excessively elevated INRs. In this study, we describe the management and course and estimate the short-term bleeding rate associated with an INR greater than 6.0. We report our findings from a predominantly elderly cohort receiving long-term warfarin therapy and discuss the implications for outpatient intervention.
PATIENTS AND METHODS

IDENTIFICATION OF STUDY PATIENTS

Study patients were identified from outpatients managed in the Anticoagulant Therapy Unit, Massachusetts General Hospital, Boston, between April 24, 1995, and March 1, 1996. To be eligible for the study, patients had to be taking warfarin for more than 1 month and have a target INR of 2.0 to 3.0. Study patients were prospectively identified from the daily log of routinely scheduled outpatient INR tests.

Consecutive outpatients with INRs greater than 6.0 were identified. We chose an INR greater than 6.0 because this was the threshold INR recommended for phytanadione intervention.10 Patients could be included only once. Results of INR tests were routinely verified by a duplicate test. All INR tests leading to enrollment in the study were obtained as part of routine management. No patients were known to be bleeding at the time of study entry.

A companion cohort was assembled from randomly selected patients in the Anticoagulant Therapy Unit with target INRs of 2.0 to 3.0 whose actual INRs recorded in the daily log were between 1.7 and 3.3. At any given time during the study period, approximately 2200 patients (75%) in the Anticoagulant Therapy Unit had INR targets of 2.0 to 3.0. The INR range of 1.7 to 3.3 was chosen because this was the range of INR values in the Anticoagulant Therapy Unit that did not trigger a change in management. Approximately twice as many patients with in-range INRs were selected each week as patients with INRs greater than 6.0.

CLINIC OPERATING PROCEDURES

At the start of therapy, patients attend a 60-minute introductory session describing warfarin and the clinic's operating procedures. Patients are provided with a summary informational booklet including protocol for adverse events, eg, "If bleeding does occur, it should be reported to the Anticoagulation Unit and your physician as soon as it is noticed." Anticoagulant Therapy Unit staff promptly notify patients and their physicians of out-of-range INRs; intervention with phytonadione is at the discretion of the patient's treating physician and not the staff.

RESULTS

Clinical characteristics of patients with INRs greater than 6.0 and those with INRs between 1.7 and 3.3 ("in-range") are described in Table 1.

Seventy-two (63%) of 114 patients with high INRs were 70 years and older compared with 147 (55%) of 268 patients with in-range INRs (P=.14). There were no significant differences in sex, indication for anticoagulation therapy, or duration of warfarin therapy. Nearly two thirds of patients had taken anticoagulants for longer than 1 year. For patients with high INRs, the mean value was 8.1 (range, 6.1-29.8), and 16 (14%) had INRs greater than 10.0. The last routine INR measurement (mean) for patients with INRs greater than 6.0 vs those with in-range INRs was 3.0 vs 2.4 (P<.001), with a mean testing interval of 20 vs 21 days, respectively (Figure 1). None of the patients with INRs greater than 6.0 had symptoms of bleeding at the time of the test, and all were managed conservatively with temporary discontinuation of warfarin therapy. All patients were initially advised to hold 2 consecutive doses of warfarin, with subsequent dosing decisions individualized based on entry and follow-up INRs.

HEMORRHAGIC EVENTS

During the 2-week follow-up, 10 patients (8.8%; 95% confidence interval, 4.3%-15.5%) with INRs greater than 6.0 sought medical attention for abnormal bleeding, and 5 of these (4.4%, 95% confidence interval, 1.4%-9.9%) ex-
experienced a major hemorrhage compared with none of the patients with in-range INRs ($P<.001$ by log-rank test). No patient experienced a thromboembolic event during follow-up. Of 5 patients with nonmajor bleeding episodes, 1 was evaluated for hemoptysis and sent home from the emergency department; 2 were evaluated for gross hematuria, with 1 ultimately being hospitalized for cystoscopy and treatment with fresh frozen plasma to stop the bleeding; and 2 were admitted to the hospital for evaluation of extensive ecchymoses, with 1 treated with fresh frozen plasma. None of these patients had any appreciable decrease in hematocrit values.

Clinical features of the 5 patients who experienced a major hemorrhage are detailed in Table 2. Their mean age was 76 years, and the mean entry INR was 8.9. Two of the hemorrhages were fatal, and 1 of these was intracerebral. The rate of major bleeding in the first week was 2.6%. Two patients presented within 1 day of their elevated INR, 1 on day 6, and 2 between days 7 and 14 (Figure 2). International normalized ratios at hospital admission for these last 3 patients were 3.8, 3.1, and 3.3. Predisposing factors, other than anticoagulation therapy, were present in 2 of 5 patients with major bleeding events; 1 had procarcinamide hydrochloride–induced thrombocytopenia (platelet count, $7 \times 10^9/L$) and another had gastritis identified by endoscopy likely secondary to use of nonsteroidal anti-inflammatory medications. Of 2 patients with delayed clinical presentations, both had symptoms referable to bleeding the week before hospital admission.

### RATE OF INR DECAY

Of 114 patients with INRs greater than 6.0, 105 had subsequent outpatient INR tests performed. The other 9 patients were either admitted to the hospital or permanently discontinued from warfarin therapy without further testing. Of the 105 patients, 64% had another INR measurement within 48 hours, 72% within 72 hours, 86% within 96 hours, 95% within 120 hours, and 99% within 168 hours (day 7 postentry INR). By interpolation, 33% of patients had INRs less than 4.0 within 24 hours, 55% within 48 hours, 73% within 72 hours, and nearly 90% within 96 hours (Figure 3). Eleven (10%) of the 105 patients had INRs greater than 4.0 within 48 hours. However, nearly 45% of patients still had INRs greater than 4.0 ninety-six hours after the study INR test. Only 1 of these patients had an entry INR greater than 10.0. The mean number of days to an INR less than 4.0 was 2.9 for the 92 patients with entry INRs between 6.1 and 10.0 and 3.6 for the 13 patients with entry INRs greater than 10.0 ($P=.26$). The observed time point for the actual INR test less than 4.0 is displayed in Figure 3.

### COMMENT

This is the first study to prospectively quantify the short-term rate of hemorrhage among outpatients after an isolated episode of INR greater than 6.0. Of 114 outpatients consecutively identified with an asymptomatic elevation in INR, 8.8% (95% confidence interval, 4.3%-15.5%) sought medical attention for abnormal bleeding and 4.4% (95% confidence interval, 1.4%-9.9%) experienced a major hemorrhage during 14-day follow-up. No patient experienced a thromboembolic event. We also found wide interpatient variation in the rate of INR decay after discontinuation of warfarin therapy. Thirty-three percent of patients with entry INRs greater than 6.0 had their INR reduced to less than 4.0 within 24 hours. However, nearly 45% of patients still had INRs greater than 4.0 forty-eight hours after cessation of warfarin therapy. As found in other studies, prophylactic administration of phytonadione to nonbleeding patients in an outpatient setting was not routine.

The 1- and 2-week incidence rates of major hemorrhage of 2.6% and 4.4%, respectively, are high when contrasted with aggregate annual rates of major and fatal hemorrhage of 1.4% and 2.7%, respectively. It is likely that the high short-term incidence of major hemorrhage among outpatients was due to an increased risk of bleeding associated with the time course of warfarin therapy. A rate of 2.6% major hemorrhage is similar to that found in other studies of inpatients. It seems advisable to consider outpatient monitoring of INRs close to the time of discontinuation of warfarin therapy.

### Table 2. Clinical Features of Patients With INRs Greater Than 6.0 and Patients With INRs of 1.7 to 3.3

<table>
<thead>
<tr>
<th>Variable</th>
<th>&gt;6.0 (n = 114)</th>
<th>1.7-3.3 (n = 268)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
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<td></td>
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<tr>
<td>Age, mean (range), y</td>
<td>71 (39-94)</td>
<td>69 (39-94)</td>
<td>.26</td>
</tr>
<tr>
<td>Female</td>
<td>54 (47)</td>
<td>120 (45)</td>
<td>.64</td>
</tr>
<tr>
<td>Anticoagulation therapy indication†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>57 (39)</td>
<td>128 (40)</td>
<td>.16</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>47 (32)</td>
<td>80 (25)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>13 (9)</td>
<td>28 (9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>30 (20)</td>
<td>82 (26)</td>
<td></td>
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<tr>
<td>Duration of warfarin therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 and &lt;3 mo</td>
<td>15 (13)</td>
<td>44 (16)</td>
<td></td>
</tr>
<tr>
<td>3-12 mo</td>
<td>26 (23)</td>
<td>48 (18)</td>
<td>.70</td>
</tr>
<tr>
<td>&gt;1 y</td>
<td>73 (64)</td>
<td>176 (66)</td>
<td></td>
</tr>
<tr>
<td>Entry INR</td>
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<tr>
<td>1.7-3.3</td>
<td>NA</td>
<td>268 (100)</td>
<td></td>
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<tr>
<td>&gt;6 and &lt;=10</td>
<td>98 (86)</td>
<td>NA</td>
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<tr>
<td>&gt;10 and &lt;=20</td>
<td>15 (13)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>1 (1)</td>
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<td></td>
</tr>
<tr>
<td>Previous INR, mean</td>
<td>3.0</td>
<td>2.4</td>
<td>&lt;.001</td>
</tr>
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</table>

*Data are given as number (percentage) of patients, except as indicated otherwise. INR indicates international normalized ratio; NA, not applicable.
†Categories were not mutually exclusive.
Hemorrhage in our study reflects the older age distribution of our patients, the presence of other bleeding risk factors, and the elevated INRs. This rate of hemorrhage, coupled with the varying rates of INR decay and the varying time course to bleeding, suggests there might be a window for preventive treatment with phytonadione. However, data supporting intervention with phytonadione is limited. Two recent retrospective studies support conservative management over intervention with phytonadione. Glover and Morrill conducted a retrospective chart review of 51 patients with INRs of 6.0 or greater identified from 2 anticoagulation clinics between 1993 and 1994. Forty-eight patients (94%) were treated with temporary discontinuation of warfarin therapy; there was only 1 episode of minor bleeding. The 3 patients who received phytonadione did not experience any bleeding, but 1 required a prolonged course of subcutaneous heparin because of difficulty in achieving therapeutic anticoagulation. In another retrospective chart review conducted in a health maintenance organization, 248 patients with 301 episodes of INR greater than 6.0 were identified from a laboratory database between 1994 and 1995. Forty-eight patients (94%) were treated with temporary discontinuation of warfarin therapy; there was only 1 episode of minor bleeding. The 3 patients who received phytonadione did not experience any bleeding, but 1 required a prolonged course of subcutaneous heparin because of difficulty in achieving therapeutic anticoagulation. In another retrospective chart review conducted in a health maintenance organization, 248 patients with 301 episodes of INR greater than 6.0 were identified from a laboratory database between 1994 and 1995. Most patients were managed conservatively; there were 2 episodes of major hemorrhage (0.9%). Of the 52 episodes of excessive anticoagulation treated with phytonadione, including patients presenting with bleeding, 2 developed thrombotic complications and 3 became resistant to warfarin therapy. The authors concluded that conservative management was safe and cost-effective when the INR was between 6.0 and 10.0.

Studies of phytonadione intervention have had limitations in study design. Most have not included a control group, have included inpatients, have focused on the rate of INR reduction and not on patient outcomes, and have not had adequate lengths of follow-up to thoroughly evaluate complications such as thrombotic risk and induced refractoriness to warfarin therapy. Weibert et al published a retrospective case series of 81 patients identified from 2 anticoagulation clinics between 1989 and 1996 with INRs greater than 5.0 who had been given 2.5 mg of oral phytonadione in addition to withholding warfarin therapy. Seven patients were bleeding at presentation. Seventy-three percent of patients reached INR levels between 2.0 and 5.0 within 48 hours; 17% were less than 2.0 and 10% were greater than 5.0. No information is presented on patients during the 7-year study with INRs greater than 5.0 who were managed conservatively. Based on this selected series of patients, the authors conclude that withholding warfarin therapy and administering 2.5 mg of oral phytonadione is reliable, safe, and an inexpensive way to rapidly correct excessive anticoagulation for patients with INRs between 5.0 and 10.0.

In a recent prospective study, 62 patients with INRs between 4.5 and 10.0 were given 1.0 mg of phytonadione orally via insulin syringe in addition to withholding warfarin. Forty-nine of these patients (79%) were inpatients and 25 (40%) had only started warfarin therapy
within the previous 7 days. The mean entry INR of 5.8 decreased to 2.9 within 16 hours. Eighty-five percent of patients had their INRs reduced to less than 4.0, and 35% had their INRs reduced to less than 1.9. Although no adverse events were reported, the authors cautioned that the study was not designed to examine rates of bleeding and thromboembolism. Follow-up was 6 days. Their conclusion advocated use of 1 mg of phytonadione for asymptomatic nonbleeding patients with INRs between 4.5 and 10.0. This study lacked a control group, making it difficult to define the incremental benefit of phytonadione therapy when contrasted with conservative management. Also, results from inpatient use of phytonadione might not generalize to the far less controlled outpatient setting.

In a small trial, Pengo et al10 randomized 23 patients with INRs between 5.0 and 8.0 to either withholding warfarin therapy or receiving 2 mg of oral phytonadione. Although more patients in the treated group had INRs less than 5.0 within 24 hours, by day 2, 92% of patients managed conservatively had INRs less than 5.0 compared with 91% of those who received phytonadione. By day 9, 83% vs 73%, respectively, had INRs in the target range. Data on clinical events were not provided.

Before phytonadione will be widely embraced as a therapeutic intervention, studies must first demonstrate that it improves patient outcomes and that the downside risks of its administration are negligible. Prophylactic intervention with phytonadione is intended to decrease bleeding through a more rapid reduction in INR than would occur spontaneously. To realize the potential benefit, phytonadione must be administered in a timely fashion. It demands rapid turnaround of test results, timely communication with the patient, and ease of administration. Convenient oral forms of low-dose phytonadione are not widely available. Because parental administration of phytonadione requires a subcutaneous or intravenous injection, the logistics of arranging for an immediate return by the patient to the office or emergency department or of scheduling a nurse home visit are challenging in an outpatient setting. If intervention with phytonadione is ultimately shown to improve patient outcomes, barriers to its real-world use will need to be removed to ensure its effective translation into clinical practice.

STRENGTHS AND LIMITATIONS

Several distinctive features of our study warrant discussion. Our patients came from a large anticoagulation clinic that provides care for most patients receiving long-term anticoagulation therapy in our medical center. During the 44-week study period, we prospectively followed up approximately 2200 outpatients receiving warfarin anticoagulation therapy who had an INR target range of 2.0 to 3.0. From among these patients, we assembled our cohort of 114 unique patients with INRs greater than 6.0 and a random comparison sample of patients with INR levels of 1.7 to 3.3. Eighty-seven percent of our patients with INRs greater than 6.0 were taking warfarin for 3 months or longer, and all patients had to be taking warfarin for longer than 1 month to be eligible for the study. This avoided the bias of enrolling patients with erratic control more typical of the initial titration period, which has been shown in several studies10,13,17 to be the period conferring the highest risk of bleeding. Patients with INRs greater than 6.0 were only included once, thereby avoiding oversampling of patients with higher INR variability, which itself has been reported to be a risk factor for bleeding.17 In addition, all of the INR tests in our study were obtained as routinely scheduled outpatient monitoring tests among patients not known to be bleeding. Inclusion of high INR tests triggered by bleeding events would result in biased overestimates of rates of hemorrhage. Telephone follow-up was obtained for all of the 114 patients with elevated INRs because the natural history of these patients was the focus of our study. For all of these reasons, we believe this study provides an objective and generalizable estimate of the true short-term risk of major hemorrhage after an INR greater than 6.0 among a predominantly elderly outpatient population taking anticoagulants managed conservatively without use of phytonadione. Our estimates of the rates of INR decay are based on interpolation of the entry and subsequent INR values. Because our patients did not have uniform preset intervals for repeat blood draws, interpolation likely underestimates the rate of INR decay.

CONCLUSIONS

Asymptomatic outpatients with INRs greater than 6.0 face a 2-week risk of major hemorrhage of 4.4% when managed conservatively. The rate of INR decline after temporary discontinuation of warfarin therapy is highly variable. The rate of hemorrhage coupled with the varying rates of INR decay and varying time course to bleeding suggest a window and provide a rationale for intervention with phytonadione. Randomized trials with adequate lengths of follow-up are needed to determine the aggregate benefit of phytonadione therapy. Studies of the factors leading to individual variability in INR decay are needed to optimize the care of the heterogeneous population of outpatients taking warfarin. Reliably predicting the patients with spontaneous rapid reduction in INR would obviate unnecessary intervention in the one third of patients whose INR decreased to less than 4.0 within 24 hours of withholding warfarin therapy. Targeted study of patients with prolonged elevation of INRs may minimize overcorrection of the INR, decrease subsequent warfarin therapy resistance, and thereby minimize the risk of thromboembolism.

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