Evaluation of Excessive Anticoagulation in a Group Model Health Maintenance Organization

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Background: The fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy recently published guidelines that included recommendations regarding the management of excessive anticoagulation. Limited data are available to support these recommendations.

Objectives: To assess management and outcomes of excessive anticoagulation in a group model health maintenance organization, compare management with the published guidelines, and analyze the cost of treatment strategies.

Methods: A search of computerized laboratory information identified patients with an international normalized ratio (INR) of greater than 6.0 during the 9-month study. Pertinent data were collected through a retrospective medical record review. Information was concurrently collected for cost analyses.

Results: The analysis included 301 episodes of excessive anticoagulation among 248 patients. Most (83%) episodes of elevated INRs were managed conservatively by a temporary discontinuation of warfarin sodium therapy until the INR was in a therapeutic range. Conservative management resulted in no sequelae in 212 (85.1%) of 249 episodes. Two episodes (0.8%) of major bleeding evolved in patients managed conservatively. No sequelae were documented in 23 (44%) of 52 episodes of phytonadione (vitamin K1) administration. Sixteen (31%) episodes of major bleeding were documented, but bleeding occurred before phytonadione administration in all cases. Administering phytonadione resulted in hospital admission for 3 patients—2 (3.8%) because of thromboembolism and 1 (1.9%) for the administration of heparin sodium. Cost-effectiveness analysis determined that treatment with phytonadione is 7 times more costly than conservative management when INRs are between 6.0 and 10.0.

Conclusions: Most episodes of excessive anticoagulation were not managed per consensus guidelines. The higher the INR, the more likely were interventions to adhere to the guidelines. Administering phytonadione to patients with a moderate elevation of INRs (6.0-10.0) may be unnecessary. Based on this study, conservative management is a viable option.

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RAL anticoagulant therapy has demonstrated clinical effectiveness for several indications, including the prevention and treatment of thromboembolism and the prevention of systemic embolism in patients with artificial heart valves or atrial fibrillation. Consequently, each year more than 1 million patients are treated with warfarin sodium in the United States. The main complication associated with warfarin therapy is bleeding. In a summary of various studies involving oral anticoagulant therapy, the average annual frequency of total, major, and fatal bleeding was estimated to be 9.6%, 3.0%, and 0.6%, respectively.

The risk of bleeding is directly related to the intensity of anticoagulation and rises dramatically once the international normalized ratio (INR) exceeds 5.0. Therapeutic options for correcting excessive anticoagulation include temporarily discontinuing warfarin therapy until the INR falls within the therapeutic range, administering phytonadione, or administering fresh frozen plasma (FFP) or prothrombin complex concentrate. Treatment decisions are based on such factors as the urgency of the situation (presence or absence of bleeding), other risk factors for bleeding, indication for anticoagulation, the extent of the INR elevation, and the international sensitivity index (ISI) of the thromboplastin used to determine the prothrombin time. The ISI is an important consideration because with excessively prolonged prothrombin times, the use of less sensitive thromboplastins may result in erroneously high INRs, leading to overly aggressive treatment. Moreover, the risk of bleeding must be weighed against the risk of thromboembolism associated with the reversal of anticoagulation.
METHODS

This study was a retrospective review of patients' medical records conducted in a large group model health maintenance organization in the western United States that serves about 325,000 members. A search of computerized laboratory information identified all episodes of INRs greater than 6.0 from December 1, 1994, through August 31, 1995. During this interval, 2 lots of Dade (Miami, Fla) rabbit brain thromboplastin C plus were used by the laboratory to determine prothrombin times. The ISI of the thromboplastins used were 1.97 and 1.94.

Data were collected for all episodes identified through the laboratory search using a standardized form. Anticoagulation flow sheets were obtained to supplement information in the medical record. Data extracted included patients' age and sex, warfarin dose (milligrams per week) before and after elevated INRs, indication for anticoagulation, plausible reason(s) for excessive anticoagulation, treatment (conservative vs administration of phytonadione, FFP, or both), and clinical outcomes. Conservative treatment was defined as the temporary discontinuation of warfarin therapy until the INR fell to within the therapeutic range. Clinical sequelae were recorded as none, major bleeding, minor bleeding, thrombosis, and refractoriness to continued oral anticoagulant therapy requiring the administration of heparin sodium. Major bleeding was defined as overt hemorrhage associated with a decrease of 20 g/L or more in the hemoglobin level; a transfusion requirement of 2 units or more of blood; or any intracranial, gastrointestinal, intraarticular, or retroperitoneal bleeding. Minor bleeding was defined as any bleeding not meeting the above criteria and included increased bruising, bleeding from gums, epistaxis, and bleeding from a minor trauma site. Thrombosis was defined as an embolic cerebrovascular accident, pulmonary embolism, deep venous thromboembolism, or other systemic thromboembolic events documented through objective evidence (ventilation-perfusion scan, ultrasonography, or computed tomographic scan).

The appropriate use, route of administration, and dose of phytonadione for reversing excessive anticoagulation are not well established. There is a risk of hematoma formation associated with intramuscular administration, and this route should be avoided.7 Case reports document anaphylactoid reactions associated with intravenous administration.8 Although oral administration is an option in patients with intact gastrointestinal and hepatobiliary tracts, variable plasma concentrations of phytonadione have been reported when given by this route.9 Doses of phytonadione greater than 10 mg have been associated with difficulty in reestablishing therapeutic oral anticoagulation.10 An examination of the pharmacodynamic response to the administration of 10 mg of phytonadione revealed that the effects of warfarin on clotting factor synthesis were antagonized at 168 hours.11 Lower doses of phytonadione are less likely to cause this problem. In a study evaluating low-dose phytonadione (0.5 vs 1 mg given intravenously) for the treatment of patients with INRs greater than 5.0,12 at 24 hours, the INR fell below 2.0 in 50% of patients receiving 1 mg of phytonadione and ranged from 2.1 to 5.5 in all patients who received 0.5 mg. No hemorrhagic complications were reported, and there was no difficulty in reestablishing warfarin therapy.

The fourth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy recently published guidelines that include recommendations regarding the management of excessive anticoagulation (Table 1).2 Limited data are available to support these guidelines. Only 2 studies have compared conservative management with the administration of phytonadione for the treatment of excessive anticoagulation.13,14 In a small, prospective, randomized trial, Pengo et al13 compared suspension of warfarin sodium therapy with the oral administration of 2 mg of phytonadione in 23 patients with INRs greater than 5.0. By day 9 of the study, 10 of 12 (83%) patients who temporarily stopped warfarin therapy and 8 of 11 (73%) patients who were administered phytonadione had INRs in the therapeutic range. Clinical outcomes (hemorrhagic and thromboembolic episodes) were not reported. In a retrospective review, Glover and Morrill14 compared the temporary discontinuation of warfarin therapy with the adminis-

STATISTICAL ANALYSIS

Patient-specific data were classified according to the severity of the INR elevation (6.0-10.0, 10.1-20.0, or >20.0) and analyzed for comparability. For patients having multiple episodes of excessive anticoagulation, the INR values were averaged and the patient information was included in the resulting INR classification.

Continuous variables were compared using analysis of variance. The level of significance for these comparisons was corrected to .02 to account for multiple comparisons among the 3 groups. Nominal data were compared using either χ² or the Fisher exact test with a level of significance of .05. Data are presented as the means±SD unless otherwise specified.

ECONOMIC ANALYSES

Cost information was concurrently collected for laboratory tests, doses of phytonadione given, follow-up telephone calls, physician visits (primary care physician, cardiologist, or oncologist), urgent care visits, emergency department visits, and hospital admissions. The perspective taken for the economic analyses was that of the health maintenance organization. Therefore, all values assigned reflected the actual costs incurred by the organization. A total cost of treatment was calculated for each episode. Episodes of excessive anticoagulation were categorized according to the initial INR (6.0-10.0, 10.1-20.0, or >20.0) and treatment strategy (conservative vs the administration of phytonadione). A cost-effectiveness analysis was conducted when the efficacy to prevent an episode of major bleeding differed between conservative management vs management with phytonadione. Consistent with accepted economic guidelines, sensitivity analyses were completed to test the robustness of the cost-effectiveness ratio. If the treatment strategies were shown to be equally efficacious, then a cost-minimization analysis was performed.
We conducted a retrospective review of patients with elevated INRs within this organization and analyzed the cost of various clinical interventions. The objectives of this study were to assess the management and outcomes of excessive anticoagulation in a managed care organization, compare the management of elevated INRs within this organization with the ACCP guidelines, and analyze the cost-effectiveness of different treatment strategies.

RESULTS

CLINICAL OUTCOMES

Of 262 patients with INRs greater than 6.0 during the 9-month study, 248 patients were included in the analysis. Thirteen patients were excluded because of the inaccessibility of essential information (11 patients had insufficient documentation in their medical records, and medical records were unavailable for 2 patients). One patient was excluded because of continuing clot extension despite an INR of 6.6. In all, 40 patients had multiple incidents of excessive anticoagulation during the study period (2 episodes in 31 patients, 3 episodes in 7 patients, 4 episodes in 1 patient, and 6 episodes in 1 patient), accounting for a total of 301 episodes included in the analysis. Patient data are presented in Table 2. No significant differences were found between patients having the various levels of excessive anticoagulation.

### RESULTS

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excessive anticoagulation could not be identified in 41% of episodes managed conservatively and in 25% of episodes managed with the administration of phytonadione or FFP, respectively. This difference was statistically significant (P = .04). When a probable cause for excessive anticoagulation could be determined, no differences were seen between episodes managed conservatively vs those episodes managed with the use of phytonadione or FFP. Drug interactions accounted for 47 episodes of excessive anticoagulation. The combination of trimethoprim and sulfa-methoxazole was the most common interacting agent, accounting for 26% of drug-drug interactions.

Management and outcomes are summarized in Table 4. The results are presented according to INR categories specified in the ACCP guidelines and management strategy. Episodes of elevated INRs ranged from 6.1 to 41.8 (234 between 6.0 and 10.0, 50 between 10.1 and 20.0, and 17 with INRs >20.0). Most (83%) cases of INR elevation were managed conservatively. Doses of warfarin were withheld an average (±SD) of 3.2±2.0 days, and the weekly dose was decreased about 25% from baseline when therapy was resumed. Conservative management resulted in no sequelae in 212 (85.1%) of 249 episodes. In 32 episodes, patients were having minor bleeding (epistaxis, increased bruising, etc) before warfarin therapy was temporarily discontinued. Minor bleeding developed after the temporary discontinuation of warfarin in 3 patients. Two episodes of major bleeding evolved in patients managed conservatively. One patient who was receiving warfarin for a mechanical heart valve had an initial INR of 7.0. Laboratory workup detected heme-positive stools and a decreased hematocrit. The patient in whom this occurred was admitted to the observation unit and received 2 units of packed red blood cells. A second patient, who was being treated by an oncologist and had an initial INR of 6.6, had intraarticular bleeding develop with hemATOMA formation in the hip.

A total of 52 episodes of excessive anticoagulation were treated with phytonadione, FFP, or both. Fifty-six doses of phytonadione were given. Phytonadione was most commonly administered subcutaneously (39%) and intramuscularly (38%). The mean (±SD) doses given subcutaneously and intramuscularly were 12.6±9.7 and 12.7±14.3 mg, respectively. Nine (16%) doses of phytonadione were administered orally, and 4 (7%) doses were given intravenously. The mean (±SD) doses given by these patients were 10 (orally) and 50 mg (20 mg orally and 30 mg subcutaneously). The second patient also received 4 U of FFP. In 3 episodes, patients became refractory to oral anticoagulant therapy following aggressive management and required heparin therapy. Two patients required heparin therapy for 4 days, and 1 patient required it for 2 days.

Most INR elevations were not treated according to the ACCP guidelines for the management of excessive anticoagulation (Table 1). Phytonadione was administered in only 5% of episodes when the INR was between 6.0 and 10.0 and patients were not actively bleeding. The mean (±SD) dose of phytonadione administered was 12.3±9.2 mg. Moreover, the INR was checked within 24 hours in only 17% of episodes. The mean (±SD) time to the determination of the second INR was 5.1±9.5 days. When the INR was between 10.1 and 20.0 and patients were not actively bleeding, phytonadione was administered approximately 32% of the time at a mean (±SD) dose of 9.5±4.6 mg. No patient had an INR checked within 6 hours. Patients received phytonadione in 73% of episodes when the INR was greater than 20.0, and the mean

### Table 4. Management and Outcomes of Excessive Anticoagulation*

<table>
<thead>
<tr>
<th>Management</th>
<th>No Sequelae</th>
<th>Minor Bleeding</th>
<th>Major Bleeding</th>
<th>Thrombosis</th>
<th>Refractory to Warfarin Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 6.0-10.0 (total No. of episodes = 234)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative (n=217)</td>
<td>186 (85.7)</td>
<td>29 (13.4)</td>
<td>2 (0.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Phytonadione (n=14)</td>
<td>7 (50)</td>
<td>3 (21.4)</td>
<td>2 (14.3)</td>
<td>1 (7.1)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>FFP (n=1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Phytonadione plus FFP (n=2)</td>
<td>0 (0)</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>INR 10.0-20.0 (total No. of episodes = 50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative (n=30)</td>
<td>24 (80)</td>
<td>6 (20)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Phytonadione (n=14)</td>
<td>11 (78.6)</td>
<td>2 (14.3)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>FFP (n=1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Phytonadione plus FFP (n=5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>INR &gt;20.0 (total No. of episodes = 17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative (n=2)</td>
<td>2 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Phytonadione (n=7)</td>
<td>5 (71.4)</td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Phytonadione plus FFP (n=8)</td>
<td>1 (12.5)</td>
<td>2 (25)</td>
<td>5 (62.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Values represent the number of episodes, with percentage given in parentheses. INR indicates international normalized ratio; FFP, fresh frozen plasma.
†In 28 episodes, minor bleeding was present before warfarin dose was withheld.
‡In all episodes, bleeding was present before phytonadione or FFP administration.
§In 4 episodes, minor bleeding was present before warfarin dose was withheld.
¶In 1 episode, the patient had major bleeding, received phytonadione, and subsequently had pulmonary embolism and required heparin therapy.
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Resource use and cost for episodes of INRs ranging between 6.0 to 10.0 and 10.1 to 20.0 are displayed in Table 5. The 17 episodes of INRs of greater than 20.0 were excluded from the cost analyses because of the small number of episodes (n=2) in the group that was managed conservatively. In 13 episodes of INRs between 6.0 and 10.0 and 1 episode of an INR between 10.1 and 20.0, patients were admitted to the hospital for reasons other than excessive anticoagulation but also had documentation of an INR greater than 6.0 during their hospital stay. It was not possible to separate the cost associated with the management of excessive anticoagulation from the total cost of hospitalization. Therefore, these episodes were excluded from the cost analyses. In addition, in 4 episodes of INRs between 6.0 and 10.0 and 7 episodes of INRs between 10.1 and 20.0, patients were bleeding before treatment with phytonadione was initiated. These episodes were also excluded because analysis was designed to evaluate the effectiveness of each treatment in preventing major bleeding. Cost analyses were completed on the remaining 216 episodes of INRs between 6.0 and 10.0 and 43 episodes of INRs between 10.1 and 20.0.

Of the 216 INR elevations ranging from 6.0 to 10.0, patients were administered phytonadione in only 11 episodes. The cost per episode was $111.41 to treat conservatively and $382.70 when phytonadione was administered. Resource use is shown as a percentage of the total cost in both groups, accounting for 46% of the total cost in the conservatively managed group and 75% of the total cost in those administered phytonadione. The rate of major bleeding episodes differed between the 2 treatment groups; thus, a cost-effectiveness analysis was conducted. The equation used to determine the cost-effectiveness ratio is displayed in Figure 2. The cost-effectiveness analysis determined that treatment with phytonadione is about 7 times more costly than conservative management. Therefore, to prevent 1 major bleeding episode, an additional $70 500 would be spent treating with phytonadione compared with the temporary withdrawal of warfarin therapy. Sensitivity analyses were performed on the cost-effectiveness analysis by 2 methods. First, the effect on the cost-effectiveness ratio of decreasing the efficacy of conservative management to prevent major bleeding was evaluated. If 3 or 4 bleeding episodes would have evolved instead of only 2, the additional amount that would be spent treating with phytonadione compared with conservative management to prevent 1 major bleeding episode decreased to $47 240 and $35 400, respectively. Second, it was assumed that lower doses of phytonadione may not have resulted in the extension of deep venous thromboembolism or the requirement of intravenous heparin administration and the subsequent hospital admissions associated with these complications. Excluding hospitalization cost in the group treated with phytonadione decreased the cost of treatment per episode from $802.70 to $242. Inserting this value into the cost-effectiveness equation revealed that treatment with phytonadione would be about twice as expensive as the temporary discontinuation of warfarin therapy. Furthermore, the additional amount that would be spent treating with phytonadione to prevent a major bleeding episode decreased to $13 500.

Of the 43 episodes of INRs between 10.1 and 20.0, 30 were managed conservatively and 13 were managed with phytonadione. The cost per episode was $152.65 to treat conservatively and $346.64 to treat with phytonadione. Resource use is shown as a percentage of the total cost in Figure 3 for each treatment group. Again,
hospitalization accounted for most of the total cost, 47% in episodes in which patients were treated conservatively and 62% in episodes in which patients were given phytonadione. The results of a cost-minimization analysis indicate that treatment with phytonadione is about $192 more costly per episode than conservative management.

COMMENT

In this study, we examined the treatment of patients with elevated INRs and compared 2 treatment strategies—conservative management or the administration of phytonadione and/or FFP. Most episodes of excessive anticoagulation in this study were managed conservatively. This is in contrast to ACCP recommendations that advise administering phytonadione. Conservative management was effective in preventing major bleeding in 99% of episodes, and phytonadione therapy was 100% effective. For patients receiving oral anticoagulant therapy, however, resistance to continued warfarin treatment and the risk of thromboembolism must also be considered when phytonadione is given. In this study, the administration of phytonadione resulted in 2 hospital admissions due to thromboembolic episodes and 1 hospital admission for the administration of intravenous heparin. Two of these hospital admissions were in patients with INRs between 6.0 and 10.0, which accounted for the decreased cost-effectiveness of phytonadione use in patients who were not actively bleeding. The results suggest that the incremental cost of using phytonadione instead of conservative management to prevent 1 bleeding episode was about $70,000.

No difference in the prevention of major bleeding was shown between treatment strategies in episodes of INRs greater than 10.0. This lack of difference is probably attributable to the small number of episodes within these INR ranges that were evaluated. Although the results of a cost-minimization analysis indicated that treatment with phytonadione costs about $192 more per episode when the INR is between 10.1 and 20.0, conclusions regarding the optimal treatment of patients with excessive anticoagulation and INRs in this range cannot be made solely on the basis of these few episodes.

Limitations of this study are related to the problems inherent in a retrospective analysis. Thorough and accurate records are essential to ensure quality data. In 115 episodes of excessive anticoagulation, a probable cause could not be identified. The difference was statistically significant (P = .04) between episodes managed conservatively compared with episodes managed with phytonadione or FFP administration. It is difficult to determine with a retrospective analysis whether knowing the reason(s) for excessive anticoagulation influenced the decision to administer phytonadione or FFP. Also, the possibility that patients more likely to have complications or with more comorbid diseases were preferentially given phytonadione cannot be excluded. Furthermore, the lack of randomization and the inability to control for group size made comparisons between treatment strategies difficult because of the difference between the number of episodes in each group. Patients who were not actively bleeding received phytonadione in only 33 episodes. Moreover, in episodes where patients received phytona-

Figure 1. Resource use and cost for international normalized ratios between 6.0 and 10.0. In the key, f/u indicates follow-up; ED, emergency department visits; and UC, urgent care visits.

Figure 2. A cost-effectiveness analysis for international normalized ratios between 6.0 and 10.0. In the equation, TC indicates total cost of treatment; E, effectiveness in preventing major bleeding.

Figure 3. Resource use and cost for international normalized ratios between 10.1 and 20.0. In the key, f/u indicates follow-up; ED, emergency department visits; and UC, urgent care visits.
dione and complications developed, much larger doses were given than are recommended in the ACCP guidelines (10-20 vs 1-2 mg). It is difficult to speculate whether these complications would have developed if lower doses had been given. The routine administration of excessive phytonadione doses emphasizes the need to educate physicians to avoid both adverse clinical outcomes and increased cost. In addition, phytonadione was frequently administered intramuscularly. This also underscores the need for education because administration by this route is not recommended because of the risk of hematoma formation.7

The results from this study are consistent with those reported by Glover and Morrill14 in their retrospective review of 51 patients. Forty-eight (94%) patients included in their study were managed conservatively, and only 3 (6%) received phytonadione. A lack of compliance with the ACCP guidelines is probably related to the limited data available to support these recommendations. Conservative management was shown to be safe and cost-effective when the INR was between 6.0 and 10.0. Based on the results of these studies, ACCP’s recommendation of phytonadione administration to patients with INRs ranging from 6.0 to 10.0 may be unnecessary, and conservative management appears to be a reasonable option. Prospective, randomized trials would aid in confirming the safety and efficacy of conservative management compared with phytonadione administration, the optimal dose of phytonadione, and the INR range in which conservative management would be most appropriate.

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