Acetaminophen and Other Risk Factors for Excessive Warfarin Anticoagulation

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Context.—Warfarin is highly effective in preventing thromboembolism, but increases the risk of hemorrhage, particularly at an international normalized ratio (INR) greater than 4.0. Identifying causes of excessive anticoagulation in clinical practice could help target patients at risk for elevated INRs.

Objective.—To determine causes of INRs greater than 6.0 in a clinical practice setting.

Design.—Case-control study.

Setting.—Outpatient anticoagulant therapy unit.

Patients.—Outpatients followed up prospectively from April 1995 to March 1996 who had been taking warfarin for more than 1 month, had a target INR of 2.0 to 3.0, and were able to be interviewed within 24 hours of their reported INR. Case patients had INRs greater than 6.0; controls were randomly selected from patients having INRs between 1.7 and 3.3.

Main Outcome Measures.—Factors associated with INRs greater than 6.0, including medication use, recent diet, illness, alcohol consumption, and actual warfarin use.

Results.—A total of 93 cases and 196 controls were interviewed; they did not differ in age, indication for warfarin, length of therapy, warfarin dose, number of prescription medications, or previous INR or long-term INR variability. Acetaminophen ingestion was independently associated in a dose-dependent manner with having an INR greater than 6.0 (P for trend <.001). For the highest-dose category of acetaminophen intake, 9100 mg/wk or more, the odds of having an INR greater than 6.0 were increased 10-fold (95% confidence interval [CI], 2.6-37.9). Other factors independently associated with an INR greater than 6.0 were new medication known to potentiate warfarin (odds ratio [OR], 8.5; 95% CI, 2.9-24.7), advanced malignancy (OR, 16.4; 95% CI, 2.4-111.0), recent diarrheal illness (OR, 3.5; 95% CI, 1.4-8.6), decreased oral intake (OR, 3.6; 95% CI, 1.3-9.7), and taking more warfarin than prescribed (OR, 8.1; 95% CI, 2.2-30.0). Higher vitamin K intake (OR, 0.7; 95% CI, 0.5-0.9) and habitual alcohol consumption of from 1 drink every other day to 2 drinks a day (OR, 0.2; 95% CI, 0.1-0.7) were associated with decreased risk.

Conclusions.—These data suggest that acetaminophen is an underrecognized cause of overanticoagulation in the outpatient setting. Several other clinically important risk factors were identified. Increased monitoring of INR values when such risk factors are present or modification of the risk factors themselves should reduce the frequency of dangerously high levels of anticoagulation.

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WARFARIN is highly effective in preventing thromboembolism in a variety of conditions. However, its major complication is hemorrhage, which can cause severe morbidity and death. In addition, fear of major hemorrhage frequently dissuades patients and physicians from use of anticoagulants in conditions for which such agents are beneficial. Major hemorrhage in patients receiving warfarin is strongly associated with the intensity of anticoagulation. In particular, the risk of intracranial hemorrhage, the most feared complication of anticoagulation, increases dramatically at international normalized ratio (INR) levels greater than 4.0.
focused on INR values greater than 6.0, because such levels convey markedly increased risk of major hemorrhage12 and are unlikely to be the result of usual interindividual fluctuations. Of 111 patients identified, 96 (87%) were eligible to participate. The others were excluded for the following reasons: 3 did not speak English and had no appropriate proxy, 3 were admitted to the hospital, and 9 could not be reached by telephone within the designated 24-hour time period. Of the 96 patients who were eligible, 93 (97%) were interviewed. The other 3 patients refused to participate.

Controls

Control patients were randomly selected from among all the anticoagulant therapy unit patients with a target INR of 2.0 to 3.0 whose actual INR value recorded in the daily log was between 1.7 and 3.3. This is the range of INR values that in our anticoagulant unit did not trigger a dose change. We sought to enroll twice as many controls as cases during each week of the study. Of 279 randomly selected control patients, 216 were eligible to participate. The others were excluded for the following reasons: 10 did not speak English, 3 were too cognitively impaired to participate meaningfully in the interview, 1 was severely hearing impaired, 1 was admitted to the hospital, and 48 patients could not be reached by telephone within the 24-hour window after 3 attempts. Of the 216 patients who were eligible, 196 (91%) agreed to be interviewed.

Sources of Data

Two trained interviewers contacted patients by telephone, explained the purpose of the study, obtained informed consent, and conducted a structured interview from a previously piloted instrument. The script introduced the study as follows:

We’re calling some of our patients within a day of their blood test to ask some questions about things like medications and diet. This is part of a quality check on our procedures in an effort to improve our patient care.

There was no specific mention of out-of-range INRs. The interview lasted approximately 10 to 15 minutes. Interviews were periodically observed to ensure uniformity in data collection. Because of concerns about the risk of bleeding, uniform binding of the patients to their INR prior to the study interview was not ethically feasible. Forty-eight case patients (52%) had been notified of their INR value by clinical staff, unrelated to the study, before the study interview. Our findings were essentially the same for both the blinded and unblinded groups.

After consenting to participate, patients were asked to list the medications they were currently taking and to identify any that were newly prescribed within the preceding 4 weeks and the date treatment with the new medication was started. If patients were unsure, the interviewer instructed the patients to read directly from their medication list or pill bottle labels. Patients were also asked about changes in medications or in dose of their medications and use of over-the-counter medications during the previous 4 weeks. All medications, prescription and over-the-counter, were classified according to their reported effect on warfarin’s metabolism, ie, as potent inhibitors, inhibitors, or having no effect.9-11 To increase the reliability of patient responses, 4 different questions regarding use of prescription and nonprescription medications were asked at different points of the interview. For 21 case patients (22%) and 33 controls (17%), a caretaker was identified as responsible for the patient’s medications. Such caretakers were then interviewed.

Patients were specifically asked to quantify their use of acetaminophen, aspirin, other nonsteroidal anti-inflammatory drugs, and any other pain medications during the 7 days preceding their blood test. Analgesic drugs were referred to by their common brand names. If patients were unsure of the strength or the specific acetaminophen preparation, the interviewer instructed the patient to read the label of the pill bottle. Text describing the duration of acetaminophen use was recorded on the interview form when available. Four case patients and 1 control were unable to retrieve the specific acetaminophen dose; for these patients, the lowest strength of acetaminophen was assigned. Our calculation of acetaminophen use included acetaminophen contained in over-the-counter cold and sinus formulations and in combination analgesics that included narcotics. The weekly acetaminophen dose was categorized according to the following scheme: 1 to fewer than 7 regular-strength (325-mg) tablets per week, 7 to fewer than 14 tablets per week, 14 to fewer than 28 tablets per week, and 28 tablets or more per week.

Vitamin K intake was qualitatively assessed with 2 screening questions. The first question asked about gross changes in diet over the past week, ie, eating more, less, or the same as usual. The second question asked patients to contrast their usual weekly food intake with vitamin K content12 (avocado, broccoli, Brussels sprouts, cabbage, chickpeas, green peas, green tea, kale, lettuce, liver, spinach, and greens [eg, beet, collard, dandelion, mustard, turnip]) with the intake of these same items during the week preceding their prothrombin time test. A value of 1 was assigned for each food item consumed, with the sum of such values providing aggregate scores for the number of items from this list consumed routinely and the number consumed in the prior week. Further quantification of each item was coded as more, less, or the same as usual. Alcohol intake was categorized as none, 1 to 2 drinks per week, 1 drink every other day to 2 drinks per day, more than 2 drinks per day, or binge. Information on intake of vitamin K–rich foods was missing for 6 cases and 3 controls. Information on alcohol use was missing for 1 case patient and 2 controls.

Other questions asked about diarrhea or febrile illness during the previous week and recent hospitalization. We categorized patients as having an advanced malignancy if they listed chemotherapy agents among their medications or if pain related to cancer was the indication for analgesic use. For such patients, metastatic disease or extensive local invasion was subsequently confirmed by pathology or operative reports.

Compliance with warfarin was assessed with a series of questions about missed or extra doses of warfarin and by patient report of the warfarin doses actually taken on each day of the week preceding the prothrombin time test. The patient-reported doses were compared with the anticoagulant unit–prescribed doses. Other questions concerned age, sex, and race.

Data extracted directly from the anticoagulant unit database included length of warfarin therapy, indication for anticoagulation, assigned warfarin dose, and INR value immediately preceding the 4-week study period. The INR preceding the study period was measured an average of 35 days prior to the study INR. This INR measurement was not necessarily the patient’s last INR test prior to the study INR.

The study protocol was approved by the institutional review board at Massachusetts General Hospital.

Statistical Analysis

For univariate comparisons between patients with an INR greater than 6.0 and the controls, we assessed statistical significance using χ² tests and the Fisher exact test, where appropriate, for categorical data and the Student t test for continuous variables. Odds ratios with 95% confidence intervals (CIs) were calculated by standard methods.13,14 The test of trend was done using the Cochran-Mantel-Haenszel test.15 The Kolmogorov-Smirnov test was used to test the equality of the continuous skew dis-
the significance of interaction terms. Statistical analyses were performed with SAS (SAS Institute, Cary, NC), S-plus (Statistical Science, MathSoft, Seattle, Wash), and StatXact (Cytel Software, Cambridge, Mass) software.

RESULTS

Demographic Features and Anticoagulation History

We interviewed 93 case patients with an INR of greater than 6.0 and 196 controls with an INR in the range of 1.7 to 3.3 within 24 hours of their reported prothrombin time test. In both the case and control groups the mean age was 70 years, about half were female, and nearly all were white. The conditions prompting anticoagulation also did not differ between groups, with atrial fibrillation as the leading indication. Seventy-eight cases (84%) and 162 controls (83%) had been taking warfarin for longer than 3 months (Table 1).

The mean INR for the cases was 8.3 (range, 6.1-29.8) and 2.4 (range, 1.7-3.3), which was an eligibility criterion for the controls. For most cases, their excessively high INR value represented a recent deterioration in control of anticoagulation. The mean INR value for the prothrombin time test obtained immediately prior to the 4-week study period was 2.5, with 73% of these values in the acceptable range of INR of 1.7 to 3.3. These measures were very similar to the controls’ values (mean INR immediately prior to the 4-week study period was 2.4 with 74% of values between 1.7 and 3.3) (Figure). The weekly warfarin dose did not differ for cases (mean, 28.9 mg) vs controls (mean, 26.7 mg) \( (P = .22) \). Three cases (3%) and 9 controls (5%) had had their warfarin dose increased within the 2 weeks prior to the study INR. The coefficient of variation used to assess long-term INR variability did not differ significantly between cases and controls.

Concomitant Medications

Twenty cases (22%) reported recently starting to take a medication known to potentiate warfarin’s anticoagulant response compared with 7 controls (4%). These potentiating medications were antibiotics in 12 of the 20 cases and in 2 of the 7 controls (Table 1). Case patients were taking a mean of 5.1 prescription medications other than warfarin vs 4.3 for controls \( (P = .01) \).

Analgesic and Antipyretic Use

Fifty-two cases (56%) and 70 controls (36%) reported taking acetaminophen

Table 1.—Clinical Features of Case Patients (INR >6.0) and Controls (INR, 1.7-3.3)†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=93)</th>
<th>Controls (n=196)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>70 (39-94)</td>
<td>70 (32-94)</td>
<td>.65</td>
</tr>
<tr>
<td>Female sex</td>
<td>44 (47)</td>
<td>94 (48)</td>
<td>.85</td>
</tr>
<tr>
<td>White race</td>
<td>91 (98)</td>
<td>186 (95)</td>
<td>.68</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>45 (48)</td>
<td>90 (46)</td>
<td>.98</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>21 (23)</td>
<td>48 (24)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>7 (7)</td>
<td>13 (7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20 (22)</td>
<td>45 (23)</td>
<td></td>
</tr>
<tr>
<td>Length of warfarin therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 and &lt;3 mo</td>
<td>15 (16)</td>
<td>34 (17)</td>
<td>.56</td>
</tr>
<tr>
<td>3-12 mo</td>
<td>22 (24)</td>
<td>35 (18)</td>
<td></td>
</tr>
<tr>
<td>&gt;1 y</td>
<td>56 (60)</td>
<td>127 (65)</td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New potentiating medication†</td>
<td>20 (22)</td>
<td>7 (4)</td>
<td>.001</td>
</tr>
<tr>
<td>No. of prescription medications, mean (range)</td>
<td>5.1 (0-14)</td>
<td>4.3 (0-13)</td>
<td>.01</td>
</tr>
<tr>
<td>Analgesic/antipyretic use‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>52 (56)</td>
<td>70 (36)</td>
<td>.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>9 (10)</td>
<td>34 (17)</td>
<td>.05</td>
</tr>
<tr>
<td>Other nonsteroidal anti-inflammatory</td>
<td>7 (7)</td>
<td>10 (5)</td>
<td>.29</td>
</tr>
<tr>
<td>None</td>
<td>27 (29)</td>
<td>95 (48)</td>
<td>.002</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported weekly intake of 12 vitamin K–rich foods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>61 (66)</td>
<td>79 (40)</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>27 (29)</td>
<td>92 (47)</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>5 (6)</td>
<td>25 (13)</td>
<td></td>
</tr>
<tr>
<td>Decreased oral intake</td>
<td>22 (24)</td>
<td>11 (6)</td>
<td>.001</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>75 (81)</td>
<td>121 (62)</td>
<td></td>
</tr>
<tr>
<td>1-2 Drinks per week</td>
<td>11 (12)</td>
<td>32 (17)</td>
<td></td>
</tr>
<tr>
<td>1 Drink every other day to 2 drinks per day</td>
<td>4 (4)</td>
<td>36 (18)</td>
<td>.0039</td>
</tr>
<tr>
<td>&gt;2 Drinks per day</td>
<td>3 (3)</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>Binge</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Concurrent illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute diarrhea</td>
<td>20 (22)</td>
<td>15 (8)</td>
<td>.001</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (9)</td>
<td>6 (3)</td>
<td>.04</td>
</tr>
<tr>
<td>Advanced malignancy</td>
<td>9 (10)</td>
<td>2 (1)</td>
<td>.001</td>
</tr>
<tr>
<td>Hospital discharge within 7 d</td>
<td>7 (8)</td>
<td>1 (1)</td>
<td>.002</td>
</tr>
<tr>
<td>Warfarin dose exceeds prescribed</td>
<td>11 (12)</td>
<td>5 (3)</td>
<td>.001</td>
</tr>
</tbody>
</table>

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Risks for Excessive Coagulation—Hylek et al

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Table 2.—Relative Odds for an INR Greater Than 6.0 According to Intake of Acetaminophen *

| Acetaminophen, mg/wk (325-mg Tablets) | No. (%) of Case Patients (n=113) | No. (%) of Control Patients (n=112) | Adjusted Analysis, Odds Ratio (95% CI)† | P Value
|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------------|--------
| 0                                    | 41 (37)                          | 126 (64)‡                           | 1.0                                    | . . .   
| 325-2267 (1-7)                       | 15 (16)                          | 46 (23)                             | 1.1 (0.5-2.5)                          | .77    
| 2275-4549 (7-<14)                    | 11 (12)                          | 10 (5)                              | 3.5 (1.2-10.0)                         | .02    
| 4550-9099 (14-<28)                   | 11 (12)                          | 9 (5)                               | 6.9 (2.2-21.9)                         | .001   
| ≥9100 (>=28)                         | 15 (16)                          | 5 (3)                               | 10.0 (2.6-37.9)                        | .001   

*INR indicates international normalized ratio; CI, confidence interval.
†Adjusted via model presented in Table 3 for multivariate model.
‡P trend for univariate analysis <.001.

Table 3.—Independent Risk Factors for INR Greater Than 6.0 Among Outpatients With INR Target of 2.0 to 3.0

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced malignancy</td>
<td>16.4 (2.4-111)</td>
<td>.004</td>
</tr>
<tr>
<td>Newly started potentilating medica</td>
<td>8.5 (2.9-27.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Warfarin dose more than prescribed</td>
<td>8.1 (2.2-30)</td>
<td>.002</td>
</tr>
<tr>
<td>Decreased oral intake</td>
<td>3.6 (1.3-9.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Acute diarrheal illness</td>
<td>3.5 (1.4-8.6)</td>
<td>.007</td>
</tr>
<tr>
<td>Vitamin K intake†</td>
<td>0.7 (0.5-0.9)</td>
<td>.003</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 Drinks per week</td>
<td>0.7 (0.3-1.6)</td>
<td>.37</td>
</tr>
<tr>
<td>1 Drink every other day to 2 drinks per day</td>
<td>0.2 (0.1-0.7)</td>
<td>.01</td>
</tr>
<tr>
<td>&gt;2 Drinks per day or binge</td>
<td>0.9 (0.2-4.2)</td>
<td>.90</td>
</tr>
</tbody>
</table>

*INR indicates international normalized ratio; CI, confidence interval.
†Coded as a continuous variable (0-12) based on reported weekly intake of 12 vitamin K-rich foods.

the week preceding the study INR (Table 1). These included 11 cases (12%) and 6 controls (5%) who reported taking an acetaminophen–narcotic combination preparation, mostly codeine and oxycodeine formulations. Fever was the reason for taking acetaminophen in only 7 case patients and 4 controls. More controls than cases reported taking aspirin, but the percentage was small in both groups. Use of other nonsteroidal anti-inflammatory drugs was uncommon and did not differ between case and control groups.

Diet

The number of vitamin K–rich foods consumed in the past week was inversely correlated with an INR greater than 6.0 (P for trend, .001) (Table 1). Sixty-one cases (66%) compared with 79 controls (84%) reported routinely consuming one or none of the 12 listed foods high in vitamin K content. Usual consumption of these items did not differ significantly from that during the week preceding the prothrombin time test (for cases, 1.6 vs 1.4, respectively; for controls, 2.2 vs 2.0, respectively). An overall decrease in oral intake during the previous 7 days was also strongly associated with having an INR greater than 6.0.

Alcohol Intake

Patients were asked to quantify their usual alcohol intake and their intake over the preceding 7 days. Seventy-five cases (81%) reported never or rarely drinking alcohol compared with 121 controls (62%). Alcohol consumption was inversely correlated with the risk of having an INR greater than 6.0 (P for trend, .002) (Table 1). For most cases and controls, the amount of alcohol consumed during the week prior to the prothrombin time test was the same as usual. Too few patients reported drinking more than 2 drinks per day to meaningfully assess the effect of this amount of alcohol intake.

Concurrent Illness

Twenty cases (22%) compared with 15 controls (8%) reported having had diarrhea during the week preceding their prothrombin time test. Few patients had had a recent fever, but fever was more commonly reported by case patients. Recent hospitalization was unusual but was more common among the cases, 7 cases (8%) vs 1 control (1%). Nine cases (10%) and 2 controls (1%) had an advanced malignancy (Table 1).

Compliance

Eleven cases (12%) and 5 controls (3%) reported taking more warfarin than the anticoagulant unit had prescribed (Table 1). For 6 of these 11 case patients, the higher dose of warfarin they were taking had been prescribed by a treating physician who had not coordinated care with the anticoagulant unit.

Quantifying the Effect of Acetaminophen Ingestion

Case patients were more likely than controls to ingest acetaminophen, and they ingested greater amounts than controls (81%) reported never or rarely drinking alcohol compared with 121 controls (62%). Among those patients reporting taking acetaminophen, the mean weekly dose was 6756 mg for the cases (approximately 21 tablets per week of the regular-strength dose of 325 mg) compared with 2938 mg for the controls (approximately 9 tablets per week) (P= 0.001). Beginning at the equivalent of 7 regular-strength tablets per week, compared with no intake of acetaminophen, there was a dose-dependent monotonic increase in the adjusted relative odds for having an INR greater than 6.0, increasing from 3.5 (95% CI, 1.2-10.0) for 2275-mg to 4549-mg intake of acetaminophen per week, to 6.9 (95% CI, 2.2-21.9) for 4550-mg to 9099-mg intake per week, to 10.0 (95% CI, 2.6-37.9) for 9100-mg intake or more per week (Table 2). These large effects were seen at standard doses of acetaminophen. Indeed, only 5 cases reported a cumulative weekly dose exceeding 18.2 g (or 56 regular-strength tablets) per week corresponding to the maximum recommended daily dose of 2.6 g. 30 Acetaminophen intake of the 48 cases who knew their INR prior to the study interview (median weekly intake, 4175 mg; mean, 7304 mg) did not differ from that of the 45 cases who did not know their INR at the time of the interview (median weekly intake, 3125 mg; mean, 5109 mg) (P=.37).

To help define the temporal relationship between acetaminophen and its potentiation of warfarin’s effect, we examined the duration of acetaminophen use among those patients taking the doses that conferred the greatest risk. Twenty-three case patients and 12 controls reported taking more than 4550 mg of acetaminophen during the 7-day period preceding their prothrombin time test. Information on duration of acetaminophen use was recorded for 19 of the 23 case patients and for 8 of the 12 controls. All of the cases and controls had started taking acetaminophen since their previous (prestudy period) INR. The predominant indication for acetaminophen was analgesia for a variety of conditions causing acute pain. Fifteen of these 19 case patients compared with 4 of the 8 controls reported taking acetaminophen for longer than 1 week. Of these 4 controls, 1 had had an intervening INR of 5.9 prompting a decrease in warfarin dose.

Multivariate Analyses

Independently significant determinants of INR values greater than 6.0 included the effect of advanced malignancy, decreased oral intake, diarrheal illness, newly started treatment with potentiating medication, and taking more warfarin than the dose prescribed by the anticoagulant unit (Table 3). Subjects with higher vitamin K consumption and

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habitual moderate consumption of alcohol, 1 drink every other day to 2 drinks per day, were less likely to have an INR greater than 6.0. Recent hospitalization, fever, and number of prescription medications were not independent risk factors in the multivariate analyses. The independent variables had no significant 2-way interactions.

**COMMENT**

We focused on the determinants of INR values greater than 6.0 because such values represent a marked deviation from control and are high enough to clearly increase the risk of major hemorrhage. The INR values greater than 6.0 are unlikely to result from individual fluctuation in warfarin response. We limited our study to patients whose target INR was 2.0 to 3.0, since including patients with different INR targets would confound our results.

Our study design enabled us to quantify the real-world use of acetaminophen, a widely available over-the-counter medication, among a predominantly older population taking warfarin. Because the risk of life-threatening hemorrhage increases with age, intervention studies of acetaminophen’s effect on warfarin in this older population would not be feasible.

The highly significant dose-response relationship between acetaminophen and warfarin’s effect was independent of other factors thought to alter response to anticoagulation. For patients who reported taking the equivalent of at least 4 regular-strength (325-mg) tablets per day for longer than 1 week, the odds of having an INR greater than 6.0 were increased 10-fold above those taking no acetaminophen. Risk decreased with lower intakes of acetaminophen, reaching the background level of risk at an intake of 6 or fewer 325-mg tablets per week.

Severe case reports attest to the potentialization of warfarin by acetaminophen. Older clinical experiments also support such an effect. In a double-blind crossover study, Rubin et al assigned 15 healthy male volunteers on a stable dose of warfarin to 2 weeks each of acetaminophen, 4 g/d, and placebo. This dose of acetaminophen increased the prothrombin time more than 1.75 times the control in 7 of 15 subjects compared with 1 in the placebo group, and produced an increase to more than 2.0 times the control in 5 of the 15 subjects compared with none in the placebo group. The potentiating effect was initially detected after 7 days of acetaminophen intake and peaked at 12.5 days. While both warfarin and acetaminophen are eliminated primarily through hepatic metabolism, the actual mechanism by which acetaminophen potentiates warfarin is not well described.

We also assessed the impact of other clinical features on the risk of excessive anticoagulation. We found a powerful and highly significant relationship between having an INR greater than 6.0 and advanced malignancy. Possible mechanisms include a direct effect on coagulation proteins, treatment-related hepatic effects, or a potentiating interaction with warfarin. Case patients were also more likely to have recently started taking a medication known to potentiate warfarin’s anticoagulant response. The underlying mechanisms of interaction with warfarin have been previously described.

Of the 14 case patients who had recently started taking an antibiotic, only 2 patients were prescribed a antibiotic that did not have a reported potentiating effect on warfarin. This observation highlights the need to closely monitor patients taking medications that interfere with warfarin or to choose alternative therapies, if possible.

We confirmed a highly significant inverse relationship between stable consumption of vitamin K–rich foods and having an INR greater than 6.0. The interaction between dietary vitamin K and warfarin is well established. Although our assessment of vitamin K intake was crude, the significance of this finding supports the concept that individuals with diets rich in vitamin K are less sensitive to fluctuations in warfarin’s anticoagulant effect. Decreased oral intake in general was also associated with excessive anticoagulation. The mechanism for this is not clear. It may involve an aggregate decrease in other foods containing lesser amounts of vitamin K or may be secondary to other mechanisms such as decreased binding of warfarin to plasma proteins in the fasting state. We also observed a nearly 4-fold increase in risk of having an INR greater than 6.0 following a diarrheal illness. In a recent case report, an acute diarrheal illness was thought to cause excessive anticoagulation through malabsorption of vitamin K.

Long-term alcohol use has been reported to increase the metabolism of warfarin, likely due to ethanol-induced stimulation of hepatic microsomal enzymes. Such an effect was not seen in an experiment involving healthy young male volunteers. Our data suggest that habitual light to moderate alcohol intake in our predominantly older patient population does inhibit warfarin’s anticoagulant response.

Case-control studies must address concerns about bias. The primary concern of selection bias is minimized by nesting the case-control study within a known population. To this end we identified all potential case and control subjects during the study period and enrolled the vast majority of all of the cases and a random sample of controls. Although participation rates of the cases and controls were slightly different, it is unlikely that this small difference could explain the dose response or the 10-fold relative odds conferred by the highest acetaminophen doses. It is also unlikely that patients at higher baseline risk for poor anticoagulant control comprised the case population using acetaminophen because there was no significant difference between cases and controls in long-term INR variability or in their previous INR measurement.

Our results are necessarily based on subjects’ self-report. We sought to increase the accuracy of this information by interviewing patients within 24 hours of their prothrombin time test and by restricting the retrospective periods of interest to either 7 or 30 days. Although 52% of case subjects had been notified of their INR before the study interview, raising the possibility of a recall bias, our findings were the same when analyses were restricted to case patients who did not know their INR level prior to the study interview. Error in patients’ reports could not explain our findings since such misclassification tends to obscure significant associations and bias toward observing no effect. We minimized interviewer bias by using a scripted interview and by observing interviews periodically to ensure consistency in questioning subjects. A strong potentiating effect of acetaminophen was not anticipated prior to the study, further reducing the likelihood of interviewer bias.

The association we observed between acetaminophen and excessive INR values has several important features of a causal relationship. It is strong, dose-dependent, and biologically plausible, follows an appropriate temporal sequence, and is supported by previous case reports and small-scale clinical experiments. In addition, the relationship persisted after control for a variety of potential confounders.

Our data suggest that acetaminophen is an underrecognized cause of anticoagulant instability. Of note, several pharmacology references either do not mention an interaction between acetaminophen and warfarin or diminish its clinical significance. Acetaminophen is generally preferred over nonsteroidal anti-inflammatory agents as an analgesic and antipyretic agent because it does not inhibit platelet function or raise the risk of injury to the gastric mucosa.
unit also take acetaminophen at any given time. Thirty percent of all INR values greater than 6.0 in our anticoagulation unit population are attributable to intake of acetaminophen equivalent to 7 or more tablets per week.\textsuperscript{43}

Acetaminophen remains a valuable therapy for patients taking warfarin. However, our findings should encourage clinicians to query patients about their use of acetaminophen and to clarify its indication. Those patients taking warfarin who also require sustained high doses of acetaminophen need close monitoring of their INR levels.

The current study identifies powerful risk factors for excessive anticoagulation in real-world practice. Knowledge of such risk factors should result in changes in the management of anticoagulant therapy that will reduce hemorrhagic complications. In turn, reduced risk of hemorrhage should encourage more widespread use of warfarin among the many patients who would benefit from long-term anticoagulation.\textsuperscript{44}

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