Correlation of the Change in the International Normalized Ratio and Decreasing the Coumadin Dosage Following Total Joint Arthroplasty

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Abstract

This retrospective pilot study determined whether a change in the daily International Normalized Ratio (INR) correlates with a decrease in Coumadin (DuPont Pharma, Wilmington, Del) dosage. Four hundred seventeen patients yielded 1167 pairs of INR values and Coumadin doses. An increase in INR >0.4 units correlated 81% with a decrease in the Coumadin dose (P<.05). In patients aged ≥70 years, the correlation fell to 70% compared to an 89% correlation in patients aged <70 years (P<.05). The correlation fell to 78% in women, while men exhibited an increase to 87% (P<.05).

Although this is a pilot study, when managing postoperative Coumadin anticoagulation for orthopedic patients, an increase in INR >0.4 units correlates highly with the need to decrease the Coumadin dose. A prospective study is needed to test the usefulness of this parameter.

The oral anticoagulant Coumadin (DuPont Pharma, Wilmington, Del) is widely used postoperatively after total joint arthroplasty and hip fracture repair for the prevention of thromboembolic events such as deep venous thrombosis (DVT) and pulmonary embolism. The reported incidence of DVT after total hip arthroplasty (THA) or total knee arthroplasty (TKA) may be as high as 40%-80%, and pulmonary embolism may occur in 4%-10% of patients if anticoagulation is not prescribed.1-3

The prevalence of DVT in patients presenting with pulmonary embolism is approximately 25%,4 and the prevalence of pulmonary embolism in patients presenting with DVT is 40%-49%.5 Approximately 40% of patients with DVT without symptoms of pulmonary embolism may have evidence of pulmonary embolism based on ventilation-perfusion scan and chest radiograph.6 Despite prophylactic measures, approximately 0.5% and 2.3% of patients on anticoagulation will incur DVT or pulmonary embolism, respectively.6 Each DVT screening method has some limitations, and both DVT and pulmonary embolism generate a paucity of specific symptoms.

A recent meta-analysis assessing the efficacy of low molecular weight heparin, Coumadin, aspirin, low-dose heparin, pneumatic compression boots, and placebo for prophylaxis against DVT following THA found that Coumadin reduced DVT risk more than any other agent or device.7 Authors concluded that Coumadin was associated with the lowest risk of symptomatic pulmonary embolism and next to the lowest risk of fatal pulmonary embolism.7 In this same study, however, Coumadin rated third highest in terms of risk of major bleeding.

Prescribed since 1953, Coumadin is a clinically challenging medication due to its potential risks and variable effects. Early response to Coumadin is only partially successful in predicting the correct final maintenance dose.

In general, Coumadin dose prediction is difficult because of the pharmacokinetic and pharmacodynamic factors, including, but not limited to, patient age, the presence of advanced malignancy or other comorbidities,
acetaminophen use, medication interactions, decreased oral intake, liver function, nutritional status, dietary vitamin K intake, and patients’ sensitivity to Coumadin’s effects based on metabolism through the CYP2C9*2 enzymes.

Elderly patients may experience less excess anticoagulation outside of target therapeutic International Normalized Ratio (INR) range and an improved Coumadin safety profile if they are started on a lower loading dosage of Coumadin compared to younger patients. Lower weight individuals (<50 kg) frequently require lower doses of Coumadin to achieve a therapeutic INR within the target range. Males frequently require higher doses of Coumadin compared to females. At minimum, factors such as actual body weight, age, and gender must be considered when prescribing Coumadin.

The effectiveness and safety of Coumadin therapy depend on the maintenance of the INR in the therapeutic range. Common approaches include use of established Coumadin dosing protocols and computer-assisted dosing models. Research suggests that the use of computer-assisted Coumadin dosing shortens the time required to achieve therapeutic INR within the target range. However, many physicians have limited access to such computer programs. The Sixth American College of Clinical Pharmacy Consensus Conference on Antithrombotic Therapy recommends that Coumadin dosing computer programs be individually considered for use based on the results of clinical trials, but may be more effective than physician management alone (Grade 2B).

Although Coumadin sliding scales and computer programs are helpful when initiating Coumadin following total joint arthroplasty or hip fracture repair, it was hypothesized that a breakpoint incremental change in the daily INR may exist based on the Coumadin dosage that is selected, which could correlate highly with a change in the sliding scale dosage of Coumadin. If true, this information might be a helpful guide for orthopedic surgeons, along with Coumadin sliding scales and computer programs, to avoid excess anticoagulation, increased risk of bleeding diatheses, and the need for vitamin K reversal.

**MATERIALS AND METHODS**

A retrospective pilot study was conducted to test this hypothesis. Patients undergoing THA, TKA, or hip fracture repair at one of three TriHealth hospitals between June 1, 1997, and September 30, 1998, were eligible for participation. Patients had to receive at least two consecutive postoperative days of Coumadin. Exclusion criteria included age <18 years and any Coumadin contraindications.

Four hundred seventeen patients (139 men and 278 women) met the criteria for the study. Female patients were significantly older (mean: 66±13.2 years; range: 18-97 years) than the males (mean: 63.1±13.3 years; range: 31-91 years) (P<.05). Fifty-six percent of patients underwent TKA, 38% THA, and 1% hip fracture repair. Mean length of stay was 3.9±1.7 days (range: 2-19 days). Four (1%) patients had a clinically diagnosed thromboembolic complication (DVT/pulmonary embolism) during hospitalization, compared to the expected 0.5% in the literature. For perspective, many DVT/pulmonary embolisms are clinically silent in this patient population.

TriHealth pharmacists received written permission by orthopedic surgeons to review patient charts daily, write an order for Coumadin in the patients’ charts, and monitor patient outcomes. Physician cosignatures for pharmacy-dosed Coumadin orders were required within 24 hours. International Normalized Ratio levels were targeted between 2 and 3 for this patient population, unless nonsurgical anticoagulation indications superseded the postsurgical indication (ie, mechanical prosthetic heart valves with target INR of 2.5-3.5). The International Sensitivity Index for TriHealth INR reagents was 1.84.

When appropriate, the pharmacist directly consulted with the physician regarding pertinent clinical issues prior to writing the Coumadin order. Acting as agents of the physicians, pharmacists also were allowed per protocol to write for a subcutaneous dose of vitamin K when reversal was clinically indicated, and the orders were countersigned within 24 hours by the physician in charge, commensurate with guidelines established by the Ohio State Board of Pharmacy. Pharmacists modified Coumadin from the sliding scale recommendations based on clinically significant medication or dietary supplement interactions, and interactions were charted and monitored.

The original TriHealth Coumadin Sliding Scale, which has been modified twice after completion of the study, was used for patients enrolled in the study (Table 1). This scale was designed for patients undergoing total joint arthroplasty or hip fracture repair. The scale contains Coumadin dosing criteria based on age and actual body weight, and directs the prescription of two Coumadin loading doses beginning on the evening of the day of surgery and the evening of postoperative day 1 of a maximum 10 mg and 7.5 mg, respectively. Coumadin dosing is adjusted to 5 mg and 5 mg if the patient is aged >65 years or weighs <50 kg.

Starting with postoperative day 2, a Coumadin sliding scale dose was given based on the INR. Data was concurrently collected on admission and included medical history, patient age, actual body weight, baseline prothrombin time within 2 weeks of admission, baseline INR, and current prescription medications. In addition, subcutaneous doses of vitamin K, when appropriate, and the date of any DVT/pulmonary embolism or bleeding diatheses were documented. Postoperative daily prothrombin time, INR, and daily Coumadin dose were recorded for each patient during his or her hospital stay.

For all patients, the change in INR between each consecutive day he or she was in the hospital was calculated, starting with postoperative day 1. The value
representing the change in INR was then paired with the change in the prescribed Coumadin dose. The Coumadin dose was categorized as increasing, decreasing, or remaining the same.

Data was analyzed using BMDP New System (Statistical Solutions, Saugus, Mass). Continuous variables were evaluated by Student’s t test. Categorical data was analyzed by chi-square test or Fisher’s exact test, as appropriate. A P value < .05 was considered significant. With an alpha of 0.05 and a beta of 0.10, this retrospective study has 90% power to find a 14% difference between groups significant.

RESULTS

The 417 patients yielded 1167 pairs of INR values and Coumadin doses. Of the 417 patients, 202 (48%) achieved the targeted INR range of 2-3 for DVT prophylaxis using the Coumadin sliding scale (eg, 4 patients were within this range between the day of surgery and the first postoperative day of hospitalization; 80 patients between postoperative days 1 and 2; 71 patients between postoperative days 2 and 3; 33 patients between postoperative days 3 and 4; and 14 patients after postoperative day 4) (Table 2).

A change in INR > 0.4 units correlated 81% of the time with a decrease in the Coumadin dose (P < .05) (Table 3). Age and body weight data were normally distributed. No statistically significant difference was noted in the correlation based on actual body weight; however, age was associated with a statistically significant change in the correlation. For patients aged > 70 years, the correlation fell to 70% compared to an 89% correlation in patients aged < 70 years (P < .05). Gender also produced a statistically significant difference. The correlation fell to 78% in women, while men exhibited an increase to 87% (P < .05). For perspective, the correlation between INR changes and opportunities to increase the Coumadin dose in patients who did not reach therapeutic INR range or to maintain the same Coumadin dose in patients whose INR stayed within the target range in this pilot study were not analyzed.

Sixty-five (15%) patients overshoot the INR target therapeutic range of 2-3. Of these, INR levels in 3 (4.6%) patients increased on the day of surgery, 14 (22%) on postoperative day 1, 32 (49%) on postoperative day 2, 8 (12%) on postoperative day 3, 4 (6%) on postoperative day 4, and 4 (6%) on postoperative day 5.

The Figure illustrates the Receiver Operator Curve plotting the sensitivity versus one minus the specificity for a change in INR > 0.4 units and a
TABLE 3
The Change in INR >0.4 Units and Its Correlation to a Decrease in Oral Coumadin Dosage Stratified by Sex, Age, and Weight

<table>
<thead>
<tr>
<th>Correlation (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>81</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
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<tr>
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</tr>
<tr>
<td>Age (y)</td>
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</tr>
<tr>
<td>&gt;70</td>
<td>70</td>
</tr>
<tr>
<td>&lt;70</td>
<td>89</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>81</td>
</tr>
<tr>
<td>&lt;80</td>
<td>80</td>
</tr>
</tbody>
</table>

Abbreviation: INR = International Normalized Ratio.

- Figure: The Receiver Operator Curve plotting the sensitivity versus one minus the specificity for a change in INR >0.4 units and a dose decrease in Coumadin.

A decrease in Coumadin dose. The area under the curve was 0.8134. For all patients enrolled in the study, a change in INR >0.4 units had a sensitivity of 65% and a specificity of 91% regarding a decreased Coumadin dose. With this specificity, if the INR changed >0.4 units, then 91% of the time the Coumadin dose decreased. However, if the change in INR was ≤0.4 units, the dose stayed the same or increased only 65% of the time.

DISCUSSION
This pilot study offers an approach to postoperative Coumadin dosing reductions by using a breakpoint change in INR. Because of the suspected need to strengthen the Coumadin sliding scale with a tool to reduce overshooting target INR range with too high Coumadin loading doses during a nonsteady state, efforts were focused on determining an INR benchmark change that would help move off of the Coumadin sliding scale and reduce Coumadin doses based on objective data.

A change in INR >0.4 units was found to correlate highly at 81% with a decrease in the Coumadin dose, and was statistically significant for patients aged <70 years and men (Table 3). In addition, the Receiver Operator Curve demonstrated 91% specificity if the INR changed >0.4 units. This data is clinically meaningful because site specific patient information has been analyzed based on a select mix of orthopedic surgeons and surgical teams.

The majority of data come from patients who underwent TKA. Of note, only 48% of patients achieved the target therapeutic INR range prior to discharge, 15% overshot the target range, and 37% never reached a therapeutic INR. The latter statistic may be explained by the short length of stay (average 3.6 days) in the patient population. Patients who overshot the INR target therapeutic range were excluded from the number of patients considered "in target INR range" prior to discharge. This population included patients whose baseline INR was slightly elevated prior to surgery. Most patients were within INR range between postoperative days 1 and 2, followed by postoperative days 2 and 3. This percentage excluded patients whose INR overshot the target therapeutic INR range at any time prior to discharge. It is generally recognized that Coumadin steady state is achieved within 5-7 days for maintenance dose prediction.

Several limitations should be considered when interpreting these results. First, nonsteady state INR data during the study period was reported on patients undergoing THA, TKA, or hip fracture repair, all with or without complications. Bleeding or clotting complications, including coronary events, were not noted in >95% of the study population. However, the prevalence of DVT and other drug-related adverse events may have been under-reported. The study lacked prospective Doppler screening for DVT. The short length of stay compared to the Diagnostic Related Group average, while encouraging from a cost perspective, limited the ability to manage Coumadin dosing in a steady-state environment. Patients were not followed after discharge to determine whether any negative sequelae occurred, and primary surgery versus readmissions for surgical revisions were not stratified. Finally, medical comorbidities were not factored into Coumadin dosing adjustments. The actual INR change that was incurred by dosing excursions from the Coumadin sliding scale was not studied.
Our observational data supports the notion that although Coumadin sliding scales and computer programs have their place in refining Coumadin dosing, surgeons should consider the need to decrease the Coumadin dose if the change in INR is >0.4 units, even if the Coumadin sliding scale or computer program would direct them differently.

Future prospective research supported by this pilot study with a control group and more INR data points should include an analysis of an INR breakpoint for an increase in Coumadin dosing when the INR is subtherapeutic based on factors such as gender, actual body weight, and age. In addition, comorbidities and medication and dietary supplement interactions with Coumadin may offer significant findings relative to an INR breakpoint from a practical Coumadin dosing perspective.

CONCLUSION

Although this was a retrospective pilot study, when managing postoperative Coumadin anticoagulation for total joint arthroplasty patients, a change in INR >0.4 units correlates highly with the need to decrease the Coumadin dose. This finding could be used as an adjunct for Coumadin dosing in addition to sliding scales to minimize overshooting the target INR therapeutic range. A prospective study is needed to evaluate this phenomenon.

REFERENCES

9. Angelo S, Nardino RJ. Comparing 5-mg and 10-mg warfarin loading doses: are the groups similar? Arch Intern Med. 1999; 159:1624-1625.

EDITORIAL DISCUSSION

ORTHOPEDICS: Due to the lag time of 2-3 days between dosing and peak response to Coumadin, how valid is the International Normalized Ratio (INR) change given the short course of observation?

Rosenbaum et al: Coumadin inhibits the production of the new vitamin K-dependent clotting factors (eg, II, VII, IX, and X), not those already manufactured and present in the blood. The lag time to Coumadin’s peak steady state response, as evidenced by change in INR, has more to do with the half lives of these clotting factors than the half life of Coumadin. The half lives of the clotting factors are: Factor VII (6 hours), Factor IX (24 hours), Factor X (36 hours), and Factor II (60-96 hours). Reaching therapeutic INR is a result of the time necessary to eliminate previously manufactured vitamin K-dependent clotting factors from the bloodstream. Most of the initial change in INR is due to the depletion of Factor VII, the factor with the shortest half life. Therefore, a nonsteady state therapeutic INR on the second or third day of Coumadin therapy should serve as a warning sign for excessive Coumadin dosage, as the effects of the depletion of Factors II and X have not yet been seen. It is recommended that the clinician carefully watch changes in INR for up to 1 week until steady state is achieved and the INR is stabilized with a daily Coumadin maintenance dosage.