Anesthesiology 2010; 112:298–304

Factor VII Levels and International Normalized Ratios in the Early Phase of Warfarin Therapy

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ABSTRACT

Background: Factor VII is the most affected clotting factor during the early phase of warfarin therapy. An international normalized ratio (INR) of more than 1.4 is considered unsafe for epidural catheter placement or removal, according to the American Society of Regional Anesthesia and Pain Medicine. The authors tested the hypothesis that factor VII activities would be consistent with safe removal of the epidural catheter on postoperative day (POD) 1 regardless of INR value.

Methods: Data from 121 patients who took warfarin after undergoing total joint surgery and had INRs and factor VII levels determined were reviewed. Patient characteristics and factor VII activities were compared between patients with INRs of more than 1.4 and those with INRs less than or equal to 1.4 on PODs 1, 2, and 3.

Results: Eleven patients had INRs of more than 1.4 on POD 1; their mean ± SD factor VII activities were 60 ± 28% (normal: 50–160%). On POD 2, 78 patients with INRs more than of 1.4 had factor VII activities of 32 ± 15%, whereas on POD 3, 84 patients with INRs of more than 1.4 had factor VII activities of 44 ± 19%. Variables included in the final multiple logistic regression model as predictors of an INR of more than 1.4 on POD 2 were warfarin dose on POD 1 and factor VII activity on POD 2.

Conclusions: The range of factor VII activities in the patients with INRs of more than 1.4 within 12 h of warfarin therapy was compatible with adequate hemostasis. The authors found no evidence that epidural catheters should not be removed even with INRs up to 1.9, the highest INR on POD 1 noted in their study.

What We Already Know about This Topic

- The American Society of Regional Anesthesia suggests an international normalized ratio (INR) of less than or equal to 1.4 for removal of epidural catheters
- Factor VII activity more accurately reflects hemostasis during early warfarin therapy

What This Article Tells Us That Is New

- After total joint surgery in 121 patients, factor VII activity within 12 h of beginning warfarin was adequate for hemostasis despite INR values of more than 1.4
- It may be safe to remove epidural catheters early after starting warfarin, despite an INR of more than 1.4

COUMARINS or vitamin K antagonists are used for primary and secondary prevention of venous thromboembolism, for the prevention of systemic embolism in patients with atrial fibrillation or prosthetic heart valves, and as an adjunct in the prophylaxis of systemic embolism after myocardial infarction.[1] These drugs interfere with the synthesis of the vitamin K-dependent clotting factors II, VII, IX, and X. The onset of action of oral anticoagulants depends on their effect on factor VII, the clotting factor with the shortest half-life.

The prothrombin time is the test used most commonly to monitor therapy with vitamin K antagonists. The prothrombin time responds to a reduction of three of the four vitamin K-dependent procoagulant clotting factors, factors II, VII, and X.[1] The lack of reliability of the prothrombin time led to the use of the international normalized ratio (INR), the ratio of a patient's prothrombin time to that of a control sample.[1] The INR represents the activities of several coagulation factors during the onset and the steady-state of warfarin therapy.

An INR of more than 1.4 has been considered as unsafe for epidural catheter placement or removal by the American Society of Regional Anesthesia and Pain Medicine because of the risk of spinal hematoma.[2] The guideline is followed by clinicians even during the early phase of warfarin therapy when factor VII may be the only clotting factor affected. In this study, we tested the hypothesis that factor VII activities would be consistent with safe removal of the epidural cathe-

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Received from Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois. Submitted for publication July 10, 2009. Accepted for publication November 9, 2009. Support was provided solely from institutional and/or departmental sources. Presented at the American Society of Anesthesiologists Annual Meeting, Orlando, Florida, October 19, 2008.

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Table 1. Patient Characteristics on Postoperative Day 1

	INR ≤ 1.4	INR > 1.4	Difference (95% CI)	*P* Value
N	110	11		
Sex (male:female)	38 (34.6%):72 (65.4%)	6 (54.6%):5 (45.4%)	−20.0% (−46.1 to 8.3%)	0.324
Age (yr)	64.2 ± 12.0	61.7 ± 14.3	2.4 (−5.2 to 10.1)	0.529
BMI > 35:≤ 35 kg/m^2	28 (25.5%):82 (74.5%)	2 (18.2%):9 (81.8%)	7.3% (−23.3 to 23.8%)	0.868
ASA PS III or IV:I or II	34 (30.9%):76 (69.1%)	4 (36.4%):7 (63.6%)	−5.5% (−35.1 to 18.1%)	0.975
Cancer history Y:N	19 (17.3%):91 (82.7%)	4 (36.4%):7 (63.6%)	−19.1% (−48.3 to 3.8%)	0.256
Factor VII (%)	98.6 ± 35.4 (43–239)	60.2 ± 27.8 (22–108)	38.4 (16.6 to 60.3)	< 0.001
Creatinine clearance < 60:≥ 60 ml/min	18 (16.4%):92 (83.6%)	2 (18.2%):9 (81.8%)	−1.8% (−32.1 to 4.0%)	0.787
Hemoglobin POD 1 < 10:≥ 10 g/dl	32 (29.1%):78 (70.9%)	4 (36.4%):7 (63.6%)	−7.3% (−36.9 to 16.2%)	0.875
Estimated blood loss > 20:≤ 20%	1 (0.9%):109 (99.1%)	1 (9.1%):10 (90.9%)	−8.2% (−36.9 to 0.1%)	0.430
Blood transfusion Y:N	37 (33.6%):73 (66.4%)	5 (45.5%):6 (54.5%)	−11.8% (−40.0 to 14.4%)	0.651

Data are mean ± SD (range) or number of patients (%).

ASA PS = American Society of Anesthesiologists physical status; BMI = body mass index; CI = confidence interval; INR = international normalized ratio; POD = postoperative day.

ter on postoperative day (POD) 1 regardless of the INR values.

Materials and Methods

The current study was approved by Northwestern University (Chicago, Illinois) Institutional Review Board, which did not require written informed consent because of the retrospective nature of our study and the 1-yr interval between the determination of the factor VII activities and study approval. The sample size of the study was based on the availability of data from patients who had total joint surgery, either total hip or total knee replacement, between April 25, 2007, and June 5, 2007, and for whom INRs and factor VII levels were ordered as part of a quality assurance study at our hospital. After Institutional Review Board approval, the data of 121 consecutive patients were reviewed retrospectively. All patients had stopped taking aspirin 5–7 days before their operation and other nonsteroidal antiinflammatory drugs 2–3 days before their operation; neither these drugs nor low-molecular weight heparin was started during the hospitalization of patients. They were prescribed warfarin every night, starting with 5 mg on the night of the surgery, except for 17 patients who were older than 70 yr and for whom 4 mg was started and one 82-yr-old patient who was started on 3 mg.

The INRs and factor VII activities were determined on the morning of POD 1 (approximately 12–14 h after warfarin intake), POD 2 (36–38 h after warfarin), and POD 3 (60–62 h after warfarin). Factor VII levels, reported as percent activities, were determined by the one-stage clotting method.

Statistical Analyses

Patient characteristics were either categorical data as collected or were reduced from ordinal or continuous data to categorical data. These included sex, age, body mass index (BMI), American Society of Anesthesiologists physical status, history of cancer, creatinine clearance (CrCl) calculated by the Cockcroft-Gault equation, hemoglobin, estimated blood loss, and incidence of blood transfusion on PODs 1, 2, and 3, as indicated in tables 1–3. These data were compared between patients with INRs more than 1.4 and those with INRs less than or equal to 1.4 using Fisher exact probability test, with 95% confidence intervals for differences in percentages calculated using the Farrington and Manning score (NCSS, Kaysville, UT). Factor VII activities were compared between the patients with INRs of more than 1.4 and those with INRs less than or equal to 1.4 using the unpaired *t* test. The relationship between the INRs and factor VII activities on PODs 1, 2, and 3 were examined using the least squares linear regression. The criterion for rejection of the null hypothesis was a two-tailed *P* value of <0.05.

Multiple logistic regression analysis was performed using StatsDirect statistical software (version 2.6.5, StatsDirect Ltd., Chesire, United Kingdom) to determine the predictors of an INR of more than 1.4 on POD 2. Variables included in the initial multiple logistic regression analysis were those identified in the univariate analyses as having a value of $P < 0.10$ (table 2): age, BMI more than 35 or less than or equal to 35 kg/m^2, factor VII activity, CrCl less than 60 or more than or equal to 60 ml/min, hemoglobin less than 10 or more than or equal to 10 g/dl, blood transfusion, and warfarin dose on POD 1. In the final analyses, variables with high *P* values were removed from the model one at a time and were excluded from the final model if their removal either did not diminish the fit of the model or actually improved it, as determined by the Pearson chi-square statistic, the likelihood ratio test statistic, the Hosmer-Lemshow statistic, and the correct prediction of both positive and reference responses. The sensitivity and specificity of the logistic model were calculated from the model-predicted reference and model-predicted positive responses (using the default threshold probability for positive classification of 0.5) and the actual reference and actual positive responses. Bias-corrected

Table 2. Patient Characteristics on Postoperative Day 2

	INR ≤ 1.4	INR > 1.4	Difference (95% CI)	*P* Value
N	43	78		
Sex (male:female)	18 (41.9%):25 (58.1%)	26 (33.3%):52 (66.7%)	8.5% (−9.1 to 26.4%)	0.430
Age (yr)	60.7 ± 10.8	65.7 ± 12.6	−5.0 (−9.5 to −0.5)	0.030
BMI > 35:≤ 35 kg/m^2	18 (41.9%):25 (58.1%)	12 (15.4%):66 (84.6%)	26.5% (10.1 to 43.0%)	0.002
ASA PS III or IV:I or II	14 (32.6%):29 (67.4%)	24 (30.8%):54 (69.2%)	1.8% (−14.8 to 19.5%)	0.841
Cancer history Y:N	9 (20.9%):34 (79.1%)	14 (18.0%):64 (82.0%)	3.0% (−11.0 to 19.1%)	0.809
Factor VII (%)	74.4 ± 20.1 (41–130)	32.4 ± 14.8 (9–123)	42.1 (35.7 to 48.4)	< 0.0001
Creatinine clearance < 60:≥ 60 ml/min	2 (4.7%):41 (95.3%)	18 (23.1%):60 (76.9%)	−18.4% (−29.9 to −5.6%)	< 0.01
Hemoglobin POD 2 < 10:≥ 10 g/dl	8 (18.6%):35 (81.4%)	30 (38.5%):48 (61.5%)	−19.9% (−34.6 to −2.7%)	0.026
Estimated blood loss > 20:≤ 20%	0 (0.0%):43 (100.0%)	2 (2.6%):76 (97.4%)	−2.6% (−8.9 to 5.7%)	0.754
Blood transfusion Y:N	8 (18.6%):35 (81.4%)	34 (43.6%):44 (56.4%)	−25.0% (−39.8 to −7.7%)	0.009

Data are mean ± SD (range) or number of patients (%).

ASA PS = American Society of Anesthesiologists physical status; BMI = body mass index; CI = confidence interval; INR = international normalized ratio; POD = postoperative day.

confidence intervals for the odds ratios derived from the final logistic model were determined by bootstrapping (1,000 samples, with replacement). No external validation was attempted.

Results

The charts of 121 patients were reviewed. Eleven patients had INRs of more than 1.4 on POD 1; the mean ± SD of factor VII activities were 60 ± 28% in patients with INRs of more than 1.4 and 99 ± 35% in patients with INRs less than or equal to 1.4 ($P < 0.001$; table 1). On POD 2, 78 patients had INRs of more than 1.4 and factor VII activities of 32 ± 15%, and the 43 patients with INRs less than or equal to 1.4 had factor VII activities of 74 ± 20% ($P < 0.0001$; table 2). On POD 3, 84 patients had INRs of more than 1.4 and factor VII activities of 44 ± 19%, and 28 patients with INRs less than 1.4 had factor VII activities of 87 ± 26% ($P < 0.0001$; table 3). A closer look at the factor VII activities of the patients who had INRs of more than 1.4 on POD 1 showed that all but three of the patients had factor VII activities more than 50% (normal: 50–160% activity). Two patients with INRs of 1.5 had factor VII activities of 45 and 24%, whereas another patient with an INR of 1.8 had a factor VII activity of 22%. In contrast, of the 17 patients who had INRs of 1.4, 15 patients had normal factor VII activities, whereas two patients had factor VII activities of 48 and 23%. All the patients with INRs of less than or equal to 1.3 had normal factor VII activities. There was a weak correlation between INR and factor VII activity on POD 1 ($R^2 = 0.326$). The correlation was better on PODs 2 ($R^2 = 0.633$) and 3 ($R^2 = 0.403$; figs. 1–3).

The dose of warfarin was less in patients with INRs of more than 1.4 than in those with INRs of less than or equal to 1.4 on PODs 2 and 3 (table 4). This decreased dose and

Table 3. Patient Characteristics on Postoperative Day 3

	INR ≤ 1.4	INR > 1.4	Difference (95% CI)	*P* Value
N	28	84		
Sex (male:female)	12 (42.9%):16 (57.1%)	29 (34.5%):55 (65.5%)	8.3% (−11.4 to 29.0%)	0.499
Age (yr)	64.8 ± 12.9	64.5 ± 12.3	0.2 (−5.1 to 5.6)	0.934
BMI > 35:≤ 35 kg/m^2	9 (32.1%):19 (67.9%)	19 (22.6%):65 (77.4%)	9.5% (−8.1 to 29.9%)	0.323
ASA PS III or IV:I or II	11 (39.3%):17 (60.7%)	24 (28.6%):60 (71.4%)	10.7% (−8.4 to 31.3%)	0.348
Cancer history Y:N	6 (21.4%):22 (78.6%)	15 (17.9%):69 (82.1%)	3.6% (−11.4 to 23.1%)	0.780
Factor VII (%)	87.1 ± 26.0 (25–130)	44.0 ± 19.2 (10–93)	43.2 (34.0 to 52.4)	< 0.0001
Creatinine clearance < 60:≥ 60 ml/min	3 (10.7%):25 (89.3%)	17 (20.2%):67 (79.8%)	−9.5% (−22.2 to 8.4%)	0.280
Hemoglobin POD 2 < 10:≥ 10 g/dl	5 (17.9%):23 (82.1%)	32 (38.1%):52 (61.9%)	−20.2% (−35.6 to −0.1%)	0.082
Estimated blood loss > 20:≤ 20%	0 (0.0%):28 (100.0%)	2 (2.4%):82 (97.6%)	−2.4% (−8.3 to 9.8%)	1.000
Blood transfusion Y:N	4 (14.3%):24 (85.7%)	38 (45.2%):46 (54.8%)	−31.0% (−45.5 to −11.2%)	0.007

Data are mean ± SD (range) or number of patients (%).

ASA PS = American Society of Anesthesiologists physical status; BMI = body mass index; CI = confidence interval; INR = international normalized ratio; POD = postoperative day.

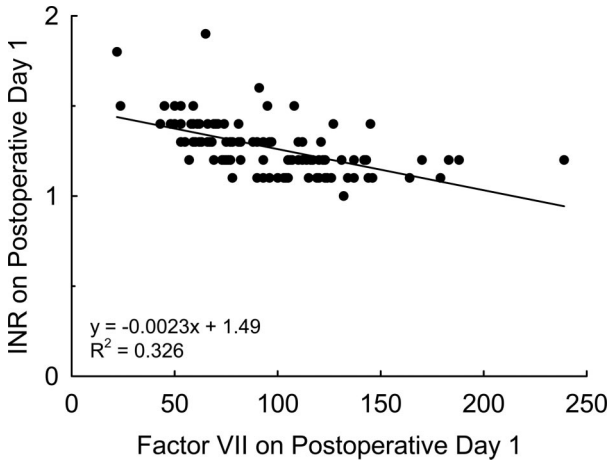

Fig. 1. Correlation between international normalized ratio (INR) and factor VII activities on postoperative day 1.

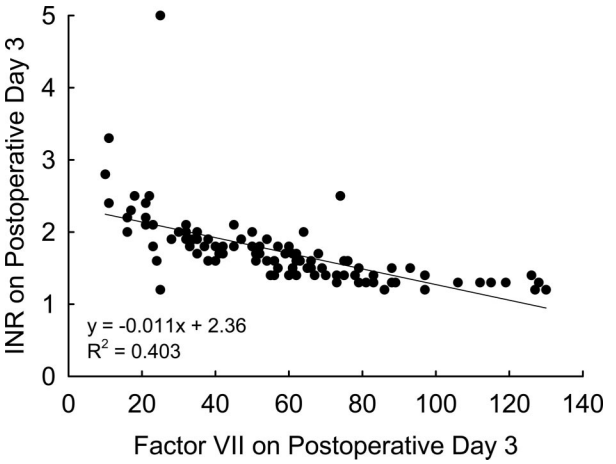

Fig. 3. Correlation between international normalized ratio (INR) and factor VII activities on postoperative day 3.

the decreasing number of patients receiving warfarin on PODs 2 and 3 (table 4) may reflect a decrease or withholding of the patients' warfarin because INRs were increased and the patients were elderly. This would prevent further increase in INRs and potential bleeding into the operated joint.

Comparison of the characteristics of the patients with INRs of more than 1.4 and those with INRs less than or equal to 1.4 revealed that factor VII activities were different on POD 1, but the other patient characteristics were not (table 1). Age, BMI, CrCl, hemoglobin, incidence of blood transfusion, and factor VII activities were significantly different between the groups of patients on POD 2 (table 2) but only the incidence of blood transfusion and factor VII levels were significantly different between the two groups on POD 3 (table 3). Initial multiple logistic regression analysis to determine the predictors of an INR of more than 1.4 on POD 2 was performed using variables identified in the univariate analyses as having a value of $P < 0.10$ (table 5). Variables included in the final multiple logistic regression model as predictors of an INR of more than 1.4 were warfarin dose on POD 1 and factor VII activity on POD 2 (table 5; Logit $P =$ 13.612–0.121 × factor VII activity − 1.443 × warfarin dose in mg; likelihood ratio test statistic = 93.146, $P < 0.0001$). The sensitivity of the logistic model was 94.5%, whereas its specificity was 86.1%.

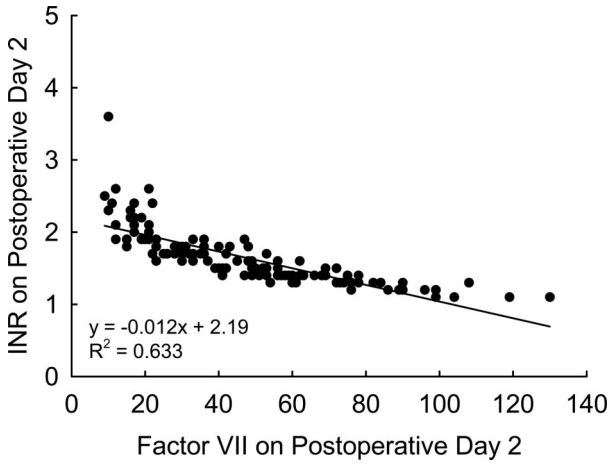

Fig. 2. Correlation between international normalized ratio (INR) and factor VII activities on postoperative day 2.

Discussion

We found that not only was the correlation between the INRs and the factor VII activities on POD 1 poor but also the factor VII activities in 8 of 11 patients with INRs more than 1.4 within 12 h of warfarin therapy were within normal limits. The correlation between the INRs and the factor VII activities were better on PODs 2 and 3. Factor VII levels were significantly different between patients with INRs of more than 1.4 and those with INRs less than or equal to 1.4 on POD 1. On POD 2, age, BMI, CrCl, hemoglobin, incidence of blood transfusion, and factor VII activities were different between patients with INRs of more than 1.4 and those with INRs less than or equal to 1.4, whereas on POD 3, only the incidence of blood transfusion and factor VII levels were different between the patient groups.

Coumarins competitively inhibit vitamin K reductase and vitamin K epoxide reductase—enzymes that maintain the vitamin K cycle. Vitamin K reductase converts vitamin K to reduced vitamin K, a cofactor in the carboxylation of precursors of procoagulant proteins (prothrombin, factors VII, IX, and X). Reduced vitamin K is then reconverted to vitamin K by the epoxide reductase.[1]

Warfarin is the most common vitamin K antagonist in clinical use. Warfarin also inhibits protein C, which is converted into activated protein C when thrombin binds to thrombomodulin. Activated protein C, together with its cofactor protein S, inactivates factors Va and VIIIa.[3] Factor VII has a relatively short half-life (6–8 h), and the INR may be prolonged within 24–36 h after warfarin administration due to a decrease of factor VII levels. The anticoagulant protein C also has a short half-life (6 to 7 h), and decreases in its activity may counteract the effect of the changes in factor VII concentrations. Although factor IX has a half-life of 24 h, ade-

Table 4. Warfarin Doses and International Normalized Ratios on Postoperative Days 1–3

	INR ≤ 1.4	INR > 1.4	Median Difference (95% CI)	*P* Value
Number of patients on POD 1	107	11	—	—
Dose (mg), night of surgery	5 (3–5)	5 (5–5)	0 (0–0)	0.142
Number of patients on POD 2	43	74	—	—
Dose (mg) POD 1	5 (4–7.5)	5 (2.5–6)	1 (0–1)	< 0.0001
Number of patients on POD 3	28	68	—	—
Dose (mg) POD 2	5 (2–8)	3.5 (0.5–10)	1.5 (1–2.5)	0.0001

Data are median (range). Warfarin was started the night of surgery, blood was drawn the next day for INR determinations. The *P* values reflect statistical differences between the patients with INRs > 1.4 and those with INRs < 1.4.
CI = confidence interval; INR = International Normalized Ratio; POD = postoperative day.

quate anticoagulation is not achieved until the levels of biologically active factors II (half-life of 48–120 h) and X (half-life of 20–42 h)[4] are sufficiently decreased. This requires 4 to 6 days.

The American Society of Regional Anesthesia and Pain Medicine recommended an epidural catheter be neither placed nor removed in patients on warfarin therapy who have INRs of more than 1.4.[2] When the INR is more than 1.4, the anesthesiologist withholds the warfarin, waits for the INR to decrease, and removes the epidural catheter when the INR is less than 1.4. This scenario has led to two complications in our hospital when followed on the morning of POD 1, 12–14 h after the patients took their warfarin. One woman developed an acute deep vein thrombosis in her right medial calf on POD 1 while her INR was 1.8. Another patient developed a pulmonary embolism on POD 2 when his INR was 2.1. In both patients, the warfarin was withheld by the clinician because of the elevated INR value on POD 1. The levels of factor VII, the factor most probably affected, and protein C were not measured in these two patients. These complications led to our interest in factor VII activities because the INR is mainly dependent on the levels of this factor in the early days of warfarin therapy.[5]

The INR in the first week of warfarin therapy is exquisitely labile and depends on levels or activities of both factor VII and protein C.[5,6] During the first few days of warfarin therapy initiated with a 5 mg dose (similar to most of the patients in our study), the average percent activities of factors VII and II were reported to be 85 and 100%, respectively, at 12 h; 58 and 83%, respectively, at 36 h; and 35 and 66%, respectively, at 60 h after initiating therapy.[5] These factor VII activities are similar to our findings (tables 1–3) and to those of an earlier report.[7] For effective anticoagulation, the levels of the vitamin K-dependent clotting factors have to be decreased to approximately 20% of their normal levels.[8] A study that looked into the importance of the individual clotting factors on the generation of prothrombinase activity in the plasma of anticoagulated patients demonstrated that the concentration below which the factors VII, IX, and X start to have a measurable effect were 5, 20, and 30%, respectively.[9]

Based on the results of our study, it is probably safe to remove the epidural catheter in the first day of therapy, despite an increase in INR up to 1.9, the highest INR noted on the first POD of our study. The factor VII activity at this time is compatible with adequate hemostasis, and the activities of the other vitamin K-dependent factors are within normal limits. If the patient has risk factors for bleeding (see the following discussion on risks for increased INR), then a factor VII activity test should be ordered.

There was a low correlation between INR and factor VII on POD 1 in the current study (fig. 1) that may be related to the competing effects of decreased factor VII and of protein C and to the washout of existing clotting factors. The better correlation between factor VII levels and INR on PODs 2 and 3 is likely due to exhaustion of the existing clotting factor VII and the initial decrease of the other vitamin K-dependent clotting factors.

Among the patient characteristics on POD 1 (12–14 h after their warfarin intake), only factor VII was significantly different between the patients whose INRs were less than or equal to 1.4 and those whose INRs were more than 1.4 in the current study. Age, BMI, CrCl, low hemoglobin (less than

Table 5. Final Model for Prediction of an INR > 1.4 on Postoperative Day 2

Variable	Regression Coefficient (SE)	Odds Ratio (95% CI)*	*P* Value
Constant	13.61 (3.19)	—	< 0.0001
Factor VII activity	−0.12 (0.03)	0.886 (0.746–0.951)	< 0.0001
Warfarin dose on postoperative day 1 (mg)	−1.44 (0.53)	0.236 (0.044–0.534)	0.007

* Bias-corrected by bootstrapping.
CI = confidence interval; INR = international normalized ratio.

10 g/dl), incidence of blood transfusion, and factor VII activity were significantly different between the patients whose INRs were less than or equal to 1.4 and those whose INRs were more than 1.4 on POD 2, or 36–38 h after initiating warfarin therapy. The incidence of blood transfusion and factor VII levels were significantly different between the patients whose INRs were less than or equal to 1.4 and the patients whose INRs were more than 1.4 on POD 3, or 60–62 h after initiating warfarin therapy. Of the patient characteristics associated with increased INRs on POD 2, only factor VII activity and warfarin dose were included in the final multiple logistic regression model (table 5).

The factors associated with increased INRs in patients on warfarin have been the subject of several studies and reviews. Advanced age has been identified as a risk factor for increased INR.[10–12] The increased risk of bleeding in elderly patients on anticoagulants may be due to reduced clearance of warfarin,[13] intercurrent illness, or drug interactions with warfarin. After adjustment of other risk factors, it was noted that age increased the risk of overcoagulation by 15% for every 10 yr.[10]

The clearance of warfarin influences the degree of elevation of INR.[14,15] We used a CrCl of less than 60 ml/min/1.73 m^2 to signify chronic kidney disease.[16] In our study, the presence of CrCl of less than 60 ml/min/1.73 m^2 differed between the groups only on POD 2.

Other patients' characteristics that affect patient's response to INR include debilitation, malnourishment, congestive heart failure, and liver disease.[1] Malignancy and anticancer chemotherapy are known risk factors for thromboembolism.[17] Tumor cells and their products activate the coagulation and fibrinolytic systems and interact with platelets, leukocytes, and endothelial cells.[17,18] Procoagulants and cytokines are released from damaged cells, and anticancer drugs have a direct toxic effect on the vascular endothelium and decreases physiologic anticoagulants.[19,20] A history of cancer did not differ between the patients with INRs less than or equal to 1.4 and those with INRs more than 1.4 in our study (tables 1–3).

Approximately 250 different drugs interact with warfarin.[21] Most notable are interactions with cardiovascular drugs, especially amiodarone that reduces the clearance of warfarin,[22] and drugs that affect platelet function.[21] None of our patients were given amiodarone, and their antiplatelet medications were stopped before their surgery.

Warfarin is metabolized primarily by the CYP2C9 enzyme of the cytochrome P450 system.[1] Mutations in the gene coding for the cytochrome P450 2C9 hepatic microsomal enzyme affect the elimination clearance of warfarin by impairing the patient's ability to metabolize S-warfarin. Other genetic factors affecting the warfarin dose-response relationship include polymorphisms of the vitamin K oxide reductase enzyme, the target of warfarin's inhibitory effect on the vitamin K cycle. Although mutations in the gene encoding for isoforms of the protein can lead to enzymes with varied sensitivities to warfarin, the American College of Chest Physicians advises against pharmacokinetic-based initial dosing of warfarin at this time.[1]

In summary, we noted that the activities of factor VII were within normal limits in 8 of 11 patients with INRs of more than or equal to 1.4 12–14 h after initiating warfarin therapy. The factor VII activities of the remaining 3 patients with INRs of more than or equal to 1.4 were compatible with adequate hemostasis. We recommend that the epidural catheter be removed at this time, in the presence of an INR that is increased up to 1.9, the highest INR noted on the first POD of our study, as long as other risk factors for increased bleeding are not present. If risk factors such as low platelets, advanced age, kidney failure, or intake of other anticoagulants are present, then the factor VII activity should be determined.

The authors thank the Anticoagulation Dosing Service of Northwestern Memorial Hospital, Chicago, Illinois, for sharing their data.

References

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G: Pharmacology and management of the vitamin K antagonists. Chest 2008; 133:160S–90S
2. Horlocker TT, Wedel DJ, Benzon HT, Brown DL, Enneking FK, Heit JA, Mulroy MF, Rosenquist RW, Rowlingson J, Tryba M, Yuan CS: Regional anesthesia in the anticoagulated patient: Defining the risks (the second ASRA consensus conference on neuraxial anesthesia and anticoagulation). Reg Anesth Pain Med 2003; 28:172–7
3. Holm J, Hillarp A, Erhart L, Berntorp E: Changes in levels of factor VII and protein S after acute myocardial infarction: Effects of low-dose aspirin. Thromb Res 1999; 96: 205–12
4. Trask AS, Gosselin RC, Diaz JA, Dager WE: Warfarin initiation and monitoring with clotting factors II, VII and X. Ann Pharmacother 2004; 38:251–6
5. Harrison L, Johnston M, Massicote MP, Crowther M, Moffat K, Hirsh J: Comparison of 5-mg and 10-mg doses in initiation of warfarin therapy. Ann Intern Med 1997; 126:133–6
6. Weinstock DM, Chang P, Aronson DL, Kessler CM: Comparison of plasma prothrombin and factor VII and urine prothrombin F1 concentrations in patients on long-term warfarin therapy and those in initial phase. Am J Hematol 1998; 57:193–9
7. Weiss P, Soff GA, Halkin H, Seligsohn U: Decline in proteins C and S and factors II, VII, IX and X during the initiation of warfarin therapy. Thromb Res 1987; 45: 783–90
8. Loeliger EA: The optimal therapeutic range in oral anticoagulation: History and proposal. Thromb Haemost 1979; 42:1141–52
9. Xi M, Beguin S, Hemker HC: The relative importance of factors II, VII, and X for the prothrombinase activity in plasma of orally anticoagulated patients. Thromb Haemost 1989; 62:788–91
10. Froom P, Milron E, Barak M: Oral anticoagulants in the elderly. Br J Haematol 2003; 120:526–8
11. Goudie BM, Donnan PT, Fairfield G, Al-Agilly SS, Cachia PG: Dependency rather than old age increases the risk of warfarin-related bleeding. Br J Gen Pract 2004; 54:690–2
12. Ribak G, Barak M, Froom P: Older age is risk for an international normalized ratio (INR) of 5 or more. Clin Lab 2007; 53:571–4
13. Russmann S, Ggohlke-Barwolf C, Jahnchen E, Trenk D, Roskamm H: Age-dependent differences in the anticoagulant effect of phenprocoumon in patients after heart valve surgery. Eur J Clin Pharmacol 1997; 52:31–5

14. Ganeval D, Fischer AM, Barre J, Pertuiset N, Dautzenberg MD, Jungers P, Houin G: Pharmacokinetics of warfarin in the nephrotic syndrome and effect on vitamin K-dependent clotting factors. Clin Nephrol 1986; 25:75–80
15. Kim SB, Lee SK, Park JS, Chi HS, Hong CD, Yang WS: Effects of low-dose warfarin on hemostatic factors in continuous ambulatory peritoneal dialysis. Am J Kidney Dis 2001; 37:343–7
16. K/DOQI Clinical Practice Guidelines on Chronic Kidney Disease Work Group and Evidence Review Team: Definition and classification of stages of chronic kidney disease. Am J Kidney Dis 2002; 39:S46–75
17. Falanga A, Levine MN, Consonni R, Gritti G, Delaini F, Oldani E, Julian JA, Barbui T: The effect of very-low-dose warfarin on markers of hypercoagulation in metastatic breast cancer: Results from a randomized trial. Thromb Haemost 1998; 79:23–7
18. Rickles FR, Levine MN, Edwards RL: Haemostatic alterations in cancer patients. Cancer Metast Rev 1992; 11: 237–48
19. Levine MN, Gent M, Hirsh J, Arnold A, Goodyear MB, Hryniuk W, DePauw S: The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. N Engl J Med 1988; 318:404–7
20. Rogers JS, Murgo AJ, Fontane JA, Raich PC: Chemotherapy for breast cancer decreases plasma levels of protein C and S. J Clin Oncol 1988; 6:276–8
21. Harder S, Thurmann P: Clinically important drug interactions with anticoagulants: An update. Clin Pharmacokinet 1996; 30:416–44
22. Almog S, Shafran N, Halkin H, Weiss P, Farfel Z, Martinowitz U, Bank H: Mechanism of warfarin potentiation by amiodarone: dose- and concentration-dependent inhibition of warfarin elimination. Eur J Clin Pharmacol 1985; 28:257–61

ANESTHESIOLOGY REFLECTIONS

Charles T. Jackson in "Ballou's Pictorial"

Clearly the most accomplished of those seeking acclaim as the anesthesia world's first etherizer, Charles Thomas Jackson (1805–1880) was a mineralogist, geologist, chemist, and physician. Indeed, it was Jackson who had first advised W. T. G. Morton (1819–1868) to try using ether for anesthetic purposes. The portrait of Jackson above (from an 1857 issue of *Ballou's Pictorial Drawing-Room Companion*, courtesy of the Wood Library-Museum) bears little resemblance to the man who died in an asylum and was then portrayed by many historians as having perished from insane jealousy of Morton. Jackson Family correspondence suggests that Charles was terminally institutionalized not for insanity but for a profound cerebrovascular accident. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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