A Randomized Trial Comparing 5-mg and 10-mg Warfarin Loading Doses

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Background: Warfarin sodium therapy is usually initiated with a loading dose to reduce the time required to elevate the international normalized ratio (INR). Warfarin loading doses are associated with early overanticoagulation and the development of a potential hypercoagulable state; they also may not hasten achieving an INR value between 2.0 and 3.0. This study was designed to prospectively confirm our observation that a 5-mg warfarin sodium loading dose is as effective as a 10-mg loading dose in achieving a therapeutic INR for 2 consecutive days on days 3 and 4 or 4 and 5 of therapy.

Methods: Fifty-three patients initiating warfarin therapy with a target INR of 2.0 to 3.0 were randomly allocated to receive an initial dose of 5 or 10 mg of warfarin. Subsequent doses were based on dosing algorithms. The INR was measured daily for 5 days. The primary end point of the study was the proportion of patients whose INR values were between 2.0 and 3.0 on 2 consecutive daily determinations on days 3, 4, or 5 of the study and whose INR did not exceed 3.0 at any point during the study.

Results: Five (24%) of 21 patients in the 10-mg group and 21 (66%) of 32 patients in the 5-mg group achieved the primary end point (relative risk 2.22, 95% confidence interval 1.30-3.70 [P < .003]). A trend toward less overanticoagulation was seen in the 5-mg warfarin group.

Conclusion: A 10-mg loading dose of warfarin is unlikely to be more effective than a 5-mg loading dose in achieving an INR of 2.0 to 3.0 by day 4 or 5 of therapy.

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Although warfarin sodium is an effective antithrombotic agent, it has a narrow therapeutic window and a widely variable dose-response relationship among patients with thromboembolic disorders. An inadequate anticoagulant effect is associated with reduced efficacy, and an excessive anticoagulant effect with increased bleeding. Consequently, the anticoagulant effect of warfarin has to be monitored carefully and the dose adjusted so that the prothrombin time (PT) is maintained in a safe and effective range. For most thromboembolic disorders, the therapeutic range for the PT is equivalent to an international normalized ratio (INR) of 2.0 to 3.0.

The need for careful monitoring and the consequences of overanticoagulation are major impediments to the use of warfarin. Three periods in the management of warfarin therapy are recognized: first, the initiation period, during which the correct patient-specific dose-response relationship is established; second, the transition period, when the correctness of the dose-response relationship is verified; and finally, the maintenance period, which occurs when a stable dose-response relationship has been established. Frequent monitoring is required during the initiation period, less frequent monitoring in the transition period, and much less frequent monitoring during the maintenance period. The initiation period lasts for a minimum of 4 to 5 days and is over when the INR has been in the therapeutic range on 2 consecutive days. At that time, the antithrombotic effect of warfarin is fully expressed and the frequency of PT monitoring can be relaxed from daily to once or twice weekly, and when a stable dose-response relationship has been established, to once every 2 to 4 weeks. When patients are treated with heparin as well as warfarin, heparin treatment is usually discontinued when the INR has been in the therapeutic range for 2 consecutive days and a minimum of 4 days of heparin therapy has been administered.

The approach to initiation of warfarin treatment has changed over time. At
Subjects and Methods

Subjects

Patients seen by the thromboembolism unit of the Hamilton Health Sciences Corporation (Henderson General Division), Hamilton, Ontario, between July 1995 and February 1996 and who were to initiate warfarin therapy with a target INR of 2.0 to 3.0 were eligible for this trial. Patients were excluded if they had a contraindication to warfarin or were geographically inaccessible. Consent was obtained from eligible patients who were then randomly allocated, using a computer-generated random number table, to receive either a 10- or 5-mg dose of warfarin on days 1 and 2 of the study. Subsequent doses were determined using published warfarin dosing algorithms.

Warfarin doses were taken in the evening. The anticoagulant effect of warfarin was monitored using the INR, which was measured daily on a morning blood sample. A 3-mL blood sample was drawn each day from each patient into blood collection tubes (Vacutainer, Becton-Dickson, East Rutherford, NJ) containing a 1:9 solution of 3.2% sodium citrate. The blood was then centrifuged within 4 hours of being drawn and the PT determined. Prothrombin times were performed at a number of laboratories using a variety of thromboplastin reagents. The PT was converted to an INR and the results reported to 1 of 3 study nurses who, based on the appropriate dosing nomogram, advised the patient of that day’s warfarin dose. Laboratory staff performing the INR determinations were blinded to treatment allocation; however, the nursing staff and physicians were not. Management of patients with INR values greater than 4.0 was left to the discretion of the attending physician. Patients had daily INR determinations until 1 of 3 conditions was met: (1) the patient had an INR of 2.0 to 3.0 on 2 consecutive days; or (2) the patient received phytonadione (vitamin K₁) treatment; or (3) 108 hours (4 days) had passed.

Data Analysis

Proportions, 95% confidence intervals (CIs), and relative risks (RRs) were calculated where indicated. The Fisher exact test or χ² test was used for comparison of proportions. Means were compared using the Student t test. The primary end point of the trial was the proportion of patients whose INR values never exceeded 3.0 and who had INR values between 2.0 and 3.0 on 2 consecutive daily determinations on days 3 and 4 or 4 and 5 of the study.

Statistical modeling was performed to account for patients who did not complete the required laboratory testing. For the model, all patients in the 10-mg group who did not complete the required blood testing were assumed to have achieved the primary end point, whereas patients in the 5-mg group who did not complete the required blood testing were assumed not to have achieved the primary end point (“worst-case scenario”).

Results

Fifty-three patients (28 women) were enrolled in the trial. The demographic data of the patients are presented in Table 1. Thirty-two patients were randomly allocated to receive an initial 5-mg warfarin dose, while 21 were allocated to receive the initial 10-mg warfarin dose. The difference in the sizes of the 5- and 10-mg groups was due to an underlying imbalance in the random number table used during the randomization process. During the study period, 1 patient in the 5-mg group received phytonadione for an INR value of 5.1 on day 2 of the study.

The INR values of the study population are presented in Table 2. Briefly, the proportion of patients with INR values of 2.0 to 3.0 was consistently higher at all time points in the group randomized to receive the 5-mg dose than the group randomized to receive the 10-mg dose.

Three patients in the 10-mg group and 2 patients in the 5-mg group did not complete the required blood testing. Five (24%) of 21 patients in the 10-mg group and 21 (66%) of 32 patients in the 5-mg group achieved the primary end point of the study (RR, 2.22; 95% CI, 1.30-
INR values of greater than 3.0 on day 4 of the study (RR, 1.00; 95% CI, 0.82-1.06). Additionally, 5 (24%) of 21 patients in the 10-mg group and 2 (7%) of 30 patients in the 5-mg group had INR results. Moreover, 3.70 [P < .003]). Modeling the worst-case scenario to account for the patients who did not complete the required blood testing did not alter the significance of the results. Additionally, 5 (24%) of 21 patients in the 10-mg group and 2 (7%) of 30 patients in the 5-mg group had INR values of greater than 3.0 on day 4 of the study (RR, 0.82; 95% CI, 0.63-1.06 [P = .11]).

**COMMENT**

Anticoagulant therapy is often started with a combination of unfractionated hirin or low-molecular-weight heparin and warfarin. The combination parenteral unfractionated hirin or low-molecular-weight heparin and oral warfarin therapy is continued until the antithrombotic effect of warfarin is fully expressed, and then the parenteral treatment is discontinued. There is indirect evidence from a number of sources that the antithrombotic effect of warfarin is not fully expressed until the prothrombin concentration is suppressed to therapeutic levels. This takes at least 4 days after starting warfarin treatment regardless of the warfarin dose, because prothrombin has a half-life of about 96 hours. In our previous study, we demonstrated that a warfarin protocol using a 5-mg initiating dose with further INR adjustments based on a dosing nomogram had theoretical advantages over a 10-mg loading dose. Thus, the 10-mg loading dose produced a potential hypercoagulable state in the first 3 days by markedly suppressing protein C levels and was associated with a much higher incidence of unwanted hypercoagulability as manifested by an INR greater than 3.0. In addition, we made the unexpected observation that patients assigned to the 5-mg initiation dosage protocol reached an INR value of 2.0 to 3.0 by day 4 as frequently as those assigned to the 10-mg initiation dosage protocol.

The present study, which was performed to confirm our previous finding, demonstrated once again that a warfarin dosing protocol using a 5-mg initiating dose does not delay the attainment of an INR of 2.0 to 3.0 on day 3, 4, or 5 of therapy. This finding, which at first might appear counterintuitive, is owing to the more predictable onset of anticoagulation in patients allocated to receive an initial 5-mg warfarin dose. These observations would seem to indicate that there is no good reason to use loading doses of warfarin when initiating therapy.

Our study is limited because we used a targeted INR of 2.0 to 3.0 as a surrogate outcome measure of efficacy and safety of warfarin. However, there is good evidence that an INR of less than 2.0 is associated with reduced efficacy and that an excessively prolonged INR is associated with an increased risk of bleeding. Therefore, it is likely that our findings are clinically relevant.

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**REFERENCES**