Time Course of Reversal of Anticoagulant Effect of Warfarin by Intravenous and Subcutaneous Phytonadione

Guna Raj, MD; Raminder Kumar, MD; W. Paul McKinney, MD

Background: Excessive anticoagulation increases the risk of hemorrhagic complications associated with oral anticoagulant therapy. Oral or parenteral phytonadione is used to reverse excessive anticoagulation. Intravenous (IV) phytonadione, while effective, is associated with a small risk of serious anaphylactic reactions. Subcutaneous (SC) administration is safer, but there is little information on its relative efficacy in small doses.

Methods: Twenty-two patients with asymptomatic prolongation of prothrombin time were prospectively randomized and treated with 1 mg of phytonadione IV or 1 mg SC. Prothrombin time was measured at baseline and at 8 and 24 hours after phytonadione administration and expressed as international normalized ratio (INR).

Results: Mean INR at baseline was 8.0 and 8.5 in the IV and SC groups, respectively (P = .70). At 8 hours, mean INR was 4.6 in the IV group and 8.0 in the SC group (P = .006). At 24 hours, mean INR was 3.1 in the IV group and 5.0 in the SC group (P = .009). Mean decrease in INR 8 hours after administration of phytonadione was 3.4 in the IV group and 0.4 in the SC group (P = .02), and mean decrease in INR after 24 hours was 4.9 in the IV group and 3.4 in the SC group (P = .18).

Conclusions: For patients who are excessively anticoagulated with warfarin, small doses of SC phytonadione may not correct the INR as rapidly or as effectively as when administered IV. Higher doses must be considered for more rapid and complete reversal of anticoagulation by the SC route.

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Patients taking long-term oral anticoagulant therapy with warfarin sodium require close monitoring to maintain their coagulation values within therapeutic range. However, fluctuations in the intensity of anticoagulation can be seen from time to time. In the European Atrial Fibrillation Trial, in which 214 patients had 4883 international normalized ratio (INR) measurements during an average of 2.1 years of follow-up, 56% of INR measurements were within the target range of 2.5 to 3.9; 35% were below and 9% above this range. In another study, in patients with mechanical heart valves, the INR was within target range of 3.6 to 4.8 for 61% of the total patient-time, below 3.6 for 31% of the time, and above 4.8 for 8% of the time.2

Excessive anticoagulation with marked prolongation of prothrombin time (PT) and INR above the target range increases the risk of hemorrhagic complications. Canneegieter et al reported a steep rise in the rate of adverse events, from 2 per 100 patient-years with an INR of 2.5 to 4.9 to 4.8 per 100 patient-years with an INR of 5.0 to 5.5 and 75 per 100 patient-years when the INR was 6.5 or above.3 In another study of 6814 patients, 162 major bleeding complications occurred during a 12-month period (2.7 per 100 patient-years). Every 1-point increment in INR above 4.0 resulted in a 42% increase in risk of bleeding.3

While infusion of fresh frozen plasma rapidly corrects the coagulopathy associated with excessive anticoagulation by repleting vitamin K–dependent coagulation factors, this therapy is reserved for patients who manifest bleeding, because of the cost and potential risk of infectious complications. In asymptomatic patients with markedly high INR values, excessive anticoagulation must be corrected to decrease the risk of bleeding. This can be done in 1 of 2 ways: (1) omitting a few doses of warfarin and/or decreasing the daily maintenance dose; or (2) administering phytonadione by oral or parenteral routes. There are few data on the conservative treatment of these patients by withholding and then reducing the dose.
PATIENTS AND METHODS

Patients receiving stable doses of warfarin who came to the anticoagulation clinic of the Dallas Veterans Affairs Medical Center, Dallas, Tex, with supratherapeutic PT, specifically with an INR greater than 6.0, were invited to participate in the study, which was approved by the Human Studies Committee at our institution. Eligible patients had to have been receiving oral anticoagulant therapy for at least 3 months and receiving a stable dose of warfarin for at least 6 weeks. Patients with any evidence of active bleeding (including minor bleeding, such as excessive bruising, epistaxis, hematuria, etc) or a history of allergy to vitamin K were excluded. After providing written informed consent, subjects were assigned to receive 1 mg of phytonadione (Aquamephyton, Merck & Co Inc, West Point, Pa) either SC or IV, by means of a random numbers table. Phytonadione (1 mg/0.5 mL) was administered SC without dilution or by slow IV injection over 60 seconds after dilution with 5 mL of isotonic sodium chloride solution (for a total volume of 5.5 mL). Patients were observed for 30 minutes for any adverse drug reaction. The PT was measured at 8 hours and again at 24 hours after administration of phytonadione and expressed as INR. All PT measurements were made on citrate samples by means of a thromboplastin reagent with an international sensitivity index of 2.0. Warfarin was withheld for at least 24 hours after administration of phytonadione, and longer if the INR at 24 hours was still greater than 6.0. The investigators were blinded to the treatment assignment; administration of phytonadione and follow-up visits were done by the study nurse. The INR values at baseline and 8 and 24 hours after phytonadione administration were compared between the 2 groups by repeated-measures analysis of variance using the Student-Newman-Keuls adjustment. Five tests were conducted at the .01 level of significance to achieve a .05 overall level of significance. The Fisher exact test was used to examine the association between the route of administration and achieving an INR of 5 or less at 8 and 24 hours. Odds ratios were calculated for these times as well.

Mean international normalized ratio (INR) at baseline and 8 and 24 hours after administration of phytonadione in the intravenous (IV) and subcutaneous (SC) groups. P = .70 for difference at baseline; P = .006 at 8 hours; and P = .009 at 24 hours. Mean decrease in INR from baseline for the IV and SC groups is 3.4 and 0.4 (P = .02) at 8 hours and 4.9 and 3.4 (P = .18) at 24 hours.

Twenty-two patients, 11 each in group, were enrolled in the study between May 1995 and December 1996. Indications for anticoagulation were as follows: atrial fibrillation (9 patients), prosthetic heart valve (6 patients), embolic cerebrovascular event (3 patients), recurrent deep venous thrombosis (2 patients), and coronary stent and dilated cardiomyopathy (1 patient each). The mean INR at baseline was 8.0 (range, 6.6-15.1) in the IV phytonadione group and 8.5 (range, 6.0-14.3) in the SC group (P = .7). The mean INR at 8 hours was 4.6 (range, 2.5-12.1) in the IV group and 8.0 (range, 4.2-12.5) in the SC group (P = .01). The mean INR at 24 hours was 3.1 (range, 1.5-6.1) in the IV group and 5.0 (range, 2.8-8.9) in the SC group (P = .01) (Figure and Table).

At 8 and 24 hours, the 2 routes of administration had yielded significantly different INR levels. Within the IV group, the mean decrease in INR 8 hours after administration of phytonadione was 3.4 (range, −0.4 to 12.6), and the mean decrease in INR after 24 hours was 4.9 (range, 2.0-13.6). The means at baseline and the 2
subsequent observation times were all significantly different from each other. In the SC group, the means at baseline and at 8 hours were not significantly different. However, the mean INR at 24 hours was significantly lower than at the other 2 times. Between baseline and 8 hours, the mean change was 0.4 (range, −1.7 to 3.4). Comparing baseline to the 24-hour period, the reduction in INR was 3.4 (range, 0.9-7.3). There was a more rapid decrease in the INR by the IV route than with the SC route, but it did not achieve statistical significance (Figure).

At 8 hours, 9 of 11 patients in the IV group and 1 of 11 patients in the SC group had an INR of less than 5 (odds ratio, 45; 95% confidence interval, 3.47-58.3). Fisher exact test yielded an observed significance of .002 in comparing the 2 groups at this time. At 24 hours, 9 of 11 patients in the IV group and 7 of 11 patients in the SC group had an INR of less than 5 (odds ratio, 2.57; 95% confidence interval, 0.36-18.33). Excluding patients with INR of 10 or more (2 in the IV group and 3 in the SC group) did not change the results significantly.

No adverse drug reactions were observed after administration of phytonadione in either group. No bleeding was noted in any patient during the study period.

**COMMENT**

Although there was no difference in the mean decrease in INR from baseline at 24 hours between the 2 groups, there was a statistically significant difference between the groups at 8 hours, with the IV group achieving a greater correction of INR. Furthermore, there was a significant difference in the mean INR between the 2 groups both at 8 hours (4.6 vs 8.0) and at 24 hours (3.1 vs 5.0), IV administration again resulting in a lower INR.

While it is important to correct excessive prolongation of the INR, in patients who are not bleeding, this should be done without putting the patient at risk of treatment-related complications and without causing resistance to subsequent anticoagulation. Low doses of IV phytonadione (0.5 to 1 mg) effectively reverse excessive anticoagulation within 8 to 24 hours without causing subsequent resistance to anticoagulation. However, IV administration of phytonadione can be associated with serious adverse reactions, such as anaphylaxis and death. Although it is difficult to estimate the frequency of such reactions from a review of the literature, even a small risk of such reactions is unacceptable in a patient who is asymptomatic. The anaphylactic reaction is thought to be related to the presence of polyoxyethylated castor oil in the phytonadione preparation. Although a phytonadione formulation with mixed micelles that does not contain the polyoxyethylated fatty acids has been developed (Konakion [Roche Laboratories, Nutley, NJ] and Aquamephyton), it still contains a polyoxyethylated fatty acid derivative. Perhaps because of this, the Konakion brand of phytonadione was not approved for IV injections and is no longer available in this country. Aquamephyton brand of phytonadione comes with a product insert warning that IV administration can be associated with serious reactions and should be reserved for emergency situations only. Three studies have evaluated the effectiveness of small oral doses (1-2.5 mg) of phytonadione in correcting excessive anticoagulation. Pengo et al. treated 11 patients with a mean INR of 5.82 (range, 5.26-7.5) with 2 mg of phytonadione orally while continuing the usual dose of warfarin. All 11 patients had an INR of less than 5 after 24 hours. In a retrospective study of 58 patients with an INR greater than 5, phytonadione in a dose of 2.5 mg given orally decreased the INR to less than 5 at 24 hours in 42 (72%). Crowther et al. treated 62 patients with a mean INR of 5.79 with 1 mg of oral phytonadione in a prospective cohort study. The INR decreased to a mean of 2.86 within 16 hours in 59 patients. Another study compared low-dose IV (<0.5 mg), high-dose IV (1-10 mg), 1 to 10 mg of SC, and 2.5 to 5 mg of oral phytonadione. Although all routes and doses were successful in decreasing the INR, it is difficult to draw any firm conclusions because of the variable dose and follow-up intervals in the different groups and within each group.

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*INR indicates international normalized ratio; IV, intravenous; and SC, subcutaneous.
†P = .70.
‡P < .01.
Our study shows that, although SC administration of 1 mg of phytonadione is effective in correcting excessive anticoagulation from warfarin therapy, the effect is neither as quick nor as complete as after IV administration. If the goal of therapy is to bring the INR rapidly to 5 or less, then SC administration of very small doses of phytonadione may not be very effective, since even at 24 hours, 4 of 11 patients in the SC group in our study had an INR greater than 5.

In conclusion, in patients who have excessive anticoagulation with warfarin, SC administration of very small doses of phytonadione may not correct the INR as rapidly and as effectively as IV administration. However, IV phytonadione may be associated with rare but serious anaphylactic reactions. Further studies are needed to evaluate the efficacy of slightly higher doses of phytonadione administered SC. Since this study was initiated, the Consensus Conference on Antithrombotic Therapy has revised its guidelines and recommends treating patients who have high INR without bleeding with oral phytonadione: 1 to 2.5 mg if the INR is above 5 but below 9 and a higher dose of 3 to 5 mg if the INR is above 9.19

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REFERENCES


