

Comparison of Oral vs Intravenous Phytonadione (Vitamin K₁) in Patients With Excessive Anticoagulation

A Prospective Randomized Controlled Study

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Background: Treatment of patients with excessive anticoagulation is routinely done by intravenous phytonadione (vitamin K₁). Oral administration of phytonadione has been shown to be an effective alternative to the intravenous route, but these methods have never been compared directly. Our objective was to compare efficacy and safety of intravenous vs oral phytonadione treatment in patients with excessive anticoagulation without bleeding.

Methods: The study was a prospective randomized controlled trial of consecutive patients presenting with excessive anticoagulation without major bleeding. Patients with a baseline international normalized ratio (INR) of 6 to 10 (n=44, 47 episodes) received either intravenous or oral phytonadione (0.5 mg or 2.5 mg, respectively), and patients with an INR greater than 10 (n=17, 19 episodes) received 1 mg or 5 mg, respectively. Efficacy and safety end points were sequential INR changes and the proportion of patients achieving therapeutic range (INR, 2-4), overcorrection (INR<2.0), or undercorrection (INR>4.0) INR values.

Results: Sixty-six episodes of excessive anticoagulation were studied. In patients with baseline INR 6-10 the response to intravenous phytonadione was more rapid than in the oral group, and the proportion of patients reaching therapeutic range INR at 6 hours (11/24 vs 0/23) and at 12 hours (16/24 vs 8/23) was significantly higher. However, mean±SD INR values were similar for both groups at 24 hours (2.9±0.8 vs 2.6±0.8). Patients in the intravenous group tended to be more often (7/24 vs 2/23) overcorrected (INR<2). In patients with baseline INR values greater than 10 efficacy and safety were comparable for both routes of administration.

Conclusion: Oral administration of phytonadione had similar efficacy and safety as intravenously administered phytonadione and may be suitable for treatment of patients with excessive anticoagulation.

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EXCESSIVE INTERNATIONAL normalized ratio (INR) response occurs in 0.2% to 0.3% of outpatients receiving long-term anticoagulation.¹ The risk of bleeding in such patients increases markedly when the INR exceeds 4.0 to 4.5 and depends on how long the patient has high INR values.¹⁻⁴ Since untreated, prolonged excessive INR values result in significantly more bleeding,^{5,6} lowering of the INR to the target therapeutic range is mandatory.

In the absence of bleeding (or given only minor hemorrhage), INR reduction is achieved either by withholding anticoagulation or by administration of phytonadione (vitamin K₁), classically by the intravenous route.⁷ Withholding anticoagulation in anticipation of INR return to the therapeutic range is time-consuming⁸ and exposes patients to prolonged periods of excessive bleeding risk. On the

other hand, concerns have been raised regarding possible adverse effects of intravenous phytonadione therapy, such as thrombosis or anaphylaxis.^{9,10} These concerns led to gradual reductions in the recommended phytonadione doses, with an intravenous dose of 0.5 mg proving to be sufficient in reversing anticoagulation in one study.¹¹ Oral phytonadione formulations were abandoned at first because of concerns about bioavailability¹² but have gained popularity in recent years and were proven to be very effective.¹³⁻¹⁵ In recent studies the different routes of phytonadione administration were compared for efficacy and safety. In 3 such studies¹⁶⁻¹⁸ oral and intravenous phytonadione administration were compared with subcutaneous administration or with warfarin withholding, and in the fourth study¹⁹ 4 oral preparations were prospectively compared with a single intravenous preparation. In this latter study,¹⁹ patients pro-

senting with a wide range of INR values (3.6-24.1) were given various different oral doses chosen by their individual physician, in a nonrandomized manner in 4 centers, without a predefined treatment algorithm. The authors concluded that responses to oral phytonadione were satisfactory but slower than responses to intravenous phytonadione, and that the response depended largely on the type of preparation used. In a recent study,²⁰ oral phytonadione was found to be superior to subcutaneous administration, with 58% of patients receiving the oral dose responding within 24 hours.

To better define an optimal treatment approach we conducted a prospective, randomized controlled comparison of the effects of oral vs intravenous phytonadione in patients presenting with varying degrees of excessive anticoagulation, allocated to treatment by baseline INR.

METHODS

PATIENTS

Consecutive patients treated with warfarin (irrespective of duration of treatment) and presenting with an INR of 6.0 or higher were considered for the study. Exclusion of patients was based on the following criteria: (1) presence of major bleeding or an urgent need to reverse anticoagulation; (2) known sensitivity to vitamin K products; (3) known presence of glucose-6-phosphate dehydrogenase deficiency; (4) pregnancy or lactation; (5) history of thromboembolic phenomena during anticoagulant therapy; (6) altered liver function test results (alanine aminotransferase, aspartate aminotransferase ≥ 3 times of normal) or renal failure (creatinine ≥ 2.0 mg/dL) at treatment onset; and (7) refusal to participate.

The study was approved by the institutional review board and all patients provided written informed consent.

PHYTONADIONE TREATMENT

Patients were hospitalized for 72 hours and were randomly assigned (sealed envelopes) by a physician not involved in the study to receive either oral or intravenous phytonadione. Doses of phytonadione were determined according to baseline INR at presentation: patients with INR values of 6 to 10 received either an intravenous dose of 0.5 mg or an oral dose of 2.5 mg. Patients with INR values greater than 10 received either an intravenous dose of 1.0 mg or an oral dose of 5.0 mg.

Intravenous phytonadione (Konakion, 10-mg ampoules; Roche, Basel, Switzerland) was serially diluted and a volume containing 0.5 or 1.0 mg was prepared in a 150-mL saline infusion bag and infused over 30 minutes. Blood pressure and pulse were determined before and after infusion. Oral phytonadione (2.5 or 5.0 mg) was administered as a single phytonadione tablet (Mephyton, 5.0 mg; Merck & Co, West Point, Pa). Any adverse event during phytonadione administration was recorded.

In all patients warfarin was withheld for 24 hours following phytonadione administration and resumed thereafter in all patients defined as responders.

INR SAMPLING SCHEDULE AND DETERMINATION

The INR values were determined prior to phytonadione administration and at 2, 4, 6, 12, 24, 48, and 72 hours. The time of starting the phytonadione infusion or administration of the oral tablet was considered time zero.

At each time point, 5-mL blood samples were collected in 1:10 calcium citrate-containing tubes, and INR was determined within 90 minutes of venipuncture on a coagulation analyzer (MLA Electra 1000; Medical Laboratory Automation Inc, Pleasantville, NY) using a thromboplastin with an international sensitivity index of 1.02 (Innovin; Dade, Miami, Fla), by standard methods. Blood samples for complete blood cell count and biochemistry profiles were also obtained.

EFFICACY AND SAFETY END POINTS

The INR range of 2.0 to 4.0 was predefined as the "safety zone" of treatment. The rate of INR decline; the proportions of patients reaching this zone at 6, 12, and 24 hours; and major bleeding events were considered end points for efficacy. Decline of INR level to less than 2.0, development of temporary resistance to warfarin (inability to raise the INR by at least 0.5 points with the patient's usual dose of warfarin for at least 2 consecutive days), occurrence of thrombosis, or the development of any side effect during or after phytonadione administration were considered end points for safety. Patients were followed up closely up to 28 days after hospitalization to identify occurrence of any new side effect, bleeding or thrombotic episodes, or development of resistance to warfarin.

DATA ANALYSIS

Statistical analyses were done with the SPSS 10.0 for Windows statistical package (SPSS Inc, Chicago, Ill). Change in INR values with time was done by repeated-measures analysis of variance. Between-group comparisons were done by *t* tests (or the equivalent nonparametric test) and by χ^2 or Fisher exact tests for proportions. All data are presented as mean \pm SD. A 2-sided $P \leq .05$ was considered significant.

RESULTS

PATIENTS

Between January 2000 and December 2001, 61 patients (35 men, 26 women) presenting with 66 episodes of excessive anticoagulation were studied. Baseline INR values were 6 to 10 in 47 (71%) of 66 episodes. Indications for oral anticoagulant therapy were prosthetic heart valves in 36 patients, atrial fibrillation in 16, stroke in 4, pulmonary embolism in 2, and peripheral vascular disease in 3. The target therapeutic range was 2.5 to 3.5 (intermediate-high intensity) in 39 patients and 2.0 to 3.0 (low intensity) in 22 patients, with no differences between groups with respect to age, weight, height, and mean weekly dose of warfarin. Mean weekly dose of warfarin was higher in men (46.8 ± 23.1 mg) compared with women (31.2 ± 14.3 mg) ($P = .002$). The most prevalent cause of excessive anticoagulation was drug interaction ($n = 18$), with antibiotics being the most common drug ($n = 8$). In 11 of the episodes treatment had been started within the previous month, a recent dose change was done in 4, patient error was the cause in 4, and dietary change in 2. No cause could be determined in 27 episodes. Increased menstrual bleeding in one patient and a superficial elbow hematoma in another were the only bleeding symptoms reported. All patients had normal renal function and in 2 patients mild elevations (1.5 times above normal range) of alanine aminotransferase and aspartate aminotransferase were noted. Patient characteristics are presented in **Table 1**.

Table 1. Baseline Patient Characteristics

| Characteristic | Baseline INR 6-10 | | Baseline INR >10 | | All INR Values | |
|-----------------------------------|------------------------|------------------------|---------------------------|---------------------------|-------------------------|-------------------------|
| | IV Group | PO Group | IV Group | PO Group | IV Group | PO Group |
| No. of episodes (No. of patients) | 24 (23) | 23 (21) | 10 (9) | 9 (8) | 34 (32) | 32 (29) |
| Age, mean ± SD, y | 66.6 ± 12.5 | 61.4 ± 16.4 | 53.4 ± 19.5 | 58.2 ± 19.1 | 64.3 ± 14.6 | 60.5 ± 16.7 |
| SSdose, mean ± SD, mg | 38.2 ± 17.0 | 41.8 ± 24.1 | 40.0 ± 15.3 | 43.9 ± 25.9 | 36.9 ± 16.7 | 42.4 ± 24.2 |
| Baseline INR, mean ± SD (range) | 7.6 ± 1.0 (6.2-9.3) | 7.7 ± 1.1 (6.1-9.6) | 13.2 ± 2.9 (10.7-19.4) | 13.0 ± 1.7 (10.4-15.1) | 9.2 ± 3.1 (6.2-19.4) | 9.1 ± 2.7 (6.1-15.1) |

Abbreviations: INR, international normalized ratio; IV, intravenously administered phytonadione (vitamin K₁); PO, orally administered phytonadione; SSdose, weekly steady-state dose of warfarin.

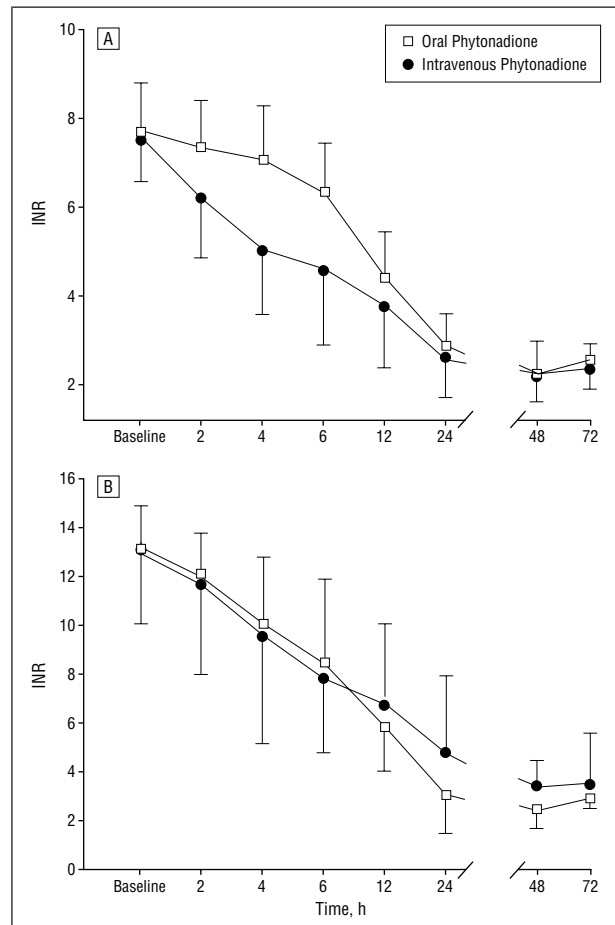
RESPONSE TO PHYTONADIONE

Responses to phytonadione treatment are presented in the **Figure**. All phytonadione doses produced significant declines in INR. In patients presenting with baseline INR 6-10 the decline was significantly more rapid in the intravenous group, reaching mean INR values of 3.8 ± 1.4 and 2.6 ± 0.8 at 12 and 24 hours, respectively. The effect of oral phytonadione first appeared after a lag period of 4 hours (INR at 4 hours was 7.1 ± 1.2) and declined rapidly afterwards, reaching a level of 4.4 ± 1.1 at 12 hours and 2.9 ± 0.8 at 24 hours, not different than that of the intravenous dose. No differences (between or within each group) were observed beyond 24 hours. In the group with baseline INR >10, mean INR values declined rapidly, reaching a nadir at 48 hours, with no further change. The INR values at the 48-hour point (3.7 ± 1.8 for the intravenous route vs 2.8 ± 1.2 for the oral phytonadione) were not significantly different.

The rate of response to phytonadione was significantly higher when it was administered intravenously in patients with baseline INR 6-10. This rate did not differ between treatments in patients with baseline INR >10. In the former group the median time to the INR range of 2 to 4 was 6 hours compared with 24 hours following the intravenous and oral administrations, respectively. The cumulative likelihood of reaching an INR of 2 to 4 is presented in **Table 2**.

Failure to respond to phytonadione (INR >4.0 at 24 hours) was observed in 6 patients overall. One failure in each group (intravenous and oral) was observed in patients with INR 6-10, and, hence, the overall failure rate was 2 (4%) of 47 in this group. In patients with INR >10, the failure rate was 4 (21%) of 19 episodes, with most failures occurring after intravenous phytonadione administration. However, in 5 of 6 patients who failed to reach an INR of 2 to 4 at 24 hours, the INR range was 4.1 to 4.6; one patient's INR at 24 hours was 7.9 and reached therapeutic values at 48 hours.

With respect to safety, INR values less than 2 (1.4-1.8) were observed in 2 patients (8.7%) with baseline INR 6-10 after oral administration of phytonadione, in contrast to 7 patients (29%) after intravenous administration (range, 1.6-1.9); however, this difference was not statistically significant (P = .16). In the group with baseline INR >10, 2 patients had INR values less than 2 after oral administration and none after intravenous administration.



Decline of international normalized ratio (INR) values in response to intravenous or oral phytonadione (vitamin K₁) treatment in patients with baseline INR of 6 to 10 (A) or INR greater than 10 (B). Data are presented as mean ± SD.

All patients resumed their usual oral anticoagulant maintenance dose at 24 hours. At 72 hours, 59 of the 61 patients were within the desired INR therapeutic range. In 2 patients who had received intravenous phytonadione, the INR values remained below 2.0 at 48 and 72 hours and they required short-term heparin therapy.

During the short-term study and over 28 days of follow-up no adverse effects were reported and none of the patients experienced bleeding or thrombotic episodes.

Table 2. Number of Episodes Reaching Prespecified Target INR Values

| Target INR | Baseline INR 6-10 | | Baseline INR >10 | |
|------------|-------------------|-------------------|-------------------|------------------|
| | IV Group (n = 24) | PO Group (n = 23) | IV Group (n = 10) | PO Group (n = 9) |
| INR 2-4 | | | | |
| 6 h | 11† | 0 | 1 | 0 |
| 12 h | 16‡ | 8 | 2 | 3 |
| 24 h | 16 | 20 | 7 | 6 |
| INR <2.0* | 7 | 2 | 0 | 2 |
| INR >4.0* | 1 | 1 | 3 | 1 |

Abbreviations: INR, international normalized ratio; IV, intravenously administered phytonadione (vitamin K₁); PO, orally administered phytonadione.

*At 24-hour time point.

†Significantly different compared with PO group, $P < .001$.

‡Significantly different compared with PO group, $P = .03$.

COMMENT

In this prospective, randomized study of patients with excessive anticoagulation, we compared the effects of oral and intravenous phytonadione as well as the impact of the degree of INR deviation from the desired therapeutic range on phytonadione dose requirements. We have shown that oral and intravenous phytonadione are comparable regarding efficacy. Both treatments exerted a significant and rapid effect on INR: decline of INR was comparable between treatments in patients with baseline INR > 10 (at all time points) and from 12 hours and longer in patients presenting with INR levels of 6 to 10. In this latter group of patients, INR declined at a slower rate and the number of patients responding adequately to treatment was also lower in the first 12 hours of treatment. Both treatments were also very similar in safety, apart from low-dose intravenous phytonadione, which was associated with an increased risk for overcorrection of INR compared with the oral treatment. Our results differ from those of Watson et al¹⁹ in that intravenous phytonadione had a more rapid effect on restoration of INR to the therapeutic range in only some of the patients (those with baseline INR 6-10). However, it is difficult to compare our results with those of that study owing to its marked heterogeneity of INR levels at presentation, the different doses and preparations of phytonadione administered, and the nonrandomized patient allocation. Interestingly, a recent prospective study by Crowther et al²⁰ found oral phytonadione to be superior to subcutaneous administration; however, conclusions regarding intravenous administration, a very common administration mode, cannot be drawn from that particular study. Compared with the 58% rate of response in that study, 20 (83%) of 24 of our patients who received oral phytonadione responded to treatment at 24 hours according to our criteria, and that figure was 17 (71%) of 24 using the criteria from Crowther et al. Possibly the higher phytonadione dose in our study (2.5 mg vs 1 mg) could be the cause for the difference in response rates.

Patients with excessive INR values are usually treated uniformly with regard to dosing of phytonadione.^{6,14,16-19} Since patients often present with a wide range of INR val-

ues, this approach may lead to failure in response on the one hand or to overcorrection of INR on the other. Indeed, one recent study demonstrated that response to phytonadione was dependent on INR at presentation.²¹ When patients in that study were categorized as severely overanticoagulated (INR > 9.5), 24-hour phytonadione treatment failure rate was 83%, whereas in mildly overanticoagulated patients (INR < 9.5) this rate was 16%. In another prospective study¹⁷ patients were allocated to receive phytonadione according to INR at presentation (below or above INR of 10). This study demonstrated that an INR-oriented dosing regimen was effective in restoring the INR to baseline levels. Nevertheless, the early effect of phytonadione could not be established since INR was measured only at 24 hours and thereafter and only a minority of patients (2 of 10) had INR > 10 and were allocated to high-dose intravenous phytonadione. Our own previous experience²² indicates that categorizing patients to moderate (INR 6-10) or highly excessive (INR > 10) values may allow more appropriate phytonadione dosing and is therefore consistent with the results of these studies. Since earlier studies^{11,14} indicated 0.5 mg of intravenous and 2.5 mg of oral phytonadione to be appropriate for most patients (with moderately excessive anticoagulation), these doses were chosen for the treatment of our patients with baseline INR 6-10, resulting in a minor failure rate of 2 of 47 (4% of episodes). In patients with baseline INR > 10, doses were empirically doubled and although failure rate was 4 of 19 (21% of episodes), only 1 patient had a significantly high INR (7.98) above the desired range, while INR values ranged from 4.1 to 4.6 in the others. Overall, in both groups, INR values at 24 hours were less than 4.7 in 64 of 66 patients (97% of episodes). Overtreatment was seen in 11 episodes, yet, in most (9/11), INR values ranged 1.8 to 1.96. In the remaining 2 patients INR was 1.43 to 1.61, and they required short-term low-molecular-weight therapy. There were no instances of hemorrhage or thrombosis. Thus, our results demonstrate the importance of allocation of phytonadione doses according to baseline INR value.

We conclude that patients with excessive anticoagulation should receive treatment according to their INR at presentation. When restoration of INR is not considered urgent, oral phytonadione is the better alternative compared with intravenous phytonadione. Since response to oral phytonadione is predictable, it may also be possible to administer phytonadione at home and avoid unnecessary hospitalization.

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