ARTICLE

Use of Oral Vitamin K_1 by Patients Taking Warfarin Sodium: Experience in an Ambulatory Care Clinic

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ABSTRACT

Background and Objective: Warfarin sodium dosing is adjusted according to the patient's international normalized ratio (INR). On occasion, the INR may be greater than 5.0, and during this time patients experience increased risk of bleeding. The use of oral vitamin K_1 has been recommended in this situation, but the tablet formulation of vitamin K_1 is not marketed in Canada. This report describes the use of vitamin K_1 (in tablet form) to reduce high INR values in patients receiving warfarin sodium.

Methods: Patients of a Canadian ambulatory care clinic were given 5-mg tablets of vitamin K_1 (phylloquinone; Mephyton, Merck Frosst Canada, Kirkland, Quebec) through special arrangement with Health Canada's Health Protection Branch. They were instructed to take the vitamin K_1, according to an agreed dose schedule, if an INR test result above 5.0 was reported. In such instances, the INR test was repeated the following day.

Results: A total of 47 INR test results above 5.0 were reported in 39 patients over a 21-month period. None of the patients reported bruising or bleeding. On 31 of these occasions, 2.5 mg of vitamin K_1 was taken, and the mean INR fell from 6.8 (range 5.1 to 8.6) to 2.9 (range 1.4 to 5.9) within 24 h. On 6 occasions, 5.0 mg of vitamin K_1 was taken, because the INR value was greater than 9.0; in these cases the mean INR fell from 11.3 (range 9.5 to 13.8) to 2.5 (range 1.8 to 3.9). Data for the remaining 10 INR results were not evaluable.

Conclusions: For ambulatory patients taking warfarin sodium, oral vitamin K_1 can be used to reduce a high INR value without the need for a clinic visit.

Key words: vitamin K_1, warfarin, ambulatory care

RÉSUMÉ

Contexte et objectif : La posologie de la warfarine sodique est ajustée en tenant compte du rapport international normalisé (INR). Or, il arrive que la valeur de l'INR soit supérieure à 5,0 ce qui, dans ces cas, augmente le risque d'hémorragie chez les patients. On a donc recommandé d'administrer de la vitamine K_1 orale dans ces cas, mais cette vitamine n'est malheureusement pas commercialisée au Canada sous forme de comprimés. Le présent rapport décrit comment les comprimés de vitamine K_1 ont été utilisés pour abaisser les valeurs élevées de l'INR chez les patients qui reçoivent de la warfarine sodique.

Méthodes : Les patients d'une clinique canadienne de soins ambulatoires ont reçu des comprimés de 5 mg de vitamine K_1 (phylloquinone ; Mephyton, Merck Frosst Canada, Kirkland (Québec)), par suite d'une entente extraordinaire avec la Direction générale de la protection de la santé de Santé Canada. On leur a expliqué qu'ils devaient prendre les comprimés de vitamine K_1 selon un schéma posologique déterminé, seulement lorsque la valeur de l'INR était supérieure à 5,0, auquel cas, on déterminait à nouveau la valeur de l'INR le lendemain.

Résultats : Sur une période de 21 mois, on a observé chez 39 patients un INR supérieur à 5,0 dans 47 cas. Aucun des patients n'a signalé d'ecchymoses ou de saignements. La vitamine K_1 a été administrée à raison de 2,5 mg dans 31 cas ; la valeur moyenne de l'INR est passée de 6,8 (fourchette de 5,1 à 8,6) à 2,9 (fourchette de 1,4 à 5,9) 24 heures après l'administration. La vitamine K_1 a été administrée à raison de 5,0 mg dans 6 cas où la valeur de l'INR était supérieure à 9,0 ; la valeur moyenne de l'INR est passée de 11,3 (fourchette de 9,5 à 13,8) à 2,5 (fourchette de 1,8 à 3,9). Les données pour les 10 autres cas n'étaient pas évaluables.

Conclusions : On peut administrer de la vitamine K_1 orale pour abaisser les valeurs élevées de l'INR chez les patients traités à la warfarine sodique, sans qu'ils n'aient besoin d'être suivis en clinique.

Mots clés : vitamine K_1, warfarine, soins ambulatoires

Can J Hosp Pharm 2003;56:82-6

INTRODUCTION

The Thrombosis Assessment and Treatment Unit (TATU) is an outpatient clinic of The Ottawa Hospital. Its primary role is to provide outpatient treatment of deep vein thrombosis and pulmonary emboli. At the time of writing, approximately 800 patients on warfarin therapy were being monitored through the clinic. Blood tests are performed at several provincially licensed laboratories across the city. Prothrombin times are measured by means of thromboplastins with international sensitivity index values of approximately 1.0 (Thromborel, Dade Behring, Mississauga, Ontario; Hemoliance, Instrumentation Laboratory, Lexington, Massachusetts), and the results are expressed as the international normalized ratio (INR). Each test result is forwarded to the TATU by fax, and the INR result, dose instructions, and next test date are reported to the patient by phone. Patients are usually asked to have their INR tests performed in the morning (before 9 AM) and to take their warfarin dose later that day, after the results of the test have been given to them.

Warfarin exerts its therapeutic effect by reducing the circulating amount of active clotting factors. It does this by competitively inhibiting vitamin K reductase enzymes. This process leads to a reduction in the amount of vitamin K available to produce gamma carboxylation of the specific coagulation cascade zymogens. The effect of warfarin can be reversed by administration of vitamin K. It is known that, for patients receiving warfarin therapy, the risk of bleeding increases at higher INR values. In large randomized trials targeting an INR of 2.0 to 3.0, the annual incidence of major bleeding was 1.3%.[1] However, Cannegieter and colleagues[2] found a 37.5-fold increase in the annual incidence of bleeding if the INR was above 6.5. Because of the increased risk of bleeding, the American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy has made recommendations for managing high INR values.[3] In the absence of bleeding, for an INR between 5.0 and 9.0, the guidelines recommend omitting 1 or 2 doses of warfarin, monitoring the INR, and resuming therapy at the same or a lower dose when the INR has fallen. Alternatively, a single dose of warfarin can be omitted, vitamin K_1 1 to 2.5 mg is administered orally, and warfarin therapy is resumed at a lower dose. For an INR of greater than 9.0 the guidelines suggest withholding warfarin, administering vitamin K_1 3 to 5 mg orally, and resuming therapy once the INR has reached therapeutic levels. In all cases, an attempt should be made to determine the reason for the high INR.

Oral administration of vitamin K_1 is an attractive option for outpatient management of high INR. The alternative involves a visit to a busy emergency department or ambulatory care unit for subcutaneous injection of vitamin K_1. However, the use of oral vitamin K_1 presents some difficulty in Canada, because an oral formulation is not marketed here. The injection formulation can be used,[4] but it may not be available or it may be difficult to administer in some situations. This report describes the authors' experience in using 5.0-mg vitamin K_1 tablets for correction of high INR values.

METHODS

Arrangements were made for the TATU to obtain a supply of 5.0-mg phylloquinone (vitamin K_1) tablets (Mephyton, Merck Frosst Canada, Kirkland, Quebec) through the Special Access Program of Health Canada's Health Protection Branch. In September 1999, each clinic patient who was receiving warfarin was given a single vitamin K_1 tablet. When a report of a high INR was received in the clinic, the patient was contacted by phone. He or she was questioned about signs of bleeding or bruising. If there was no bleeding or bruising, the patient was instructed to skip the dose of warfarin that day and to take a dose of vitamin K_1, according to the following guideline (based on published recommendations[3]). For an INR between 5.0 and 9.0 the patient was asked to take 2.5 mg of vitamin K_1 (half a tablet). For an INR greater than 9.0, the patient was asked to take 5.0 mg of vitamin K_1 (a full tablet). The patient was also instructed to have the INR measured the next morning. This INR measurement therefore occurred approximately 24 h after the high INR measurement and more than 12 h but less than 18 h after administration of vitamin K_1. If the second INR value was below 4.0, the warfarin therapy was resumed at a lower dose, and the INR was checked again in 3 to 5 days. If the INR result was 4.0 or above, subsequent warfarin doses were withheld and the INR measurement was repeated in 1 or 2 days.

RESULTS

Between September 1999 and May 2001 (21 months), the clinic was advised of 47 INR test results above 5.0. These elevated results occurred in a total of 39 patients, none of whom reported increased bruising or bleeding. Forty of the INRs were between 5.0 and

9.0, and 7 were greater then 9.0. Data for 10 of the initial INR results are not included in the tables for the following reasons: the warfarin dose had already been taken on the day the vitamin K_1 was given (3 cases), the patient was consuming excessive amounts of alcohol and the INR rose after administration of vitamin K_1 (1 case), the INR was not measured at an appropriate time (because either the vitamin K_1 dose or the INR measurement after the vitamin K_1 dose was delayed) (5 cases), or the INR measured before administration of vitamin K_1 was reported only as "greater than 8.5" (1 case). The remaining 37 elevated INR values occurred in a total of 34 patients (Table 1). The data for these 37 initial INR measurements are summarized in Table 2.

For 2 of the patients who took 2.5 mg vitamin K_1 but none of those who received 5.0 mg, the INR was greater than 4.0 at 12 to 18 h after the dose (Table 2). For the majority of patients (28 or 76%), the INR value measured after administration of vitamin K_1 fell to between 2.0 and 4.0; of these, 13 were between 3.1 and 4.0 and 15 were between 2.0 and 3.0. For 5 of the patients who received 2.5 mg of vitamin K_1 and 2 of those who received 5.0 mg, the INR was less than 2.0.

A total of 45 INR measurements were obtained in the 7 days after vitamin K_1 administration, 38 for the 31 patients who received 2.5 mg vitamin K_1 and 7 for the 6 patients who received 5.0 mg. The INR was below 1.8 for 9 (24%) of the 38 measurements in patients who received 2.5 mg vitamin K_1, but none of the patients who received 5.0 mg had an INR value below 1.8. These low INRs occurred on day 3 (1 case), day 4 (1 case), day 5 (3 cases), day 6 (3 cases) and day 7 (1 case) after administration of vitamin K_1, despite resumption of warfarin. No recurrent thrombotic events were reported in the 4 weeks after vitamin K_1 administration.

Table 1. Demographic Characteristics of 34 Patients Who Received Vitamin K_1 because of High International Normalized Ratio Values

Characteristic	Vitamin K_1 Dose; No. of Patients*	
	2.5 mg (*n* = 28)	5.0 mg (*n* = 6)
Sex ratio (male:female)	11:17	2:4
Mean age (and range), in years	60.6 (28–83)	64.0 (48–80)
Indication for warfarin		
Venous thrombosis	13	1
Venous thrombosis secondary to malignant disease	10	4
Mechanical heart valve	2	0
Antiphospholipid syndrome	2	0
Other	1	1

*Except where indicated otherwise.

DISCUSSION

Vitamin K_1 is recommended for reduction of high INR values. The optimal dose and route of administration are not known, but the available literature has been reviewed.[5] The goal of vitamin K_1 administration is to reduce the INR promptly while avoiding overcorrection and development of warfarin resistance. Prompt but modest reduction in the INR should limit the time that a patient experiences increased risk of bleeding.

Vitamin K_1 is effective when given by the IV, subcutaneous or oral route. Recent placebo-controlled studies have demonstrated the effectiveness of oral vitamin K_1 combined with temporary withholding of warfarin. Crowther and colleagues[4] used a 1-mg dose of a parenteral vitamin K_1 preparation, administered orally, to reduce INR in patients with values between 4.5 and 10.0. They enrolled 62 patients whose average age was 70.4 years. Within 16 h, the dose administered produced a drop in mean INR from 5.79 to 2.86.

Table 2. Summary of Data for 37 Elevated International Normalized Ratio (INR) Results Obtained in 34 Patients

Variable	Vitamin K_1 Dose; INR Result			
	2.5 mg (*n* = 31)		5.0 mg (*n* = 6)	
Mean INR (and range)				
Before vitamin K_1	6.8	(5.1–8.6)	11.3	(9.5–13.8)
After vitamin K_1	2.9	(1.4–5.9)	2.5	(1.8–3.9)
Mean % drop in INR (and range)	56.4	(25.3–80.0)	77.7	(68.0–85.1)
INR after vitamin K_1 (no. and % of patients)				
>4.0	2	(6)	0	(0)
3.1–4.0	12	(39)	1	(17)
2.0–3.0	12	(39)	3	(50)
<2.0	5	(16)	2	(33)

They observed no bleeding or thromboembolic complications. Seven (16%) of the patients who received vitamin K_1, but none of those who received placebo, had an INR of less than 1.8 the day after treatment. Patel and colleagues[6] compared a 2.5-mg dose (tablet) with placebo in 30 patients (mean age 66.9 years) with an INR between 6.0 and 10.0 (mean 7.1). The mean time (± standard deviation) for the INR to decline to 4.0 or less was 1.4 ± 0.5 days in the treatment group and 2.6 ± 1.5 days in the placebo group. They observed no thromboembolic complications or major bleeding. Some patients (reported as 20% patient-days) had INR values below 1.9.

Crowther and colleagues[7] also performed a randomized, controlled trial comparing oral and subcutaneous administration of vitamin K_1. They enrolled 51 patients who were receiving warfarin therapy and who had an INR between 4.5 and 10.0. Warfarin therapy was withheld, 1 mg of vitamin K_1 was given orally or subcutaneously, and the INR test was repeated the next day. The proportion of patients in whom the INR value fell to between 1.8 and 3.2 after vitamin K_1 administration was greater among those who received the agent orally (58% versus 24%). This study further supports the use of oral vitamin K_1. However, 3 patients who received vitamin K_1 orally and none of those who received the agent subcutaneously had an INR less than 1.8 the day after administration of vitamin K_1. No thromboembolic events were reported during the 1-month follow-up period.

Withholding warfarin is considered an appropriate option for patients with INR values between 5.0 and 9.0.[3] A reduction in INR of approximately 20% has been noted at 24 h.[6,8] With this approach it takes longer to lower the INR into the therapeutic range. However, no major complications have been reported, and the possibility of overcorrecting the INR is avoided. Hylek and colleagues[9] reviewed the records of 633 patients with an INR greater than 6.0. They looked for factors that might help to predict when the INR will fall slowly after temporary warfarin withdrawal. They found that a low steady-state warfarin dose, advanced age, and extreme elevation of the INR predicted a prolonged delay in the return of the INR to a therapeutic value.

In the study reported here, 5 (16%) of the 31 patients who received 2.5 mg vitamin K_1 and 2 (33%) of the 6 who received 5.0 mg had an INR of less than 2.0 the day after vitamin K_1 administration. The large percentage in the latter group is in part a reflection of the small number of patients involved. However, it does illustrate how significant the fall in INR can be after vitamin K_1 administration. In addition, low INR values were observed in some patients on the 7 days after vitamin K_1 use. This would support the practice of resuming warfarin therapy at a lower dose soon after vitamin K_1 administration.

An INR of 4.0 or less was obtained the day after an oral dose of vitamin K_1 in most of the patients in this study (35 or 95% of cases). This result is consistent with other studies that have used oral vitamin K_1.[4,6,10] The results reported here represent "real world" experience with oral vitamin K_1. It appears to be an effective treatment option in the management of high INR values associated with warfarin use. However, with this type of therapy, the INR can be lowered too far, which exposes the patient to the risk of thromboembolism. Care should be taken when selecting appropriate situations for vitamin K_1 use. Patients at high risk of bleeding would seem to be appropriate candidates for prompt INR reduction. Such patients might include those who are over 65 years of age; have a history of gastrointestinal bleeding, recent myocardial infarction, or stroke; have a hematocrit less than 30% or serum creatinine greater than 133 µmol/L; or have diabetes mellitus.[11,12] If the decision is made to use vitamin K_1 for INR values close to 5, a dose of less than 2.5 mg may prevent overcorrection. Additional studies investigating how to determine the ideal vitamin K_1 dose would be helpful. Certainly, given the widespread use of warfarin in Canada, oral formulations of vitamin K_1 should be more widely available.

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