

Reversal of Overanticoagulation with Vitamin K₁: A Plea for Oral Administration

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ABSTRACT

Objective: To evaluate the safety and efficacy of oral vitamin K₁ in reversing excessive anticoagulation and to identify barriers preventing generalized use of this compound.

Data Sources: Literature identified through searches of MEDLINE, EMBASE, and IPA (International Pharmaceutical Abstracts) databases.

Data Synthesis: To reverse overanticoagulation when the international normalized ratio remains below 20, the American College of Chest Physicians recommends oral administration of vitamin K₁ over the subcutaneous and intravenous routes of administration. However, this recommendation is not widely followed, and the subcutaneous route still predominates. Studies of oral vitamin K₁ were reviewed to reinforce the efficacy and safety of this medication.

Conclusions: Oral vitamin K₁ is effective and safe for correcting excessive anticoagulation. However, in Canada, oral tablets can only be obtained through Health Canada's Special Access Programme, which limits their use. Alternatives to tablets are presented.

Key words: vitamin K₁, oral medication, overanticoagulation, anticoagulation reversal, warfarin

RÉSUMÉ

Objectif : Évaluer l'innocuité et l'efficacité de la vitamine K₁ administrée par voie orale pour renverser une anticoagulation excessive et déterminer les obstacles qui empêchent l'utilisation généralisée de cet agent.

Sources de données : Documentation issue de recherches dans les bases de données MEDLINE, EMBASE et IPA (International Pharmaceutical Abstracts).

Synthèse des données : Pour renverser une anticoagulation excessive en présence d'un rapport international normalisé (RIN) inférieur à 20, l'*American College of Chest Physicians* recommande l'administration de vitamine K₁ par voie orale plutôt que par voie sous-cutanée ou intraveineuse. Cependant, cette recommandation n'est pas largement adoptée et l'utilisation de la voie sous-cutanée prédomine toujours. Des études sur l'administration de la vitamine K₁ par voie orale ont été analysées dans le but de confirmer l'efficacité et l'innocuité de ce médicament.

Conclusions : La vitamine K₁ administrée par voie orale permet de corriger de façon sûre et efficace une anticoagulation excessive. Cependant, au Canada, les comprimés destinés à la voie orale ne peuvent être obtenus que par le Programme d'accès spécial de Santé Canada, ce qui en limite l'utilisation. Des solutions de rechange aux comprimés sont présentées.

Mots clés : vitamine K₁, médication pour administration orale, anticoagulation excessive, renversement de l'anticoagulation, warfarine

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INTRODUCTION

Warfarin is widely used for the treatment or prevention of various thromboembolic disorders. Because of the narrow therapeutic index of this agent,¹ bleeding is a potentially serious complication that can lead to major hemorrhage and that can be life-threatening if left untreated.^{2,4} The risk of bleeding is closely related to the international normalized ratio (INR), and risk increases significantly when INR values rise above 5.0.^{2,4,6}

There are 4 ways to correct excessively prolonged INR. The first is to withhold warfarin and allow the INR to return to the therapeutic range, which usually occurs within several days. This approach is the simplest and carries a low but clinically important risk of major hemorrhage.⁷ The second method is to administer fresh frozen plasma or prothrombin complex concentrate. This method is rapid and effective, but because of the inherent risk of infection from, and allergic reactions to, blood-derived products, it should be reserved for severe cases where major bleeding is present.⁷ Although recombinant factor VIIa was successfully and safely used to reverse the toxic effects of warfarin in one small study,⁸ there have been no controlled studies comparing its outcomes, side effects, and costs with those of more traditional methods. The fourth method is to administer vitamin K₁ (phytonadione), which antagonizes the effect of warfarin by overcoming the coagulation pathways that are inhibited by coumarins.^{2,3,5,7} The American College of Chest Physicians (ACCP) has developed guidelines for the use of vitamin K₁ in managing excessive anticoagulation, which are based on the INR value and the patient's risk of bleeding.⁹⁻¹³

The optimal administration route and dose of vitamin K₁ to reverse overanticoagulation have been the subject of much debate. Reviews of major studies over the past decade have demonstrated a trend favouring oral administration of phytonadione over parenteral routes, especially when compared to the subcutaneous route for treating patients with overanticoagulation who are not bleeding.^{3,7,14} Reviews of reversal of anticoagulation by vitamin K₁ have been published,^{7,15,16} but since those reviews appeared, new data on low doses of oral vitamin K₁ in asymptomatic patients with INR greater than 10 have been published.¹⁷ This paper reviews more recent data on the safety and efficacy of oral vitamin K₁ administered for overanticoagulation and also addresses practical controversies and barriers to generalized use of this agent. Issues related to overanticoagulation, such as availability of dosage forms and practical alternatives, are considered from the Canadian perspective.

COMPARATIVE EFFICACY OF ORAL VITAMIN K₁

Major studies on vitamin K₁ for reversal of overanticoagulation published since 1993 are summarized in Table 1.^{3,6,14,17-24} Some well-structured randomized controlled trials of oral vitamin K₁ therapy have recently appeared in the literature.^{3,19,22,23} Since 1998,¹¹⁻¹³ the ACCP has recommended oral administration of vitamin K₁ for patients with an INR value greater than 5.0 but lower than 20.0, despite having recommended IV administration in 1992⁹ and the subcutaneous route in 1995.¹⁰ Furthermore, in the most recent ACCP guidelines,¹³ the suggestion to favour the oral route over the subcutaneous route for patients with mild to moderately elevated INR without major bleeding has been quoted as a grade 1A recommendation (i.e., experts are very certain that the benefits outweigh the risks, burdens, and costs; based on consistent results from randomized clinical trials). This suggests the more recent availability of stronger data supporting this recommendation.¹³

Many Canadian clinicians still use the subcutaneous route when they decide to reverse overanticoagulation with vitamin K₁. Compared with temporarily discontinuing warfarin, subcutaneous administration of vitamin K₁ leads to more rapid reversal of excessively elevated INR.¹⁸ However, administration of vitamin K₁ can potentially lead to overcorrection of the INR with repletion of the body's vitamin K stores, which might lead to resistance to warfarin. In such a state, the patient would be temporarily refractory to further warfarin treatment and would therefore be at a higher risk of thrombosis.¹⁸ Subcutaneous administration of vitamin K₁ has been associated with erratic effects^{11,14} and resistance to warfarin upon its reinstatement.²¹ Erratic effects following subcutaneous vitamin K₁ administration were observed by Crowther and others³ in a well-structured randomized study published in 2002 comparing oral and subcutaneous administration of phytonadione (vitamin K₁) in 51 patients with INR between 4.5 and 10. On the day after vitamin K₁ administration, 58% of the patients who received the oral formulation but only 24% of those who received the subcutaneous formulation had an INR between 1.8 and 3.2 ($p = 0.015$). Furthermore, 2 (7%) of the 25 patients who had received subcutaneous phytonadione (but none of the 26 who received the oral formulation) actually had an increase in INR the following day. The authors concluded that the subcutaneous route was less predictable and slower than oral administration. More studies have examined the efficacy and safety of oral vitamin K₁ to reverse overanticoagulation, and the



Table 1. Studies Evaluating the Efficacy of Subcutaneous and Oral Vitamin K₁ Administration

Study	n	Study Design	Vitamin K ₁ Regimen	Mean INR Value (before Vitamin K ₁)	Results	Reported Conclusions
<i>Subcutaneous administration only or comparison of oral and parenteral administration</i>						
Fetrow et al. (1997) ¹⁸	18	P	Group A: 1–10 mg (mean 4.9 mg) SC (n = 12) Group B: TAD (n = 6)	Group A: 12.57 ± 6.2 Group B: 7.98 ± 4.6	Mean time (h) to reach INR < 3 Group A: 31 Group B: 49.8	SC administration is an effective alternative to IV route.
Whitling et al. (1998) ¹⁴	32	Retro	Group A: LDIV (<0.5 mg) (n = 8) Group B: HDIV (1–10 mg) (n = 9) Group C: SC (1–10 mg) (n = 10) Group D: PO, formulation not specified (2.5–5 mg) (n = 6)	Group A: 11.9 Group B: 13.9 Group C: 14.9 Group D: 9.4	INR ≥ 2.0 and ≤ 5.0 by 48 h after administration Group A: 5/8 (63%) Group B: 5/9 (56%) Group C: 7/10 (70%) Group D: 5/6 (83%)	3 of 4 patients who did not reach INR < 6.0 were in Group C (SC administration). 4 of 9 patients in Group B (HDIV) had overcorrection (INR < 1.8). LDIV and PO most acceptable.
Crowther et al. (2002) ³	51	P, R	Group A: 1 mg vitamin K ₁ PO (injectable solution) + TAD (n = 26) Group B: 1 mg vitamin K ₁ SC + TAD (n = 25)	Group A: 5.8 (range 4.5–7.6) Group B: 6.2 (range 4.8–9.0)	INR 1.8–3.2 on day after treatment Group A: 15/26 (58%) Group B: 6/25 (24%) In 1-month follow-up period, no episodes of thromboembolism or bleeding in either group (OR 4.32 [95% CI 1.13–17.44])	PO administration of vitamin K ₁ reduces INR more rapidly and more predictably than SC administration in asymptomatic patients with INR 4.5–10.0.
Lubetsky et al. (2003) ¹⁹		P, R	TAD for 24 h for all patients plus: Group A (INR 6–10): vitamin K ₁ IV 0.5 mg (n = 24) Group B (INR 6–10): vitamin K ₁ PO 2.5 mg (tablets) (n = 23) Group C (INR >10): vitamin K ₁ IV 1 mg (n = 9) Group D (INR >10): vitamin K ₁ PO 5 mg (tablets) (n = 8)	Group A: 7.6 ± SD 1.0 Group B: 7.7 ± SD 1.1 Group C: 13.2 ± SD 2.9 Group D: 13.0 ± SD 1.7	INR measured at 2, 4, 6, 12, 24, 48, and 72 h <i>Efficacy</i> Fastest INR decline with IV vitamin K ₁ for baseline INR 6–10; median time to range of INR 2–4 was 6 h (IV) and 24 h (PO); comparable mean INR ± SD at 12 h (3.8 ± 1.4 [IV] vs 4.4 ± 1.1 [PO]) and 24 h (2.6 ± 0.8 [IV] vs 2.9 ± 0.8 [PO]) No difference in rate of INR decline for patients with baseline INR >10; nadir at 48 h with INR values 3.7 ± 1.8 (IV) and 2.8 ± 1.2 (PO) Failure (INR > 4 at 24 h): 4% for patients with INR 6–10 and 21% for patients with INR >10 <i>Safety (initial INR 6–10)</i> INR < 2: 2/23 (9%) vitamin K ₁ PO vs 7/24 (29%) vitamin K ₁ IV (p = 0.16) <i>Safety (initial INR >10)</i> INR < 2: 2/9 (22%) vitamin K ₁ PO vs 0/10 vitamin K ₁ IV No bleeding or thrombotic episodes at 28 days follow-up	PO and IV vitamin K ₁ are comparable in terms of efficacy and safety. When restoration of INR is not considered urgent, oral administration is preferable to IV administration. Since response to oral vitamin K ₁ is predictable, it may also be possible to administer at home and avoid unnecessary hospital admission.

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Table 1. Studies Evaluating the Efficacy of Subcutaneous and Oral Vitamin K₁ Administration – continued

Study	n	Study Design	Vitamin K ₁ Regimen	Mean INR Value (before Vitamin K ₁)	Results	Reported Conclusions
<i>Oral administration alone or compared with placebo or temporary anticoagulant discontinuation</i>						
Pengo et al. (1993) ⁶	23	P, R	Group A: TAD for 1 day (n = 12) Group B: 2 mg vitamin K ₁ PO (formulation not specified) + usual dose of warfarin (n = 11) On day 2, warfarin dose for all patients was altered according to INR	Group A: 6.14 (range 5.11–7.90) Group B: 5.82 (range 5.26–7.25)	Day 1 Group A: 7/12 had INR < 5.0 Group B: 11/11 had INR < 5.0 Day 2 Group A: 11/12 had INR < 5.0 Group B: 10/11 had INR < 5.0 Day 9 Group A: 10/12 had INR 2.0–4.5 Group B: 8/11 had INR 2.0–4.5	Most INR values were within target range after 24 h in group B but after up to 48 h in group A. All patients treated with low dose of oral vitamin K ₁ had INR within acceptable range (<5.0) after 24 h. Low-dose oral vitamin K ₁ is a convenient treatment for overanticoagulation in patients with no bleeding complications.
Weibert et al. (1997) ²⁰	81	Retro	2.5 mg PO vitamin K ₁ (formulation not specified) and TAD for 1 or 2 days	Not available; included patients with INR > 9	Decrease of INR (to less than 5.0) within 24 h in 90% of patients Regimen prevented INR from falling below 2.0 in 83% of patients Only 5 patients (6%) had INR < 1.8; none had INR < 1.5	Withholding 1 or 2 doses of warfarin and administering 2.5 mg of oral vitamin K ₁ is a rapid, safe, reliable, and inexpensive way of correcting overanticoagulation in patients with INR > 5.0 but < 10.0 without any major bleeding. No resistance to further anticoagulation.
Crowther et al. (1998) ²¹	62	O	1 mg PO vitamin K ₁ (injectable solution) + TAD	5.79 (95% CI 4.5–9.5)	Mean INR fell to 2.86 (95% CI 1.3–8.9) 16 h after vitamin K ₁ administration. INR decreased in 95% of patients. <i>Mean INR in 37 patients restarted on warfarin</i> Day 2: 2.20 (95% CI 1.93–2.47) Day 3: 2.14 (95% CI 1.85–2.44)	No warfarin resistance upon reinstatement. Oral vitamin K ₁ more convenient, less expensive, and safer than parenteral vitamin K ₁ . No adverse effects or major bleeding. Should be considered in all nonbleeding patients with INR 4.5–9.5.
Patel et al. (2000) ²²	30	P, R	TAD for all patients Group A: placebo (n = 15) Group B: 2.5 mg vitamin K ₁ PO + TAD (n = 15)	Group A: 7.0 ± SD 0.96 Group B: 7.2 ± SD 0.99	<i>Time (days) to reach INR < 4.0</i> Group A: 2.6 ± SD 1.5 Group B: 1.4 ± SD 0.5 <i>% of patient-days with INR < 1.9</i> Group A: 7% Group B: 20%	Addition of oral phytonadione reduces the time to achieve INR below 4.0 by about 1 day relative to simply withholding INR. No difference in adverse effects between groups but more overcorrection in patients receiving vitamin K ₁ .
Crowther et al. (2000) ²³	92	P, R	TAD for all patients Group A: placebo (n = 46) Group B: 1 mg vitamin K ₁ PO (injectable solution) (n = 46)	Group A: 5.9 (range 4.5–9.8) Group B: 5.4 (range 4.5–9.8)	<i>Proportion with INR 1.8–3.2 next day</i> Group A: 9/44 (20%) Group B: 25/45 (56%) <i>Proportion with INR < 1.8 next day</i> Group A: 0 Group B: 7/45 (16%) <i>Bleeding episodes within 3-mo follow-up</i> Group A: 8/44 (18%) Group B: 2/55 (4%)	1 mg oral vitamin K ₁ lowers INR value more rapidly than withholding warfarin in nonbleeding patients with INR between 4.5 and 10.0 without causing resistance.



Table 1. Studies Evaluating the Efficacy of Subcutaneous and Oral Vitamin K₁ Administration – continued

Study	n	Study Design	Vitamin K ₁ Regimen	Mean INR Value (before Vitamin K ₁)	Results	Reported Conclusions
Lewis and Wells (2003) ²⁴	39	P	TAD and vitamin K ₁ PO INR 5.0–9.0: 2.5-mg dose (n = 31) INR > 9.0: 5.0-mg dose (n = 6)	2.5 mg: 6.8 (range 5.1–8.6) 5.0 mg: 11.3 (range 9.5–13.8)	Mean INR after vitamin K ₁ (next morning, i.e., 12–18 h after dose) 2.5-mg dose: 2.9 (range 1.4–5.9) (INR < 2 in 5 patients) 5-mg dose: 2.5 (range 1.8–3.9) (INR < 2 in 2 patients)	Effective treatment option in the management of high INR values without needing a clinic visit.
Gunther et al. (2004) ¹⁷	89	O, Retro	85 patients, 89 episodes Group A: vitamin K ₁ PO 2 mg (1 mg vitamin K ₁ in 0.5 mL injectable solution diluted in fruit juice) and TAD (n = 51 episodes; 45 patients evaluable) Group B: TAD only (n = 24 episodes; 15 patients evaluable) Group C: Hospital admission for bleeding or unexplained symptoms (n = 14 patients/episodes)	INR > 10 Precise values not specified	Clinical outcome in 88 patients No thrombotic episodes Bleeding after warfarin discontinuation: 0 patients in Group A and 3 patients in Group B (p < 0.05) No difficulty with re-anticoagulation in Groups A and B or for 2 patients in Group C INR assessed in 74 patients with value available on day 3 INR > 5: 5/45 (11%) patients in Group A (2 patients restarted warfarin in error on day 2) vs 7/15 (47%) patients in Group B (p = 0.006) INR < 1.5: 6/45 (13%) in Group A vs 1/15 (7%) in Group B	Outpatient management for INR > 10 with low-dose oral vitamin K ₁ appears safe and effective. A 2-mg dose of oral vitamin K ₁ for patients with INR > 10 is adequate, and this dose may reduce the occurrence and duration of subsequent subtherapeutic INR values (relative to higher doses). Further large clinical trials are required to provide accurate estimates of risk of hemorrhage and thrombosis.

HDIV = high dose, intravenous administration, INR = international normalized ratio, LDIV = low dose, intravenous administration, O = observational, P = prospective, PO = oral administration, R = randomized, Retro = retrospective, SC = subcutaneous administration, SD = standard deviation
TAD = temporary anticoagulant discontinuation.

most recent of these are methodologically solid randomized controlled studies.^{3,19,22,23}

Oral Vitamin K₁ for Patients with INR above 4.5 but below 10

Oral administration of vitamin K₁ is now considered a well-documented, reliable, and rapid way to reverse excessive anticoagulation in patients with INR above 5 but less than 10.^{6,20-22,24} Pengo and others⁶ reported in 1993 that 2 mg of oral vitamin K₁ decreased the INR to an acceptable range (less than 5.0) more rapidly (within 24 h) than simply discontinuing warfarin (average of 48 h). In this small randomized study of patients with INR between 5.1 and 7.9, 11 patients received vitamin K₁ and 12 patients simply discontinued the warfarin. In 1998, Crowther and others²¹ studied the effect of temporarily discontinuing warfarin and administering 1 mg of oral vitamin K₁ in a larger sample (62 patients). In this prospective cohort study of patients with INR between 4.5 and 10, the injectable preparation of aqueous phytonadione was administered orally without dilution. The tolerability of this form was not mentioned, but one

of the authors has stated elsewhere¹⁵ that the intravenous solution can be diluted in orange juice to mask its unpleasant taste. Of the 62 patients, 59 (95%) achieved a lower INR 16 h after phytonadione administration. The mean INR decreased from 5.79 (95% confidence interval [CI] 4.5 to 9.5) to 2.86 (95% CI 1.3 to 8.9). Warfarin was then restarted in 37 patients. On the second and third day after administration of vitamin K₁, the mean INR values in these patients were 2.20 (95% CI 1.93 to 2.47) and 2.14 (95% CI 1.85 to 2.44), respectively. The authors concluded that this method of administration (giving 1 mg of an injectable preparation orally, with reinstatement of warfarin therapy once the INR value reached 2.0 to 3.0) was an inexpensive and convenient way to treat excessive anticoagulation, without causing warfarin resistance or increased sensitivity. Researchers led by the same author later conducted a placebo-controlled, double-blind, randomized trial²³ to further evaluate the effectiveness of 1 mg of phytonadione in asymptomatic patients with an INR between 4.5 and 10. As in their 1998 study, the 1 mg/mL vitamin K₁ preparation for parenteral injection was given orally, since the tablet form of



vitamin K₁ is not readily available in Canada. An INR between 1.8 and 3.2 was achieved the day after treatment for 25 (56%) of the 45 patients who received vitamin K₁ but only 9 (20%) of the 44 patients who received placebo. Oral vitamin K₁ corrected INR more rapidly, but overcorrection was observed in 7 (16%) of the patients who received the vitamin K₁, and these patients had an INR value of less than 1.8 the day after treatment. This might be a concern for patients at high risk of thrombosis. Temporary discontinuation of anticoagulant only might be preferable for these patients if they are not at high risk of bleeding. An interesting observation from that study²³ was that significantly fewer patients in the vitamin K₁ group reported bleeding episodes at the 3-month follow-up (4% and 18%, respectively).

Patel and others²² studied a 2.5-mg dose of oral vitamin K₁ in a randomized, double-blind, placebo-controlled trial of 30 patients. Half of the patients received the vitamin K₁. For asymptomatic patients with INR values between 6.0 and 10.0, giving vitamin K₁ plus temporary withdrawal of warfarin reduced the time to achieve therapeutic INR by approximately 1 day, relative to discontinuing warfarin alone. These authors reported no significant differences in adverse effects, such as thromboembolic episodes or bleeding, between the groups. However, they did not specify the assessment period for evaluation of these complications.

Oral Vitamin K₁ for Patients with Elevated INR (Including Patients with INR above 9)

In 1997, Weibert and others²⁰ published a case series of 81 patients who received 2.5 mg of oral vitamin K₁ in addition to omission of 1 or 2 doses of warfarin. The INR value at presentation was 9 or above in 26 (32%) of the patients and between 5.1 and 8.9 in the remainder. INR was measured at 24 or 48 h after vitamin K₁ administration and between 4 and 7 days after warfarin therapy had resumed. The oral administration of vitamin K₁ resulted in a reduction of INR to less than 5 in 73 (90%) of the patients within 24 to 48 h. This method prevented the INR from dropping below 2 in 67 (83%) of the patients; only 5 (6%) of the patients had an INR decrease to 1.8, and none had INR below 1.5. The authors concluded that this method was effective in correcting overanticoagulation without exposing patients to excessive thrombotic risk. Overcorrection of INR was less frequent in this study than in some others, but it is noteworthy that a third of the patients had an initial INR above 9, whereas most other studies of oral vitamin K₁ therapy have included only patients with INR of 5 to 9.

In 1998, Whitling and others¹⁴ published a retrospective study evaluating INR measured up to 48 h after administration of phytonadione by several routes and doses. Baseline INR values preceding administration of vitamin K₁ were between 5.7 and 37.8. Only 4 of the 33 patients did not achieve an INR less than 6.0, and 3 of these patients were in the group that received vitamin K₁ subcutaneously. Overcorrection was most frequent in the group that received high-dose (1 to 10 mg) vitamin K₁ by the IV route, with 4 of the 9 patients having an INR less than 1.8. The authors observed that it was more difficult to achieve an INR of less than 6 following subcutaneous administration (1 to 10 mg) and concluded that moderate oral (2.5 or 5 mg) or low IV (0.1 to 0.5 mg) doses were the most effective and safest ways to correct excessive anticoagulation in nonemergency situations. However, the IV route has been associated with anaphylactic reactions²⁵ and although this reaction is rare, it is an important safety consideration that could further establish the oral route as being more advantageous. These data, although having the limitations of any small retrospective study, nevertheless brought forward the superior effect of oral over subcutaneous vitamin K₁ and the frequent problem of overcorrection observed with higher doses of IV vitamin K₁. It is noteworthy, however, that the oral group and the low-dose IV group had the lowest mean initial INR (9.4 and 11.9, respectively); mean INR was 13.9 and 14.9 for the high-dose IV and subcutaneous groups, respectively. Furthermore, the 3 highest initial values of INR (21.5, 28.9, 37.8) were all in the subcutaneous group.

In a Canadian study conducted in an ambulatory anticoagulation clinic, 5-mg vitamin K₁ tablets were used to correct the INR of overanticoagulated patients.²⁴ Every patient attending the clinic was given a single 5-mg vitamin K₁ tablet to be kept in reserve. If subsequent INR monitoring showed an INR value above 5.0, staff in the clinic contacted the patient with instructions for taking the vitamin K₁: for INR between 5.0 and 9.0, patients were instructed to take half the tablet (2.5 mg) and for INR above 9.0, they were instructed to take the whole tablet (5 mg). Patients were also told to have INR checked the following day. A total of 47 INR values above 5.0 occurred in 39 patients over 21 months, but data for 10 of these results could not be assessed because of protocol violation and were excluded from analysis. An INR of 4.0 or less was obtained in 35 (95%) of the cases following administration of either 2.5 mg ($n = 31$) or 5 mg ($n = 6$) vitamin K₁. INR fell below 2 in 5 (16%) cases for patients who had taken 2.5 mg of vitamin K₁ and 2 (33%) cases for those who had taken



5 mg. In addition, there were no thrombotic events in the 4 weeks after vitamin K₁ administration, and none of the patients reported bruising or bleeding. The authors concluded that oral vitamin K₁ tablets can effectively reduce elevated INR without a visit to the clinic, but the optimal dose is still to be determined. Use of doses lower than 2.5 mg may prevent overcorrection. This study was interesting because it documented the use of vitamin K₁ in a “real- life” Canadian context and confirmed the efficacy of a moderate dose of oral vitamin K₁ to reverse anticoagulation with INR below 9. However, the small number of patients ($n = 6$) with initial INR above 9 limits the strength of the data for the higher INR category.

In 2003, Lubetsky and others¹⁹ published the first prospective randomized controlled study of oral vitamin K₁ for reversal of anticoagulation, which included patients with INR above 10. They compared oral and IV vitamin K₁ in terms of efficacy and safety. Patients with INR of 6 to 10 were given 0.5 mg of IV or 2.5 mg of oral vitamin K₁, whereas patients with INR greater than 10 received 1 mg of IV or 5 mg of oral vitamin K₁. Patients were admitted to hospital for the study and were followed closely for up to 28 days after discharge. An interesting feature was the sequential measurement of INR at 2, 4, 6, 12, 24, 48, and 72 h following vitamin K₁ administration. The response to vitamin K₁ appeared significantly faster with IV administration for patients with baseline INR between 6 and 10. The effect of oral vitamin K₁ first appeared after a lag period of 4 h. However, comparative mean INR values at 12 and 24 h were 3.8 ± 1.4 and 2.6 ± 0.8 for IV administration and 4.4 ± 1.1 and 2.9 ± 0.8 for oral administration.

The rate of INR decline did not differ between treatments in patients with baseline INR above 10. At 24 h, there was no significant difference in INR values between or within each group. Overtreatment was seen in 11 episodes (7 with IV and 4 with oral administration), yet in most cases (9/11), the INR values ranged from 1.80 to 1.96. This rigorously conducted study confirmed that IV vitamin K₁ represents a better choice when INR requires urgent reversal but that oral vitamin K₁ is an excellent alternative in other circumstances and allows avoidance of unnecessary hospital admission.

Gunther and others¹⁷ recently confirmed the efficacy and safety of 2 mg of oral vitamin K₁ in a larger sample of 51 patients with INR above 10. Although this was a retrospective quality assessment study, it included the largest sample to date of patients with INR above 10 who received oral vitamin K₁ and, as such, the study yielded valuable results. The authors reported INR decline in assessable patients (for whom an INR value was

available on day 3 after oral vitamin K₁ administration and/or warfarin discontinuation). They observed that significantly fewer patients (5/45 or 11%) who were given oral vitamin K₁ had an INR above 5 on day 3 than was the case for patients who underwent warfarin withdrawal only (7/15 or 47%) ($p = 0.006$). Overcorrection of INR (to less than 1.5) was more frequent in the oral vitamin K₁ group than in the group with warfarin discontinuation only (6/45 or 13% and 1/15 or 7%, respectively). Clinical outcome was assessed in 88 patients. No thrombotic episodes were documented for patients in the anticoagulation clinic database. No bleeding after warfarin discontinuation was observed in the vitamin K₁ group, whereas 3 bleeding episodes were noticed among the 23 patients with warfarin discontinuation only ($p < 0.05$). One bleeding episode during the hospital stay was observed in the subgroup of 14 patients admitted to hospital. No difficulty with re-anticoagulation was encountered in either outpatient group (with or without vitamin K₁), but 2 cases occurred in the hospital subgroup. These patients had received high-dose (10-mg) IV doses of vitamin K₁.

BARRIERS TO THE GENERALIZED USE OF ORAL VITAMIN K₁

Despite the latest ACCP recommendations favouring oral administration, vitamin K₁ is often administered subcutaneously to reverse excessive anticoagulation. In a 2002 survey of oral vitamin K₁ use in 53 anticoagulation clinics in the southwestern United States,²⁶ 25% of respondents reported never using oral vitamin K₁, despite the changes outlined in the 1998 ACCP recommendations. Some respondents mentioned fear of thrombosis with high-dose vitamin K₁. In addition, 34% indicated that their clinics still used subcutaneous vitamin K₁. Misconceptions about faster onset of action with subcutaneous vitamin K₁ than with oral administration might also contribute to reluctance to use oral vitamin K₁. Furthermore, this change of practice, like any other, involves significant time and educational investments.

In Canada, only 5-mg vitamin K₁ tablets are available, and they can be obtained only through Health Canada's Special Access Programme*; however, the formalities associated with requests and the availability of only one dosage form (5-mg tablets) constrain use of the oral formulation. Therefore, in Canada, vitamin K₁ is still administered subcutaneously in most cases. This

*Staff of Health Canada's Special Access Programme. Personal communications, December 2002.

approach may not be optimal, as suggested by a drug utilization review conducted at the Cité-de-la-Santé de Laval Hospital, Montréal, Quebec, in 2000.²⁷ The authors of that study observed that 87% of patients who received subcutaneous vitamin K₁ for excessive anticoagulation experienced overcorrection, even though the hospital protocol for treating excessive anticoagulation was generally followed appropriately. In the protocol, the recommended vitamin K₁ doses and intervals were comparable to the 1998 and 2001 ACCP guidelines for oral vitamin K₁ but the drug was administered subcutaneously. An observation of concern was that 50% of patients with overcorrection of INR were also considered to have a high risk of thrombosis. These data, combined with the evidence from many studies of the efficacy and reliability of oral vitamin K₁, should encourage clinicians to review protocols for the management of overanticoagulation implemented in anticoagulation clinics and hospitals where vitamin K₁ is still given subcutaneously.

One way to circumvent the limited availability of phytonadione tablets is to administer an injectable solution orally. An extensive literature search using MEDLINE, IPA (International Pharmaceutical Abstracts), and EMBASE databases and key words such as “oral vitamin K”, “phytonadione preparations”, “formulation”, and “stability” identified only one study that evaluated the formulation and stability of an oral suspension prepared with injectable phytonadione. Sewell and others²⁸ prepared a 1 mg/mL solution with injectable vitamin K₁, Cremophor EL solubilizer and stabilizer, and water for injection BP, which was then transferred into 1-mL amber syringes for oral administration to neonates as prophylaxis against early hemorrhagic disease of the newborn. This preparation has a shelf life of 6 months and could be adapted for correcting excessive anticoagulation with warfarin by using 3-mL or 5-mL syringes to accommodate the larger dose that is often needed in these situations. However, Cremophor EL (a mixture of polyethoxylated castor oils) has been associated with anaphylactoid reactions, alterations in blood viscosity, and erythrocyte aggregation,²⁸ which limits its use. Therefore, in another study, Cremophor was replaced with simple syrup to create an oral suspension.²⁹ Sterile water for injection USP can also be used. The preparation is stable at room temperature for 104 days in water or 111 days in syrup²⁹ and must be kept in an amber bottle since the injectable preparation is sensitive to light.^{29,30} This option is interesting because it is easy to compound and can be prepared ahead of time, thus eliminating the need for immediate manipulation in situations where vitamin K₁ is indicated. It could

therefore be considered for situations where anticoagulation reversal is often required or if frequent ampoule manipulation is not desired, such as in anticoagulant clinics or emergency rooms.

Single-dose syringes for administration directly into the mouth could also be prepared from the injectable solution of phytonadione if it is to be given immediately. In the 3 studies performed by Crowther and colleagues,^{3,21,23} vitamin K₁ was administered directly in its liquid form; it was drawn into an insulin syringe with a filter needle and then administered by mouth under observation.

RECOMMENDATIONS

On the basis of the extensive literature cited here, including the 1998, 2001, and 2004 ACCP recommendations, we believe that warfarin should be discontinued for 24 h or more whenever INR exceeds 5 (vitamin K₁ was administered without warfarin discontinuation in only one study⁶ of those reviewed here).

When use of vitamin K₁ is justified, anticoagulation clinics should favour oral administration of low-dose vitamin K₁ over subcutaneous administration in patients with excessively elevated INR who are not bleeding. Indeed, some studies have shown that administering vitamin K₁ orally is a faster alternative for correcting excessive anticoagulation than simply withholding warfarin. In addition, the effect is more reliable and there is less overcorrection than with the subcutaneous route. Also, warfarin resistance (after reinstatement of warfarin therapy) was not associated with oral vitamin K₁. The method of oral vitamin K₁ administration selected by each clinic should be based on the clinic's needs and preferences, since oral tablets are not readily available in some countries, including Canada, and only 5-mg tablets are marketed in the United States. Other options for administering vitamin K₁ orally include directly administering the injectable solution by mouth, diluting the injectable solution in a small amount of orange juice just before oral administration, or preparing a solution using simple syrup or sterile water with the injectable solution.

When the INR is 5 or higher but still less than 9, and there is no sign of bleeding, vitamin K₁ is optional. In that situation, the decision to administer vitamin K₁ should be based on the risk of bleeding and the assessment of thrombotic risk. Potential benefits of vitamin K₁ administration were reported by Crowther and others,²³ who observed fewer instances of minor bleeding at 3 months among patients receiving 1 mg vitamin K₁ than among those receiving placebo (4% and 17%,



respectively; $p = 0.05$). Hylek and others³¹ reported that when 2 doses of warfarin were withheld from patients whose INR was above 6.0, the INR returned to normal more slowly if the maintenance dose was lower, the patients were of older age, they had a high initial INR, or they had decompensated congestive heart failure or active cancer. These patients especially might benefit from vitamin K₁. However, if the patient is considered at high risk of thrombosis, it might be better not to administer vitamin K₁ unless the patient is also at high risk of bleeding, since overcorrection has been observed in as many as 16% of patients, even with an oral dose of vitamin K₁ as small as 1 mg.²³ In the event of overcorrection in a patient with high thrombotic risk (e.g., mitral valve replacement or acute deep vein thrombosis less than 1 month before), a low-molecular-weight heparin (LMWH) should be administered until INR returns to the

target range. LMWH would be considered if INR drops below 1.8 (if the target is 2 to 3) or if INR drops below 2 (if the target is 2.5 to 3.5). The 2004 ACCP antithrombotic guidelines¹³ recommend a dose of 1 to 2.5 mg of oral vitamin K₁ for INR of 5 or more but less than 9. Given that a 1-mg dose of vitamin K₁ led to a significant decline in INR within 24 to 48 h in 3 studies^{3,21,23} an initial 1-mg dose (with a second 1-mg dose 24 h later if the INR remains over 5) is recommended to avoid overcorrection.

When the INR is over 9 without associated bleeding, vitamin K₁ should be administered orally. The most recent ACCP antithrombotic guidelines¹³ recommend a dose of 5 to 10 mg, whereas the earlier guidelines (1998¹¹ and 2001¹²) recommended a dose of 3 to 5 mg; the reason for this change is not specified in the guidelines. The literature reviewed here supports the efficacy of

Table 2. Management of Elevated INR according to 2004 ACCP recommendations¹³

Patient's INR	Recommendations*
< 5.0 (no significant bleeding)	Lower the dose of warfarin or Omit 1 dose of warfarin, monitor more frequently, and resume warfarin at a lower dose when INR is within therapeutic level. If the INR is only minimally greater than the therapeutic range, dose reduction may not be required. (Grade 2C recommendation)
≥ 5.0 and < 9.0 (no significant bleeding)	Omit 1 or 2 doses of warfarin, monitor more frequently, and resume warfarin at a lower dose when INR is within therapeutic level or Omit 1 dose of warfarin and administer 1 to 2.5 mg vitamin K ₁ orally (especially if patient is at increased risk of bleeding) If more rapid reversal is needed because urgent surgery is required; administer up to 5 mg vitamin K ₁ orally; reduction in INR should occur within 24 h. Repeat with 1 to 2 mg vitamin K ₁ orally if INR remains high. (Grade 2C recommendation)
≥ 9.0 (no significant bleeding)	Withhold warfarin, and administer 5 to 10 mg vitamin K ₁ orally; substantial reduction in INR should occur within 24 to 48 h. Monitor more frequently and use additional vitamin K ₁ if necessary. Resume warfarin at a lower dose when INR is within therapeutic level. (Grade 2C recommendation)
Elevated, with serious bleeding	Withhold warfarin, and administer 10 mg vitamin K ₁ by slow IV infusion, at a rate not exceeding 1 mg/min. Administer fresh plasma or prothrombin complex concentrate or recombinant factor VIIa depending on urgency of the situation. Repeat vitamin K ₁ every 12 hours as needed. (Grade 1C recommendation)
Elevated, with life-threatening bleeding	Withhold warfarin. Administer prothrombin complex concentrate or recombinant factor VIIa supplemented with 10 mg vitamin K ₁ by slow IV infusion, at a rate not exceeding 1 mg/min. Repeat the procedure if necessary, depending on INR. (Grade 1C recommendation)
Additional suggestion	For patients with mild to moderately elevated INR without major bleeding, administer vitamin K ₁ orally rather than subcutaneously. (Grade 1A recommendation)

INR = international normalized ratio, ACCP = American College of Chest Physicians.

*Definitions of grades: 1 = experts are very certain that benefits do, or do not, outweigh risks, burdens, and costs; 2 = experts are less certain of the magnitude of the benefits and risks, burdens, and costs and thus are less certain of their relative impacts; A = based on consistent results from randomized clinical trials (RCTs); B = based on inconsistent results from RCTs; C+ = based on observational studies with very strong effects or secure generalizations from RCTs; C = based on observational studies.



doses from 2 to 5 mg to reduce highly elevated INR (above 9) to a safer range (below 5) within 48 to 72 h. However, overcorrection of INR was observed in a significant number of patients even with lower doses of 2 and 2.5 mg. In the opinion of the current authors, using the higher vitamin K₁ doses (5 to 10 mg) recommended in the 2004 ACCP guidelines might lead to frequent overcorrection of INR. A better approach might be to use the minimally effective dose of oral vitamin K₁ and administer a supplementary dose 24 h later if necessary. If the risk of bleeding is not very high, a 2-mg dose might be sufficient. A supplementary dose (1 mg if INR is over 4, 2 mg if INR is over 9) could be administered after 24 h. This approach is supported by the data of Gunther and others,¹⁷ who found that 40 (89%) of 45 patients with initial INR above 10 who received a 2-mg oral dose of vitamin K₁ had INR less than 5 by day 3. Even at this low dose, overcorrection (INR less than 1.5) was noted in 6 (13%) of 45 patients. For patients with a higher risk of bleeding, a higher initial dose (5 mg) of vitamin K₁ might be safer. In the absence of bleeding, the current authors would be reluctant to administer a dose higher than 5 mg.

If urgent reversal of anticoagulation is needed in the absence of bleeding, IV administration of 1 mg vitamin K₁ could be recommended. In cases of major bleeding, a total reversal of anticoagulation with a 10-mg IV dose of vitamin K₁ is recommended. Fresh plasma, prothrombin complex concentrate, or recombinant factor VIIa can also be administered, depending on the urgency of the situation. The vitamin K₁ is repeated every 12 h as needed.

The recommendations of the 2004 ACCP antithrombotic guidelines are summarized in Table 2.

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