Oral vitamin K reversed warfarin-associated coagulopathy faster than subcutaneous vitamin K

Crowther MA, Douketis JD, Schnurr T, et al. **Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial.** Ann Intern Med. 2002;137:251-4.

QUESTION

In asymptomatic patients with warfarin-associated coagulopathy, is oral vitamin K more effective than subcutaneous vitamin K?

DESIGN

Randomized (allocation concealed*), unblinded,* controlled trial with 1-month follow-up.

SETTING

2 teaching hospitals: 1 in Canada and 1 in Italy.

PATIENTS

51 patients (mean age 70 y, 53% women) who were receiving warfarin with a target international normalized ratio (INR) of 2.0 to 3.0 and presented with an INR of 4.5 to 10.0. Exclusion criteria were requirement for immediate normalization of the INR, current hemorrhage, or high risk for hemorrhage. All patients were included in the analysis.

INTERVENTION

Patients stopped receiving warfarin for ≥ 1 day and were allocated to 1 mg of vitamin K orally ($n = 26$) or subcutaneously ($n = 25$). In Canada, vitamin K1 in liquid form (phytonadione) was given both orally and subcutaneously; in Italy, phytomenadione liquid was given orally and the subcutaneous form was diluted to 1 mg/mL.

MAIN OUTCOME MEASURES

INR within the therapeutic range (between 1.8 and 3.2) the day after drug administration. Secondary outcomes were thromboembolic events or hemorrhage at 1 month.

MAIN RESULTS

Analysis was by intention to treat. The a priori sample size of 54 patients was not achieved. More patients who received oral vitamin K had an INR of 1.8 to 3.2 than did those who received subcutaneous vitamin K (Table). 3 patients who received oral vitamin K and none who received subcutaneous vitamin K had an INR < 1.8 the day after randomization. No difference was seen between the groups in Canada and Italy in the proportion of patients who achieved the therapeutic INR range. No patients had episodes of thromboembolism or hemorrhage at 1 month.

CONCLUSION

In asymptomatic patients with warfarin-associated coagulopathy, oral vitamin K was more effective than subcutaneous vitamin K in lowering the international normalized ratio to the therapeutic range.

Source of funding: No external funding.

For correspondence: Dr. M.A. Crowther, St. Joseph's Hospital, Hamilton, Ontario, Canada. E-mail crowthrm@mcmaster.ca.

*See Glossary.

Oral vs subcutaneous vitamin K in warfarin-associated coagulopathy at 1 day after drug administration†

Outcome	Oral	Subcutaneous	RBI (95% CI)	NNT (CI)
INR of 1.8 to 3.2	58%	24%	140% (18 to 431)	3 (2 to 16)

†INR = international normalized ratio. Other abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

The trial by Crowther and colleagues was small, which probably accounted for some differences between the 2 groups in their baseline characteristics. However, the only difference that might affect the response to therapy was the fact that 8% of patients in the oral vitamin K group had received warfarin for < 7 days, compared with 20% of patients in the subcutaneous group (those recently started on warfarin might be more likely to have an increasing INR). The other methodological quibble is that the mean number of hours after randomization on which the "day 1" INRs were measured was not reported—thus, readers cannot be certain that the timing of the primary outcome measure was similar in the 2 groups.

That said, it is probable that these results are valid, thus supporting the use of 1 mg of oral vitamin K for asymptomatic anticoagulated patients with an INR between 4.5 and 10.0. Although no episodes of bleeding occurred among the patients in this study, others have found a clinically important incidence of bleeding in untreated patients with high INRs (1). 3 patients in the oral vitamin K group had an INR below 1.8 on day 1. Although no thromboembolic complications occurred, more than 1 mg of oral vitamin K should not be given.

The advantage of the oral route, aside from its efficacy, is that patients do not have to come to the clinic for an injection. However, 1 mg tablets of vitamin K are not available, requiring patients to swallow 1 mg of the parenteral preparation. An informal survey in the Toronto area found that the liquid form of vitamin K is not currently available in many community pharmacies, which would require outpatients to visit their hospital or an anticoagulation clinic to receive it. Perhaps the results of this study will lead more pharmacies to stock the product.

Andreas Laupacis, MD
Institute for Clinical Evaluative Sciences
Toronto, Ontario, Canada

Reference

1. **Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE.** Prospective study of the outcomes of ambulatory patients with excessive warfarin anticoagulation. Arch Intern Med. 2000;160:1612-7.