Administration of Injectable Vitamin K Orally

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Abstract

Background: Vitamin K, or phytonadione, is available in both injectable and oral formulations. Oral vitamin K is available as 5-mg tablets, but the key drawbacks for using vitamin K tablets consist of availability of only 1 dose strength and recent tripling of the product's cost over a 2-year period. An interest exists for utilization of injectable vitamin K via oral route. **Method:** A literature search was performed on April 26, 2017, to identify any studies describing the use of injectable vitamin K for oral administration. The search involved PubMed and Embase and utilized various combinations of keywords *vitamin K*, *phytonadione*, *IV*, *intravenous*, *injectable*, and *oral*. The results were limited to studies that discussed oral administration of injectable vitamin K. The efficacy of the injectable preparation of vitamin K administered orally was explored in 6 studies and one cost-savings project. **Results:** Based on the available literature, the administration of injectable vitamin K via oral route is effective and safe. Injectable vitamin K for oral administration can be prepared as an undiluted solution or as a compounded solution. These 2 formulations have different beyond-use dates depending on ingredients used. **Conclusion:** Information on efficacy and stability of injectable vitamin K formulations prepared for oral administration provides an additional option for health care systems when vitamin K tablets are unavailable or cost-prohibitive to use.

Keywords

vitamin K, phytonadione, injectable, oral administration, stability, compounding

Background

Phytonadione, or vitamin K₁, is a water-insoluble vitamin that is indicated for the treatment of various coagulation disorders due to a lack of or a decrease in factors II, VII, IX, and X.^{1,2} The interplay of these factors in the coagulation cascade leads to formation of thrombin and then fibrin that is responsible for clot stabilization.³ Warfarin prevents production of these clotting factors by inhibiting vitamin K oxide reductase. This enzyme converts oxidized vitamin K into reduced vitamin K, which is involved in production of clotting factors II, VII, IX, and X.

Vitamin K is available in injectable and oral formulations.^{1,2,4} According to the product's labeling, vitamin K solution for injection can be administered intravenously, intramuscularly, and subcutaneously with higher preference for the subcutaneous route due to the risk of anaphylaxis with the intravenous route.^{2,3} The package insert for injectable formulation has a boxed warning describing severe anaphylaxis reactions such as shock, cardiac arrest, and respiratory arrest when vitamin K is administered intravenously. However, trials have shown that subcutaneous administration of vitamin K does not provide consistent correction of international normalized ratio (INR) when reversing warfarin effects, and administration via the intramuscular route could result in hematoma.^{3,5} The

occurrence of anaphylaxis with intravenous route is rare, and some literature suggests that newer formulation of vitamin K carries less risk for anaphylaxis.⁵ Therefore, the intravenous route is the preferred route for administration of injectable vitamin K in clinical practice.³ Vitamin K tablet, marketed under the brand name of Mephyton, is administered orally.¹ The key drawbacks for administering oral formulations of vitamin K consist of single dosage strength available on the market and cost.⁶ Oral vitamin K is available only as a 5-mg tablet.⁴ In the United States, the cost of vitamin K tablets has tripled from 2014 to 2016 due to drug availability from one manufacturer.⁷ Therefore, health-systems developed an interest in using injectable vitamin K for oral administration. This article reviews literature on oral administration of injectable vitamin K and provides recipes for preparation of oral formulations from injectable vitamin K.

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Guidelines

Numerous guidelines mention the use of vitamin K, mainly for the management of an elevated INR in patients receiving vitamin K antagonists, mainly warfarin.^{5,7,8} The guidelines from the American College of Chest Physicians (ACCP), the British Committee for Standards in Haematology (BCSH), and the Australasian Society of Thrombosis and Haemostasis (ASTH) describe indications, dosing, and route for vitamin K for reversal of warfarin effects. Only the ASTH guideline mentions that the injectable preparation of vitamin K can be administered orally.⁵ In fact, the guideline states that the injectable vitamin K administered via oral route or intravenous route is the preferred formulation when vitamin K is used for reversal of warfarin effects. The guideline does not provide any additional information regarding preparation of injectable vitamin K for oral administration or outcomes with the use of injectable formulation orally.

Literature Review

A literature search was performed on April 26, 2017, to identify any studies describing the use of injectable vitamin K for oral administration. The search involved PubMed and Embase and utilized various combinations of keywords *vitamin K*, *phytonadione*, *IV*, *intravenous*, *injectable*, and *oral*. The results were limited to studies that discussed oral administration of injectable vitamin K. The efficacy of the injectable preparation of vitamin K administered orally has been evaluated in 6 studies.⁹⁻¹⁴ The transition to utilize injectable vitamin K orally was described in one health-system's cost-saving project.⁷

In 1998, Crowther and colleagues explored whether administering injectable vitamin K 1 mg orally would reverse INR.⁹ A prospective cohort study was completed at 2 tertiary teaching hospitals in Canada and enrolled 62 patients on warfarin therapy with INR ranging between 4.5 and 10. At the time of the study, the tablet formulation of vitamin K was not available in Canada, and thus, the protocol required oral administration of injectable vitamin K. An insulin syringe with a filter needle was used to draw up 1 mg of vitamin K, which was then administered orally. The mean INR was 5.79 at baseline. The mean INR was at 2.86 (range, 1.3-8.9) when levels were measured 16 hours postdose, and 2.2 on day 2 and 2.14 on day 3. Patients did not experience any adverse events or bleeding complications.

A double-blind, randomized controlled study by Crowther and colleagues from 2000 focused on the efficacy of low-dose injectable vitamin K administered orally for reversal of INR.¹⁰ The study included 89 patients receiving warfarin who presented with INRs between 4.5 and 10.0. Participants were randomized to receive either placebo (n = 44) or injectable vitamin K 1 mg given orally (n = 45). On the day following treatment administration, 56% of patients in the vitamin K group and 20% of patients in the placebo group

had INRs between 1.8 and 3.2 (odds ratio [OR], 0.21; 95% confidence interval [CI], 0.07-0.57; $P = .001$). Overall, a lower rate of bleeding was reported with vitamin K as compared with placebo by the end of the third month (OR, 0.187; 95% CI, 0.019-0.999, $P = .0499$). Two patients developed thrombotic events during follow-up period: a myocardial infarction 3 days following administration of vitamin K and a deep venous thrombosis 22 days following administration of placebo. The authors concluded that low-dose injectable vitamin K administered orally is effective for reducing INR values of 4.5 to 10.0.

In 2002, Crowther conducted a multicenter, open-label, randomized controlled trial with the objective to determine whether oral vitamin K was more effective than subcutaneous vitamin K for reversing INR.¹¹ The study was conducted at 2 teaching hospitals in Canada and Italy. The inclusion and exclusion criteria were similar to the above-mentioned studies. Patients taking warfarin and presenting with INR between 4.5 and 10 were randomly assigned to receive 1 mg of vitamin K either orally or subcutaneously. In Canada, injectable vitamin K was used for both oral and subcutaneous administration, and in Italy, patients were given a commercially available 1 mg/mL oral solution of vitamin K. The trial enrolled 51 patients: 36 from Canada and 15 from Italy. At baseline, mean INR was 5.8 in the oral vitamin K group and 6.2 in the subcutaneous vitamin K group. Following vitamin K administration, 58% of patients receiving oral vitamin K and 24% of patients receiving subcutaneous vitamin K had INRs between 1.8 and 3.2 (OR, 4.32; 95% CI, 1.13-17.44, $P = .015$). Patients did not report thromboembolism or bleeding events. The authors concluded that oral vitamin K might be more effective than subcutaneous vitamin K for reversing INRs between 4.5 and 10. The majority of enrolled patients were from Canada, where injectable vitamin K was administered orally during the study.

A retrospective analysis by Baker and colleagues in 2006 employed a protocol in which injectable vitamin K was administered orally according to the following regimen: For an INR >8 but <12, patients received 2.5 mg, and 5 mg was administered for an INR ≥ 12 .¹² Vitamin K was prepared as a 2 mg/mL oral liquid from injectable vitamin K by the pharmacy. After vitamin K administration, INR measurements were performed on day 1 (morning after vitamin K administration). The analysis included 223 patients, who were divided into 3 groups based on the initial INR value: 8.0 to 11.9 (n = 166), 12.0 to 20.0 (n = 36), and >20.0 (n = 21). On presentation, median INR for the first group was 9.2 and fell to 3.8 roughly 14 hours following the administration of vitamin K. About 77% of patients had measured INRs between 2.0 and 4.9 on day 1, and 12 patients were subtherapeutic with INRs between 1.5 to 1.9. The 36 patients presenting with INRs between 12.0 and 20.0 experienced decreases in INR to a median of 3.0 on day 1. About 52% of patients had INRs between 2.0 and 4.9, 17% were subtherapeutic with INR <2, and 9% of patients had INR values that remained

Table 1. Key Information on Stability and Consideration for Administering Injectable Vitamin K Orally.^{6,7,9,15-19}

Preparation method	Stability	Key considerations
Undiluted injectable vitamin K administered orally	<ul style="list-style-type: none"> Stable for 30 days at both room and refrigerated temperatures when protected from light. 	<ul style="list-style-type: none"> A filter needle may be used for withdrawal of vitamin K from the vial. Orange juice can mask the unpleasant taste of undiluted vitamin K.
Compounded 1 mg/mL oral solution utilizing injectable vitamin K Basic recipe: <i>Injectable vitamin K 100 mg</i> <i>Cremophor EL 2.0 g</i> <i>Water for injection added to 100 mL</i>	<ul style="list-style-type: none"> The solution must be stored in amber containers to protect from light. Stable for 6 months when refrigerated (4°C to 6°C) if prepared with Cremophor EL. Stable for 111 days at room temperature if prepared with simple syrup. Stable for 104 days at room temperature if prepared with sterile water for injection. 	<ul style="list-style-type: none"> Cremophor EL has been associated with anaphylactoid reactions, changes in blood viscosity, and erythrocyte aggregation.

between 8.0 and 11.9 on day 1. In the third group (INR readings >20), 44% had measured INR values between 2.0 and 4.9, 29% had INRs <1.9, and 10% of patients had INRs that remained between 8.0 and 11.9 on day 1 following vitamin K administration. The authors concluded that the oral administration of injectable vitamin K provides safe and predictable reversal of anticoagulation.

A study by Watson and colleagues published in 2001 compared the effects of 3 formulations of vitamin K available in the United Kingdom on reversal of INR.¹³ The study enrolled 64 patients receiving warfarin with supratherapeutic INRs; INRs were not limited to a specific range. Patients were randomized to receive Orakay 1-mg oral capsule, Menadiol 5-mg oral tablet, and Konakion 2 mg and 5 mg. Konakion was an injectable colloidal formulation of vitamin K that was administered orally. In addition, 12 patients received Konakion 2 mg intravenously. Although the study was not randomized, authors noticed that oral administration of Konakion had trends for more effective reversal of over-anticoagulation with 75% to 93% of patients reaching INR less than 4 at 24 hours depending on the dose used. However, 33% to 73% had subtherapeutic INR at less than 2, depending on the dose used. The effects of Orakay and Menadiol were unpredictable, and at least 50% of patients in each group had INR greater than 4 at 24 hours.

A double-blinded, randomized, placebo-controlled study in 20 patients in Venezuela compared administration of injectable vitamin K 1.25 mg orally versus withholding warfarin in patients with INR ranging between 6 and 10.¹⁴ At 24 hours, INR fell below 3.5 in 70% of patients in the vitamin K group compared with 20% of patients in the group withholding warfarin. Adverse events were not observed at 24 hours. The authors concluded that oral administration of injectable vitamin K is safe and effective. The article is only available in Spanish while abstract has an English translation.

Finally, a letter was published describing a health-system's cost-saving project focusing on injectable vitamin K.⁷ The University of Michigan Health System recently implemented administration of injectable vitamin K orally due to

increasing cost of vitamin K tablets. The organization dilutes the injectable vitamin K 10 mg/mL with sterile water for injection to form vitamin K 1 mg/mL oral solution. The product is stored in amber glass bottles with beyond-use date of 104 days at room temperature. Sandoz Canada provided the information for beyond-use dating. The individual doses are prepared by drawing up the solution into amber plastic oral syringes, which can be stored up to 24 h at room temperature.

Preparation of Injectable Vitamin K for Oral Administration

Injectable vitamin K can be administered orally either as an undiluted solution or as a compounded solution. Table 1 provides the summary of key information and considerations for stability and preparation of these 2 formulations.

Direct Administration of Injectable Vitamin K by Oral Route

Injectable vitamin K can be directly administered via the oral route. A study by Crowther and colleagues in 1998 used an insulin syringe with a filter needle to withdraw vitamin K from the vial.⁹ The taste of undiluted vitamin K can be unpleasant, and mixing it with orange juice can mask this taste.¹⁵

Wong and Ho evaluated the stability of injectable vitamin K 2 mg/mL repackaged as 0.75 mL into amber glass bottles and white polyethylene plastic bottles for oral administration.^{16,17} The solutions were stored at room temperatures ranging from 25°C to 32°C and refrigerated temperatures of 4°C to 8°C for 30 days. Samples stored at room temperature were exposed to daylight and fluorescent light. Less than 10% of vitamin K was lost when stored in amber bottles at both temperatures. Similarly, vitamin K stored in white polyethylene plastic bottles at refrigerated temperatures and protected from light showed less than 10% loss over 30 days. On the contrary, vitamin K stored in white plastic bottles at room temperature and exposed to light experienced greater than 10% medication loss

by 40 hours.¹⁶ Vitamin K is light sensitive and needs to be protected from light.

Compounding of Oral Solution From Injectable Vitamin K

Injectable vitamin K can also be compounded into a solution for oral use.^{16,18} Sewell and Palmer studied stability of vitamin K 1 mg/mL oral solution prepared with Cremophor EL.¹⁸ Cremophor EL is a mixture of polyethoxylated castor oils that serves as a solubilizer and stabilizer for compounds. The recipe consists of combining 100 mg of injectable vitamin K with 2 g of Cremophor EL. The mixture is further diluted with water for injection to a final volume of 100 mL. The solution needs to be sparged with nitrogen for 3 minutes and then passed through a 0.2- μ m filter. The final solution is transferred to 1-mL amber syringes for oral administration. The authors concluded that the solution has a shelf life of 6 months when stored at 4°C to 6°C as no loss of vitamin K and no microbial contamination was noted for 25 weeks.

Cremophor EL has been previously associated with various undesirable reactions such as anaphylactoid reactions, changes in blood viscosity, and erythrocyte aggregation.¹⁸ Therefore, one study used simple syrup or water for injection instead of Cremophor EL.^{6,19} The authors concluded that the suspension prepared with syrup can be stored for 111 days and the suspension with water for injection for 104 days at room temperature as long as both suspensions are packaged in amber bottles. This Canadian study was published in French, and the original reference is not cataloged in PubMed. Thus, the results of this study need to be carefully interpreted as no access to the original article is available, and methods of the study cannot be properly evaluated. However, the University of Michigan Health System confirmed the listed beyond-use dating for compounding with simple syrup or sterile water with Sandoz Canada.⁷

USP 795 Guidelines

The United States Pharmacopeia (USP) recommendations for nonsterile compounding, USP 795, include statements regarding beyond-use dating.²⁰ The USP 795 guideline states, Oral formulations containing water should have beyond-use dating of 14 days at refrigerated temperatures. If oral solutions do not contain water, the beyond-use dating can be extended to 6 months or to the expiration date of individual ingredients, whichever is earlier. Per USP 795, the recommended beyond-use dates only apply to products without available stability information.

Conclusion

Previous studies have shown that intravenous vitamin K is well tolerated when administered orally and works quickly

to correct supratherapeutic INRs. Injectable vitamin K can be given orally using the undiluted injectable formulation or compounded into an oral solution. The stability of undiluted injectable formulation is limited to 30 days while compounded oral solutions have longer stability depending on the recipe used. Because recipes have stability information, the more restrictive USP 795 guidelines would not apply to these formulations. Information on efficacy and stability of injectable vitamin K formulations prepared for oral administration provides an additional option for health care systems when vitamin K tablets are unavailable or cost-prohibitive to use.

Author's Note

Some elements of this article appear on the University of Illinois Drug Information Group website: <https://pharmacy.uic.edu/departments/pharmacy-practice/centers-and-sections/drug-information-group/2014/2015-faqs/nov-2015-faqs>. These elements have been written by the same author—Janna Afanasjeva.

Declaration of Conflicting Interests

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