

Phytonadione (Vitamin K1)

Phytonadione (Vitamin K1) is an antidote to Vitamin K antagonists, such as warfarin. There are also warfarin-like compounds used as long acting anticoagulant rodenticides (LAARs), including brodifacoum, bromadiolone, and diphacinone. When supratherapeutic or toxic levels of warfarin or LAARs are attained, deficiencies in Vitamin K occur, which results in a lack of active clotting factors and therefore an increased risk of severe bleeding events.

Indications/Mechanism: Phytonadione is given as an antidote when there is evidence of over-anticoagulation (elevated INR) requiring intervention. Phytonadione supplements the patient with exogenous Vitamin K that is now able to be reduced and incorporated into clotting factors to promote clotting and reduce the risk of bleeding. Vitamin K3, another commercially available preparation known as menadione, is ineffective and should not be used. Vitamin K3 lacks the phytyl side chain of the parent Vitamin K compound, and this compromises the potency and efficacy in reversing coagulopathies caused by warfarin.

Dosing: The oral route for Vitamin K1 administration is preferred. Vitamin K1 may be administered IM, IV, and SC; however, the IM and IV routes have been associated with anaphylactic reactions and skin lesions, and the SC route has erratic absorption.

Dosing in adults and in children who require anticoagulation (taken from *Chest* 2008; 133(6 suppl): 160S-198S):

- **INR <5 and no significant bleeding:** Vitamin K1 not indicated.
- **INR >5 but <9 with no significant bleeding:** Omit next 1 or 2 warfarin doses, monitor INR more frequently, and resume warfarin at a lower dose when INR is in the therapeutic range. Alternatively, give phytonadione 1.25-2.5 mg PO. If more rapid reversal is required because the patient requires urgent surgery, give vitamin K1 at a maximum of 5 mg PO and repeat INR in 24 hrs.
- **INR ≥ 9 with no significant bleeding:** Hold warfarin for several doses and give 2.5 to 5 mg of Phytonadione. If INR is not sufficiently reduced in 24 hrs, use additional phytonadione as necessary.
- **Significant bleeding at any INR elevation:** Hold warfarin therapy and give 10 mg Vitamin K1 by slow IV infusion and/or fresh frozen plasma IV prn and/or prothrombin complex concentrate IV prn and/or intravenous recombinant factor VIIa prn. Phytonadione can be repeated every 12 hrs.

Dosing in adults and children who ingest warfarin and do not require anticoagulation:

Vitamin K1 is reserved for patients not requiring anticoagulation with known ingestions of warfarin if they have elevated INR's. In such cases, 1 to 5 mg orally (child) or 10 mg orally (adult) of Vitamin K1 is administered until the INR is < 2 or close to normal. Vitamin K1 may be used parenterally if there is active bleeding. Prophylactic doses of Vitamin K1 may occasionally be given to patients not requiring anticoagulation with known ingestions of warfarin. Single acute ingestions do not commonly result in significant coagulopathies in patients not on chronic warfarin, so prophylactic administration is usually not warranted.

Phytonadione (continued)

Dosing for long acting anticoagulant rodenticide poisoning:

Vitamin K1 should not be administered prophylactically to asymptomatic patients with LAAR overdose. One or two doses of Vitamin K1 will not be effective to treat a coagulopathy that will persist for weeks. It will also cause a delay in the onset of INR abnormality which may impair the clinician's ability to diagnose the problem. The only data on management of LAAR poisoning is generated from case reports. Some cases have required doses of 50 to 250 mg of Vitamin K daily for weeks to months. Initial management of LAAR overdose with an elevated INR can be attempted with 25 to 50 mg of Vitamin K1 three to four times daily for the first one to two days. The INR should be monitored frequently at first and then every 1-2 weeks when INR approaches normal. Vitamin K dose is adjusted as needed and titrated downward when the INR is <2.

Administration:

Oral Vitamin K1 is available as Mephyton[®] in 5 mg tablets. Although the preferred route is oral, Vitamin K1 is also available for IV, IM, and SC administration as AquaMEPHYTON[®] and phytonadione injection emulsion in 2 mg/mL and 10 mg/mL concentrations. The preparation should be diluted with preservative-free 5% dextrose, 0.9% NaCl, or 5% dextrose in 0.9% NaCl, and administered slowly, at a rate not to exceed 1 mg/min in adults to avoid risk of anaphylaxis. Parenteral administration should be reserved for cases of life-threatening bleeding.

Contraindications: Hypersensitivity to phytonadione products

Adverse Effects: Oral Vitamin K1 is well-tolerated with no reports of adverse effects. IV and IM phytonadione administration have led to anaphylaxis and respiratory and cardiac arrest even when the drug has been diluted and rapid infusion has been avoided.

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For more on phytonadione:

- Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE. *Goldfrank's Toxicologic Emergencies. 9th Edition. New York: McGraw Hill; 2011. 1940 p.*
- Ansell J, Hirsch J, Hylek E, Jacobson A, Crowther M, Palareti G. *Pharmacology and Management of the Vitamin K Antagonists: American College of CHEST Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest [Internet]. 2008 [Cited 2010 Oct 10]; 133:160S-198S. Available from: http://chestjournal.chestpubs.org/content/133/6_suppl/160S.full.pdf+html.*

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