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Vitamin K

Updated: May 9, 2016.

OVERVIEW

Introduction

Vitamin K is an essential fat soluble vitamin that is important in maintaining normal coagulation, serving as a cofactor in the activation of several clotting factors and anticoagulant proteins. There is no evidence that vitamin K supplementation, in physiologic or even higher doses, causes serum enzyme elevations, liver injury or jaundice.

Background

Vitamin K is a fat soluble vitamin that exists in two natural forms: phytonadione (K1: fye toe" na dye' one) which is derived from plant sources and menadione (K2: men" a dye' one) which is derived from bacterial sources. Vitamin K is a cofactor in the photosynthetic electron-transport system in green plants, which are the major dietary source of vitamin K for humans. High levels of vitamin K1 are found in leafy green vegetables while vitamin K2 is found in meat, milk and butter. In humans, vitamin K is an essential cofactor in the gamma-carboxylation of glutamate residues of several clotting factors and anticoagulant proteins. The gamma-carboxylation activates these factors and allows for their interactions with calcium and membrane phospholipids, essential for the coagulation cascade. Dietary deficiency of vitamin K is rare; the usual causes of deficiency being malabsorption or pharmacologic inhibition. The body stores of vitamin K are not high and its absorption is highly dependent upon bile. For these reasons, patients with cholestatic liver disease, cirrhosis and small bowel malabsorption may develop vitamin K deficiency. In addition, warfarin and other coumadin derivatives are potent anticoagulants that act by blocking vitamin K-dependent gamma-carboxylation of clotting factors. High doses of vitamin K can reverse these effects. Vitamin K is also used to treat hemorrhagic disease of the newborn, although the role of vitamin K in this syndrome is not completely clear. Finally, vitamin K may also play a role in prevention of osteoporosis, although its efficacy in restoring bone density has not been shown. The human requirement for vitamin K has not been defined precisely, but the recommended daily adequate intake for adults is 120 µg for men and 90 µg for women. Vitamin K is available over-the-counter in multiple forms, including tablets, capsules and oral solutions and is also found in many multivitamin preparations (in typical concentrations of 30 to 80 µg). Parenteral formulations are available by prescription and are used to treat severe vitamin K deficiency particularly in the face of active bleeding, either as phytonadione (also known as phylloquinone) or menadione (also known as menaquinone) generically or under brand names including Aquamephyton, Konakion and Mephyton. Vitamin K is also given routinely to newborns to treat or prevent hemorrhagic disease of the newborn. The parenteral formulations should be given subcutaneously as intravenous administration has been associated with anaphylactic-like reactions.

Hepatotoxicity

Neither normal nor excessively high doses of vitamin K have associated with adverse events, ALT elevations or clinically apparent liver injury.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

It is not clear how vitamin K might cause liver injury. Vitamin K is taken up and stored in the liver, but does not undergo metabolism by the liver cytochrome P450 system.

Drug Class: Vitamins

Other Drugs in the Class: Vitamin A, Vitamin B, Vitamin C, Vitamin D, Vitamin E, Folate, Niacin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Vitamin K – Generic, Aquamephyton®

DRUG CLASS

Vitamins

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

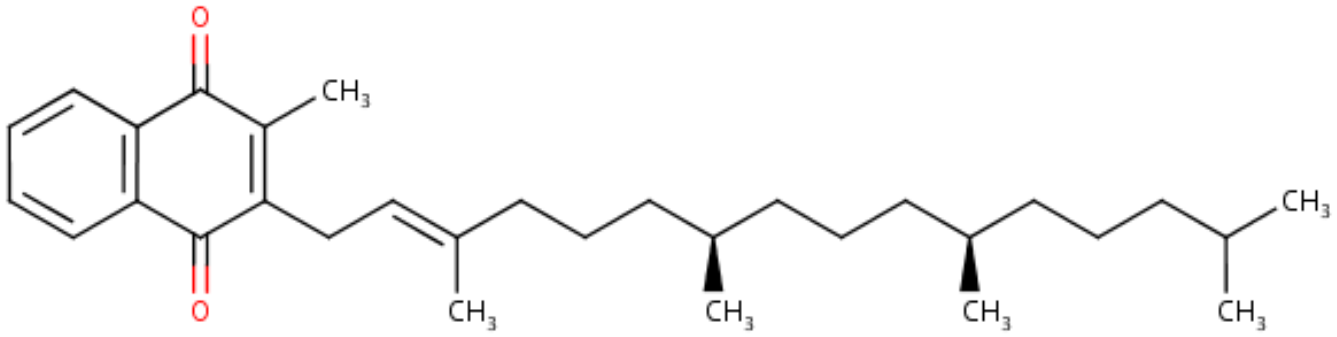
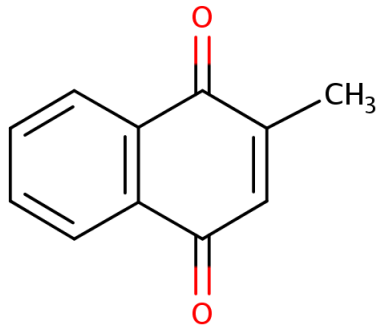
DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Phytonadione	84-80-0	C31-H46-O2	

Table continued from previous page.

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Menadione	58-27-5	C11-H8-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 09 May 2016

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Expert review of hepatotoxicity published in 1999; does not discuss vitamin K as a hepatotoxin).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013: pp, 631-57.

(Review of hepatotoxicity of dietary supplements, does not discuss vitamins and minerals).

Weitz JI. Blood coagulation and anticoagulation, fibrinolytic and antiplatelet drugs. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 849-76.

(Textbook of pharmacology and therapeutics).

Olson RE. Vitamin K. In, Shils ME, Olson JA, Shike M, Ross AC, eds. Modern nutrition in health and disease. 9th ed. Baltimore: Williams & Wilkins, 1998; pp 363-80.

(Textbook of nutrition).

Food and Nutrition Board, Institute of Medicine. DRI dietary reference intakes for vitamin A, vitamin K, arsenic, boron, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington DC: National Academy Press, 1998.

(Reports from the Food and Nutrition Board of the Institute of Medicine on reference values for vitamin intake, replacing the previously published Recommended Dietary Allowances).

https://ods.od.nih.gov/factsheets/list-all/VitaminK/.

(Fact sheet on vitamin K maintained and regularly updated by the Office of Dietary Supplements, National Institutes of Health).

(Fact sheet on vitamin K maintained and regularly updated by the Office of Dietary Supplements, National Institutes of Health).

Shearer MJ. Vitamin K. Lancet. 1995 Jan 28; 345 (8944): 229-34. PubMed PMID: 7823718.

(Review of the structure, mechanism of action, dietary sources, pharmacokinetics, metabolism and uses of vitamin K; no discussion of adverse events or mention of hepatotoxicity).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, including 7 cases due to niacin, but none were attributed to other vitamins such as vitamin K).

Booth S. Vitamin K: food composition and dietary intakes. Food Nutr Res 2012; 56. PubMed PMID: 22489217.

(Summary of the dietary sources of vitamin K, average intakes and differences in absorption and utilization of different vitamin K molecules).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-1352. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 7 were attributed to niacin, but none were attributed to any other vitamin including vitamin K).