Vitamin K and Blood Improvement

J Perinat Med. 2006;34(2):173-6.

Maternal antenatal administration of vitamin K1 results in increasing the activities of vitamin K-dependent coagulation factors in umbilical blood and in decreasing the incidence rate of periventricular-intraventricular hemorrhage in premature infants.

Liu J, **Wang Q**, **Gao F**, **He JW**, **Zhao JH**.

Department of Neonatology, Beijing Obstetrics and Gynecology Hospital, Affiliated to Capital University of Medical Science, China. liuzhuokun@hotmail.com

AIMS: Infants less than 35 weeks' gestation age are susceptible to periventricular-intraventricular hemorrhage (PIVH). This may be partially attributable to low concentrations of vitamin K-dependent coagulation factors. The purposes of this study were: (1) to determine the umbilical blood activity levels of vitamin K-dependent coagulation factors II, VII, IX and X; (2) to investigate the change in activities of these factors in premature infants' umbilical blood after prenatal administration of vitamin K1 to the mothers; and (3) to study the prophylactic effects on PIVH after maternal antenatal supplemental vitamin K1. METHODS: Pregnant women in preterm labor at less than 35 weeks of gestation were randomly selected to receive antenatal vitamin K1 10 mg per day injection intramuscularly or intravenously for 2-7 days (vitamin K1 group, n = 40), or no such treatment (control group, n = 50). At the same period, cord blood samples were collected from thirty full-term neonates to compare the factor levels with those of premature infants. Intracranial ultrasound was performed by the same sonographer to determine the presence and severity of PIVH. RESULTS: The activities of vitamin K-dependent coagulation factors in umbilical blood in the control group were: factor II 25.64+/-9.49%, factor VII 59.00+/-17.66%, factor IX 24.67+/-8.88%, and factor X 30.16+/-5.02%. In full-term infants, the respective values were: factor II 36.70+/-4.88%, factor VII 64.54+/-10.62%, factor IX 30.18+/-5.69%, and factor X 34.32+/-12.63%. In vitamin K1 group these factors were: factor II 36.35+/-6.88%, factor VII 69.59+/-16.55%, factor IX 25.71+/-10.88%, and factor X 39.26+/-8.02%. The data suggest the absence of vitamin K-dependent coagulation factors in preterm infants, and antenatal supplement of vitamin K1 may increase the cord blood activity of factor II, VII and factor X ($P < 0.001$). In addition, the overall rates of PIVH in the vitamin K1 group and in controls were 32.4 and 52.0%, respectively ($P = 0.036$), and the frequency of severe PIVH was 5.0 and 20.0%, respectively ($P = 0.038$). CONCLUSIONS: Administration of vitamin K1 to pregnant women at less than 35 weeks' gestation age may result in improved coagulation and may reduce the incidence as well as the severity degree of PIVH.

PMID: 16519625 [PubMed - indexed for MEDLINE]

Eur J Nutr. 2004 Dec;43(6):325-35. Epub 2004 Feb 5.

Beyond deficiency: potential benefits of increased intakes of vitamin K for bone and vascular health.

Vermeer C, **Shearer MJ**, **Zittermann A**, **Bolton-Smith C**, **Szulc P**, **Hodges S**, **Walter P**, **Rambeck W**, **Stöcklin E**, **Weber P**.

Dept. of Biochemistry, University of Maastricht, P. O. Box 616, 6200 MD Maastricht, The Netherlands. c.vermeer@bioch.unimaas.nl

Vitamin K is well known for its role in the synthesis of a number of blood coagulation factors. During recent years vitamin K-dependent proteins were discovered to be of vital importance for bone and vascular health. Recommendations for dietary vitamin K intake have been made on the basis of the hepatic requirements for the synthesis of blood coagulation factors. Accumulating evidence suggests that the requirements for other functions than blood coagulation may be higher. This paper is the result of a closed workshop (Paris, November 2002) in which a number of European vitamin K experts reviewed the available data and formulated their standpoint with respect to recommended dietary vitamin K intake and the use of vitamin K-containing supplements.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 15309455 [PubMed - indexed for MEDLINE]

Arch Dis Child Fetal Neonatal Ed. 2004 Nov;89(6):F546-50.

Intracranial haemorrhage due to late onset vitamin K deficiency bleeding in Hanoi province, Vietnam.

Danielsson N, **Hoa DP**, **Thang NV**, **Vos T**, **Loughnan PM**.

Astrid Lindgren's Children's Hospital, Stockholm, Sweden.

BACKGROUND: In many developing countries vitamin K prophylaxis is not routinely administered at birth. There are insufficient data to assess the cost effectiveness of its implementation in such countries. OBJECTIVE: To estimate the burden of intracranial haemorrhage caused by late onset vitamin K deficiency bleeding in Hanoi, Vietnam. METHODS: Cases of intracranial haemorrhage in infants aged 1-13 weeks were identified in Hanoi province for 5 years (1995-1999), and evidence for vitamin K deficiency was sought. The data were compared with those on vitamin K deficiency bleeding in developed countries and used to obtain an approximation to the incidence of intracranial haemorrhage caused by vitamin K deficiency bleeding in Hanoi. RESULTS: The estimated incidence of late onset vitamin K deficiency bleeding in infants who received no prophylaxis was unexpectedly high (116 per 100,000 births) with 142 and 81 per 100,000 births in rural and urban areas respectively. Mortality was 9%. Of the surviving infants, 42% were neurologically abnormal at the time of hospital discharge. Identified associations were rural residence, male sex, and low birth weight. A significant reduction in the incidence was observed in urban Hanoi during 1998 and 1999, after vitamin K prophylaxis was introduced at one urban obstetric hospital. CONCLUSIONS: Vitamin K deficiency bleeding is a major public health problem in Hanoi. The results indicate that routine vitamin K prophylaxis would significantly reduce infant morbidity and mortality in Vietnam and, costing an estimated 87 US dollars (48 pounds, 72 Euro) per disability adjusted life year saved, is a highly cost effective intervention.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15499152 [PubMed - indexed for MEDLINE]

PMCID: PMC1721780

Pediatr Blood Cancer. 2009 Jul;53(1):92-5.

Novel splice site mutations in the gamma glutamyl carboxylase gene in a child with congenital combined deficiency of the vitamin K-dependent coagulation factors (VKCFD).

Titapiwatanakun R, **Rodriguez V**, **Middha S**, **Dukek BA**, **Pruthi RK**.

Division of Pediatric Hematology Oncology, Mayo Clinic, Rochester, Minnesota 55905, USA.

Congenital combined deficiency of the vitamin K-dependent coagulation factors is a rare bleeding disorder caused by either a defect in the gamma-glutamyl carboxylase or the vitamin K epoxide reductase enzyme complex. The diagnosis should be considered when vitamin-K dependent factor activities are decreased and liver dysfunction, vitamin K deficiency, and factitious coumarin ingestion have been excluded. We report a case of VKCFD in a child resulting from compound heterozygosity for two novel splice site mutations of the gamma-glutamyl carboxylase gene. Oral vitamin K supplementation resulted in partial resolution of proteins and complete resolution of bleeding.

Publication Types:

- Case Reports

PMID: 19340858 [PubMed - indexed for MEDLINE]

Thromb Haemost. 2009 Feb;101(2):410-1.

An oral vitamin K protocol to reverse over-anticoagulation in patients presenting with an International Normalised Ratio above 10.0.

Denas G, **Cucchini U**, **Iliceto S**, **Pengo V**.

Clinical Cardiology, Thrombosis Centre, Via Giustiniani 2, 35128 Padova, Italy.

Publication Types:

- Letter

PMID: 19190831 [PubMed - indexed for MEDLINE]

Eur J Pediatr. 2009 Feb;168(2):127-34. Epub 2008 Nov 4.

Vitamin K, an update for the paediatrician.

Van Winckel M, **De Bruyne R**, **Van De Velde S**, **Van Biervliet S**.

Department of Paediatrics, UZ Gent, De Pintelaan 185, 9000 Ghent, Belgium. myriam.vanwinckel@ugent.be

INTRODUCTION: This review summarizes current knowledge on vitamin K for the paediatrician. Vitamin K is a fat-soluble vitamin, present in plants as phylloquinone and produced by bacteria as menaquinone. It is acting as a co-factor for gamma-glutamyl carboxylase. This enzyme is responsible for post-translational modification of some glutamate side chains to gamma-carboxyglutamate. The majority of gamma-carboxylated proteins function in blood coagulation; others play a role in calcium homeostasis. DATA: Newborn babies are at particular risk of vitamin K deficiency, as placental transfer is limited and human milk is a poor source. Vitamin K prophylaxis at birth effectively prevents vitamin K deficiency bleeding (VKDB), formerly known as "haemorrhagic disease of the newborn". Recent epidemiological studies provide data on the effectiveness of different administration routes and dosing schemes. Infants of mothers taking drugs that inhibit vitamin K are at risk of early VKDB and should receive 1 mg intramuscular (i.m.) as soon as possible after birth. Classic VKDB is prevented by intramuscular as well as by oral administration of 1 mg vitamin K. In exclusively breast-fed infants, single i.m. administration at birth is also effectively preventing (rare) late VKDB but single oral administration is not. If given orally, prophylaxis should be continued by either weekly administration of 1 mg till 12 weeks or repeating 2 mg at weeks 1 and 4. Daily administration of 25 microg offers insufficient protection. The only infants not fully protected in this way are those with yet unrecognised liver disease. CONCLUSIONS: Further work is needed before firm recommendations can be made regarding dose in preterm infants and in patients with fat malabsorption/cholestasis or regarding the role of vitamin K in the prevention of osteoporosis.

Publication Types:

- Review

PMID: 18982351 [PubMed - indexed for MEDLINE]

Wien Med Wochenschr. 2008;158(13-14):385-95.

The neonatal coagulation system and the vitamin K deficiency bleeding - a mini review.

Pichler E, **Pichler L**.

Department of Paediatrics, Landeskrankenhaus Klagenfurt, Klagenfurt, Austria.

Coagulation factors do not cross the placental barrier but are synthesized independently by the conceptus. At birth, activities of the vitamin K dependent factors II, VII, IX, and X and the concentrations of the contact factors XI and XII are reduced to about 50% of normal adult values. The levels of the factors V, VIII, XIII, and fibrinogen are similar to adult values. Plasma concentrations of the naturally occurring anticoagulant proteins (antithrombin, protein C, and protein S) are significantly lower at birth than during the adult years. Plasminogen is reduced by approximately 50%. Platelet counts are within the normal range, regarding function, however, neonatal platelets seem to be hyporeactive. The von Willebrand factor contains large multimers and its concentration is increased. Properties and functions of vitamin K as well as requirement and plasma concentrations in newborns are reviewed. Regarding vitamin K deficiency bleeding (VKDB), the classical nomenclature is used: "early" (presenting within the first 24 h of life), "classical" (day 1-7 after birth), and "late" (8 days to 6 months). After the presentation of the history of vitamin K prophylaxis, vitamin K levels are described as can be expected after the administration of prophylactic doses at various routes. Subsequently, the actual schedule of vitamin K prophylaxis as recommended by the "Osterreichische Gesellschaft für Kinder- und Jugendheilkunde" is given as follows: i) the oral treatment of healthy full-term babies and orally fed preterm babies, ii) the parenteral treatment of small preterm and sick full-term babies, and iii) the treatment of mothers under medication with enzyme-inducing drugs with vitamin K during the last 15-30 days of pregnancy. The regimes of prophylactic vitamin K treatment of different countries are also given. Finally, the therapeutic use of vitamin K is addressed; the potential use of fresh-frozen plasma, prothrombin complex preparations, and recombinant factor VIIa is discussed.

Publication Types:

- Comparative Study
- Review

PMID: 18677590 [PubMed - indexed for MEDLINE]

J Toxicol Sci. 2008 Aug;33(3):307-14.

Blood coagulation-related parameter changes in Sprague-Dawley (SD) rats treated with phenobarbital (PB) and PB plus vitamin K.

Mochizuki M, **Shimizu S**, **Kitazawa T**, **Umeshita K**, **Goto K**, **Kamata T**, **Aoki A**, **Hatayama K**.

Toxicology Department, Gotemba Laboratory, Bozo Research Center Inc., Shizuoka. mochizuki@bozo.co.jp

Effects of dose and duration of phenobarbital (PB) administration and those of co-administration of PB and vitamin K on blood coagulation-related parameters were examined in specific pathogen-free (SPF) rats of Sprague-Dawley strain kept on an ordinary diet. In Experiment 1, oral administration of PB (0, 25, 50, 100 or 150 mg/kg/day) for 2 weeks induced increases in hepatic cytochrome P450 content and CYP2B expression, prolongation of coagulation time (activated partial thromboplastin time (APTT) and Thrombotest (TBT)) and an increase in anti-thrombin III (AT III) concentration in a dose-dependent manner. In Experiment 2, PB administration (100 mg/kg/day) for up to 14 days produced time-dependent increases in hepatic cytochrome P450 content and CYP2B (CYP2B1 and CYP2B2) expression. APTT was prolonged from day 1 and AT III concentration was increased from day 2, whereas the coagulation time (TBT) was prolonged from day 7. In Experiment 3, APTT prolonged by PB (100 mg/kg/day) was shortened after vitamin K(2) (30 mg/kg/day) co-administration, although AT III concentration was still increased. This suggests that not AT III but PB-induced vitamin K deficiency may play an important role in PB-induced prolongation of coagulation time in SPF rats kept on an ordinary diet.

PMID: 18670162 [PubMed - indexed for MEDLINE]

Vitam Horm. 2008;78:265-79.

Vitamin K and thrombosis.

Merli GJ, **Fink J**.

Professor of Medicine, Director Jefferson Center for Vascular Diseases, Jefferson Medical College, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA.

Vitamin K was discovered in the 1930s during cholesterol metabolism experiments in chickens. It is a fat-soluble vitamin which occurs naturally in plants as phylloquinone (vitamin K1) and is produced by gram-negative bacteria in the human gastrointestinal tract as menaquinone (vitamin K2). This vitamin was found to be essential for normal functioning of hemostasis. In addition, a number of clinical conditions in which vitamin K deficiency was found to be the underlying pathophysiologic problem were discovered. These conditions include hemorrhagic disease of the newborn, obstructive jaundice, and malabsorption syndromes. The importance of this vitamin has become more apparent with the discovery of the anticoagulant warfarin which is a vitamin K antagonist. There are millions of patients on this therapy for a variety of thrombogenic conditions such as atrial fibrillation, deep vein thrombosis, pulmonary embolism, and prosthetic cardiac valves. The wide use of this narrow therapeutic index drug has resulted in significant risk for major bleeding. Vitamin K serves as one of the major reversing agent for patients over-anticoagulated with warfarin. In the past few years, research has focused on new areas of vitamin K metabolism, which include bone and endovascular metabolism; cell growth, regulation, migration, and proliferation; cell survival, apoptosis, phagocytosis, and adhesion. These new areas of research highlight the significance of vitamin K but raise new clinical questions for patients who must be maintained on long-term warfarin therapy.

Publication Types:

- Review

PMID: 18374199 [PubMed - indexed for MEDLINE]

Vitam Horm. 2008;78:227-46.

VKORC1: a warfarin-sensitive enzyme in vitamin K metabolism and biosynthesis of vitamin K-dependent blood coagulation factors.

Wallin R, **Wajih N**, **Hutson SM**.

Departments of Internal Medicine and Biochemistry, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157.

The recently discovered enzyme VKORC1 of the vitamin K cycle, which is the target for the anticoagulant drug warfarin, has opened new opportunities to understand warfarin resistance and biosynthesis of vitamin K-dependent blood coagulation factors and other members of this protein family. Furthermore, it has opened new opportunities to study the vitamin K-dependent posttranslational gamma-carboxylational system in the endoplasmic reticulum in greater detail and its molecular operation in vivo. Other accomplishments resulting from this discovery are: (1) the finding that VKORC1 is the rate-limiting step in biosynthesis of functional vitamin K-dependent proteins, and (2) engineering of recombinant intracellular gamma-carboxylation systems in cell lines producing recombinant coagulation factor used clinically to treat bleeding disorders. The engineered cells significantly enhance production of the fraction of fully functional gamma-carboxylated proteins compared to cell lines only overexpressing the specific coagulation factor. The first described inhibitor of the gamma-carboxylation system has been identified as calumenin, a resident chaperone in the endoplasmic reticulum (ER). Together, the new information gained about the vitamin K-dependent gamma-carboxylation system will stimulate new research which will benefit medicine and our understanding of the molecular mechanisms involved in this protein modification reaction.

Publication Types:

- Review

PMID: 18374197 [PubMed - indexed for MEDLINE]

Clin Calcium. 2007 Nov;17(11):1717-26.

[Serum vitamin K concentration and nutrition]

[Article in Japanese]

Tsugawa N, **Okano T**.

Kobe Pharmaceutical University, Department of Hygienic Sciences.

Vitamin K (VK) is well known for its role in the synthesis of a number of blood coagulation factors. VK is also an important factor for bone metabolism via gamma-carboxylation of VK-dependent proteins such as osteocalcin, matrix Gla protein, and protein S. Recently, it is rare that severe VK deficiency is observed. However, low dietary VK intake or low VK status has been shown to be associated with low bone mineral density and increased hip fracture risk. These studies suggest that there is potential VK insufficiency in bone, even in sufficient VK status for blood coagulation. In the present review, the studies concerning relationship between serum VK concentration and bone health, including pharmacokinetics of VK analogues (such as phylloquinone and menaquinone) and factors which affect on blood circulation of VK, are reviewed.

Publication Types:

- English Abstract
- Review

PMID: 17982192 [PubMed - indexed for MEDLINE]

Biosci Biotechnol Biochem. 2006 Apr;70(4):926-32.

Vitamin K suppresses lipopolysaccharide-induced inflammation in the rat.

Ohsaki Y, **Shirakawa H**, **Hiwatashi K**, **Furukawa Y**, **Mizutani T**, **Komai M**.

Laboratory of Nutrition, Department of Science of Food Function and Health, Graduate School of Agricultural Science, Tohoku University , Sendai, Japan.

Vitamin K (K) is essential for blood coagulation and bone metabolism in mammals. K acts as a cofactor in the posttranslational synthesis of gamma-carboxyglutamic acid from glutamic acid residues. In addition to the liver and bone, K is found in the brain, heart, kidney and gonadal tissue. However, the physiological role of K in these various organs is not yet fully understood. It is likely that K has functions other than its role as a cofactor of protein gamma-glutamyl carboxylation. We used in this study the DNA microarray technique to identify the effect of K status on gene expression in the rat liver. The expression of genes involved in the acute inflammation response was enhanced in rats fed with a K-deficient diet relative to the control and K1-supplemented diet groups. Moreover, dietary supplementation with K1 suppressed the inflammation induced by lipopolysaccharide administration. These results indicate that orally administrated K1 suppressed inflammation in the rat.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16636460 [PubMed - indexed for MEDLINE]

Blood Coagul Fibrinolysis. 2005 Oct;16(7):525-7.

Congenital vitamin K-dependent coagulation factor deficiency: a case report.

Bhattacharyya J, **Dutta P**, **Mishra P**, **Dixit A**, **Srinivas U**, **Kannan M**, **Kumar R**, **Choudhry VP**, **Saxena R**.

Department of Haematology, All India Institute of Medical Sciences, New Delhi, India.

Congenital vitamin K-dependent coagulation factor deficiency is a very rare bleeding disorder, which usually presents with episodes of intracerebral bleed in the first few weeks of life, sometimes leading to a fatal outcome. We report a case of combined factor deficiency of vitamin K-dependent factors in which the patient presented with both intracerebral bleeding, and possibly also thrombosis, and responded to a vitamin K supplement along with fresh frozen plasma.

Publication Types:

- Case Reports

PMID: 16175013 [PubMed - indexed for MEDLINE]

Clin Calcium. 2002 Aug;12(8):1123-8.

[Vitamin K and vascular calcification]

[Article in Japanese]

Shoji S.

Internal Medicine, Inoue Hospital.

Until recently, vitamin K has been exclusively related to blood coagulation. During the last decade, a second function for vitamin K-dependent proteins has become apparent : the regulation of tissue calcification. One of them is the function of Matrix Gla Protein (MGP) : potent inhibitors of vascular calcification. The function of MGP became clear from transgenic mice (MGP-deficient mice). Further research on MGP will resolve the complicated mechanism of atherosclerosis, especially of the arterial calcification. The recommended daily allowance for vitamin K to prevent vascular calcification should be evaluated.

Publication Types:

- English Abstract

PMID: 15775408 [PubMed]

JPEN J Parenter Enteral Nutr. 2004 Nov-Dec;28(6):388-98.

Observations on possible effects of daily vitamin K replacement, especially upon warfarin therapy.

Bern M.

Cancer Center of Boston, New England Baptist Hospital, Harvard Medical School, Boston, Massachusetts, USA. mbern@cancercenter.com

Daily parenteral vitamin K supplement is now recommended by the U.S. Food and Drug Administration (FDA) for patients receiving IV hyperalimentation. This is considered as preferable to the previous recommendations of weekly parenteral or oral supplement, or as in some cases no supplement at all. Supplemental vitamin K1 will ensure adequate supplies for hepatic saturation and thus the production of clotting factors II, VII, IX, and X, plus the anticoagulants protein C, protein S, and protein Z. But this is not the entire story. This recommended supplement will affect other physiologic systems that also use vitamin K-dependent gamma-carboxylation. Vitamin K is not 1 molecule but rather 2 natural substances, vitamin K1 and K2, and the synthetic K3's. It is not understood, what, if any, effect may occur because of the saturation or competition from the vitamin K1 upon the functioning of vitamins K2 and the derivatives of K3 in vivo upon bone mineralization, cell growth, and blood vessel health, all known to be influenced by the vitamins K. There are probably other physiologic systems yet to be studied relative to vitamins K and gamma-carboxylation. This review also considers the available research upon warfarin when given to patients receiving hyperalimentation and what effects the vitamin K supplements may have. Because studies to date have not controlled for vitamin K intake, consideration is given to whether one should expect any change in previously reported outcomes when using low-dose warfarin for prophylaxis against central vein thrombosis. Also considered are possible positive or negative effects that chronic warfarin therapy may have upon the other vitamin K-dependent systems under discussion. This review offers a platform for further discussion and derived clinical research provoked by this new FDA recommendation.

Publication Types:

- Review

PMID: 15568285 [PubMed - indexed for MEDLINE]

Haemophilia. 2004 Oct;10 Suppl 4:188-95.

Acquired bleeding disorders: the impact of health problems in the developing world.

Isarangkura P, **Mahasandana C**, **Chuansumrit A**, **Angchaisuksiri P**.

Department of Pediatrics, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Several acquired bleeding disorders in the developing world have impacts on health, including late vitamin K deficiency bleeding (VKDB) in infants, dengue haemorrhagic fever (DHF), and malaria. This paper describes their clinical manifestations, mechanisms involved, and treatment.

Publication Types:

- Review

PMID: 15479397 [PubMed - indexed for MEDLINE]

J Thromb Thrombolysis. 2003 Aug-Oct;16(1-2):69-72.

Vitamin K for the treatment of asymptomatic coagulopathy associated with oral anticoagulant therapy.

Crowther MA, **Wilson S**.

Department of Medicine, McMaster University, Hamilton, Ontario, Canada. crowthrm@mcmaster.ca

Patients with asymptomatic elevated International Normalized Ratios (INRs) are commonly seen in practice, but there is no consensus on how best to manage this condition. Evidence suggests that low-dose (1 mg to 2.5 mg) oral vitamin K restores patients to INR values associated with a lower risk of hemorrhage more rapidly than discontinuing warfarin alone. Vitamin K therapy remains under-utilized despite evidence for its effectiveness. The studies discussed in this review suggest that vitamin K1 should be considered if rapid reductions in the INR are desired. For most rapid corrections in the INR, vitamin K should be administered by the intravenous route since it begins to reduce the INR within 8 hours. Subcutaneous vitamin K is relatively ineffective, and its use may be associated with over-correction of the INR.

Publication Types:

- Review

PMID: 14760216 [PubMed - indexed for MEDLINE]