

## Vitamin K

Vitamin K1 (phylloquinone) is dietary vitamin K. Dietary fat enhances its absorption. Infant formulas contain supplemental vitamin K. Vitamin K2 refers to a group of compounds (menaquinones) synthesized by bacteria in the intestinal tract; the amount synthesized does not satisfy the vitamin K requirement.

Vitamin K controls the formation of coagulation factors II (prothrombin), VII, IX, and X in the liver. Other coagulation factors dependent on vitamin K are protein C, protein S, and protein Z; proteins C and S are anticoagulants. Metabolic pathways conserve vitamin K. Once vitamin K has participated in formation of coagulation factors, the reaction product, vitamin K epoxide, is enzymatically converted to the active form, vitamin K hydroquinone. Some Trade Names

The actions of vitamin K–dependent proteins require Ca. The vitamin K–dependent proteins, osteocalcin and matrix  $\gamma$ -carboxy-glutamyl (Gla) protein, may have important roles in bone and other tissues. Forms of vitamin K are common therapy for osteoporosis in Japan and other countries.

## Vitamin K Deficiency

Vitamin K deficiency results from extremely inadequate intake, fat malabsorption, or use of coumarin anticoagulants. Deficiency is particularly common among breastfed infants. It impairs clotting. Diagnosis is suspected based on routine coagulation study findings and confirmed by response to vitamin K. Treatment consists of vitamin K given orally or, when fat malabsorption is the cause or risk of bleeding is high, parenterally.

Vitamin K deficiency decreases levels of prothrombin and other vitamin K–dependent coagulation factors, causing defective coagulation and, potentially, bleeding.

## Etiology

Worldwide, vitamin K deficiency causes infant morbidity and mortality. Vitamin K deficiency causes hemorrhagic disease of the newborn, which usually occurs 1 to 7 days postpartum. In affected neonates, birth trauma can cause intracranial hemorrhage. Neonates are prone to vitamin K deficiency because of the following:

- The placenta transmits lipids and vitamin K relatively poorly.
- The neonatal liver is immature with respect to prothrombin synthesis.
- Breast milk is low in vitamin K, containing about 2.5  $\mu\text{g/L}$  (cow's milk contains 5000  $\mu\text{g/L}$ ).
- The neonatal gut is sterile during the first few days of life.

Late hemorrhagic disease (occurring 3 to 8 wk postpartum) is usually associated with breastfeeding, malabsorption, or a liver disorder. If the mother has taken phenytoin anticonvulsants, coumarin anticoagulants, or cephalosporin antibiotics, the risk of both types of hemorrhagic disease is increased.

In healthy adults, dietary vitamin K deficiency is uncommon because vitamin K is widely distributed in green vegetables and the bacteria of the normal gut synthesize menaquinones. However, biliary obstruction, malabsorption, cystic fibrosis, and resection of the small intestine can contribute to vitamin K deficiency.

Coumarin anticoagulants interfere with the synthesis of vitamin-K dependent coagulation proteins (factors II, VII, IX, and X) in the liver. Certain antibiotics (particularly some cephalosporins and other broad-spectrum antibiotics), salicylates, megadoses of vitamin E, and hepatic insufficiency increase risk of bleeding in patients with vitamin K deficiency.

### **Symptoms and Signs**

Bleeding is the usual manifestation. Easy bruisability and mucosal bleeding (especially epistaxis, GI hemorrhage, menorrhagia, and hematuria) can occur. Blood may ooze from puncture sites or incisions.

Hemorrhagic disease of the newborn and late hemorrhagic disease in infants may cause cutaneous, GI, intrathoracic, or, in the worst cases, intracranial bleeding. If obstructive jaundice develops, bleeding—if it occurs—usually begins after the 4th or 5th day. It may begin as a slow ooze from a surgical incision, the gums, the nose, or GI mucosa, or it may begin as massive bleeding into the GI tract.

### **Diagnosis**

- Usually, prolonged PT that decreases after phytonadione

Vitamin K deficiency or antagonism (due to coumarin anticoagulants) is suspected when abnormal bleeding occurs in a patient at risk. Blood coagulation studies can preliminarily confirm the diagnosis. PT, usually reported as the INR, is prolonged, but PTT, thrombin time, platelet count, bleeding time, and levels of fibrinogen, fibrin-split products, and d-dimer are normal. If phytonadione (USP generic name for vitamin K1) 1 mg IV significantly decreases PT within 2 to 6 h, a liver disorder is not the likely cause, and the diagnosis of vitamin K deficiency is confirmed. Some centers can detect vitamin K deficiency more directly by measuring the plasma vitamin level. The plasma level of vitamin K1 ranges from 0.2 to 1.0 ng/mL in healthy people consuming adequate quantities of vitamin K1 (50 to 150 µg/day). Knowing vitamin K intake can help interpret plasma levels; recent intake affects levels in plasma but not in tissues.

More sensitive indicators of vitamin K status, such as PIVKA (Protein Induced in Vitamin K Absence or Antagonism) and under-carboxylated osteocalcin, are under study.

## **Prevention**

### Phytonadione Some Trade Names

0.5 to 1 mg IM (or 0.3 mg/kg for preterm infants) is recommended for all neonates within 6 h of birth to reduce the incidence of intracranial hemorrhage due to birth trauma, and classic hemorrhagic disease of the newborn (increased bleeding risks 1 to 7 days after birth). It is also used prophylactically before surgery. Some clinicians recommend that pregnant women taking anticonvulsants receive phytonadione 10 mg po once/day for the 1 mo or 20 mg po once/day for the 2 wk before delivery. The low vitamin K1 content in breast milk can be increased by increasing maternal dietary intake of phylloquinone to 5 mg/day.

### Treatment

- Phytonadione

Whenever possible, phytonadi should be given po or sc. The usual adult dose is 5 to 20 mg. (Rarely, even when phytonadione is correctly diluted and given slowly, IV replacement can result in anaphylaxis or anaphylactoid reactions.) INR usually decreases within 6 to 12 h. The dose may be repeated in 6 to 8 h if INR has not decreased satisfactorily. Phytonadione 2.5 to 10 mg po is indicated for nonemergency correction of a prolonged INR in patients taking anticoagulants. Correction usually occurs within 6 to 8 h. When only partial correction of INR is desirable (eg, when INR should remain slightly elevated because of a prosthetic heart valve), lower doses (eg, 1 to 2.5 mg) of phytonadione can be given.

In infants, bleeding due to deficiency can be corrected by giving phytonadione 1 mg sc or IM once. The dose is repeated if INR remains elevated. Higher doses may be necessary if the mother has been taking oral anticoagulants.

### **Vitamin K Toxicity**

Vitamin K1 (phylloquinone) is not toxic when consumed orally, even in large amounts. However, menadione (a synthetic, water-soluble vitamin K precursor) can cause toxicity and should not be used to treat vitamin K deficiency.