REPORT OF COMMITTEE ON NUTRITION

VITAMIN K COMPOUNDS AND THE WATER-SOLUBLE ANALOGUES

Use in Therapy and Prophylaxis in Pediatrics

THE PRESENT REPORT concerns the nature and functions of natural vitamin K compounds and of some synthetic naphthoquinone derivatives, referred to as vitamin K analogues. The report emphasizes the use of these compounds in pediatrics, especially for prevention and treatment of hemorrhagic disease of the newborn. The demonstration that water-soluble analogues of vitamin K may be toxic for the newborn infant makes it imperative that these substances be used judiciously.

FUNCTIONS AND REQUIREMENT OF VITAMIN K

Table I provides information concerning characteristics, sources, available preparations and routes of administration of natural and synthetic compounds with vitamin K activity.

Functions

Vitamin K is required for synthesis of prothrombin and proconvertin (stable factor, factor VII), and it probably is involved also in synthesis of Stuart-Prower factor (factor X) and PTC (plasma thromboplastic factor, factor IX) since clotting defects due to deficiencies of these factors as well as to deficiencies of prothrombin and proconvertin occur in states of vitamin K deficiency.[1-6]

Requirement and Usual Source of Supply

Available evidence indicates that vitamin K compounds cannot be synthesized by the animal organism. However, vitamin K_1 is widely distributed in nature, being present in greatest concentrations in green leafy vegetables and in somewhat lesser concentrations in seeds, tubers and fruit.[7] Although it has long been believed that bacterial synthesis of vitamin K_2 in the intestine is another important source of the vitamin,[8] recent studies with rats[9] indicate that vitamin K_2 formed in this manner is unavailable if coprophagy is prevented. Whether bacterial synthesis of vitamin K_2 in the human intestine can contribute to satisfying the requirements for this vitamin is not known, and it is therefore uncertain whether suppression of growth of intestinal micro-organisms by prolonged oral administration of antibiotics or sulfonamides is of practical importance. Quantitative determination of vitamin K requirements of the older infant, child and adult has not yet been possible because of the dietary abundance of the vitamin.

The requirement of the newborn infant for vitamin K is of particular interest, because the contents of the bowel are sterile at birth and the infant ordinarily receives little vitamin K in the diet during the first few days of life.

Vitamin K Deficiency in Older Children and Adults

Inadequate intestinal absorption (due to obstructive jaundice, biliary fistula, insufficient production of bile acids or pancreatic insufficiency) as well as hepatic injury may lead to vitamin K deficiency.[10,11] The water-soluble analogues of vitamin K are valuable in the treatment of patients with inadequate intestinal absorption of lipids.

The increasing use of the coumarin drugs in anticoagulant therapy has been accom-

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panied by wider use of vitamin K in treatment of overdosage of coumarin. In addition, the presence of clotting defects in infants born of mothers receiving anticoagulant therapy has been reported.[12, 13]

FINDINGS IN NEWBORN INFANTS

Definition and Incidence of "Hemorrhagic Disease of the Newborn"

Hemorrhagic manifestations in the newborn period may be evidences of various blood dyscrasias[14] or, more commonly, may result from trauma, anoxia or infection. Although the designation, "hemorrhagic disease of the newborn" undoubtedly has been used in the past for a variety of conditions, a suitably specific and useful definition at the present time is the following:

Hemorrhagic disease of the newborn infant is a hemorrhagic disorder of the first days of life caused by a deficiency of vitamin K and characterized by deficiency of prothrombin, proconvertin and probably other factors.

The incidence of hemorrhagic disease of the newborn appears to vary widely. Potter[15] found no clear-cut instance of the condition in 13,000 infants, one-half of whose mothers had received vitamin K; Sanford *et al.*[16] reported only two cases in 5,500 infants. The more usually cited incidence in full-term infants who did not receive vitamin K (and whose mothers did not receive vitamin K during labor) is 1 in 400.[17] In an excellent study of an indigent population in Cuba, Aballí *et al.*[5] found an incidence of hemorrhagic disease of the newborn of 1 in 200.

Recently Vietti *et al.*[18] reported the incidence of bleeding after circumcision of 470 infants at a mean age of about 24 hours. Infants born on even-numbered days of the month were given 5 mg of menadione sodium bisulfite (Hykinone) intramuscularly shortly after birth; infants born on odd-numbered days did not receive vitamin K. Bleeding after circumcision occurred in 6 of 240 infants who had been treated with menadione sodium bisulfite and 1 infant required resuturing of the foreskin. In the group of 230 infants who did not receive menadione sodium bisulfite, 32 instances of bleeding occurred, and resuturing was necessary in 14. These differences are statistically significant ($p = 0.01$). Prothrombin activity of the plasma also differed significantly between the two groups.

Abnormality in Clotting Factors

True prothrombin activity in the blood at the time of birth is less than that of normal adults, and it generally decreases even further during the first 48 hours of life but then increases slowly.[2, 19, 20] The activities of proconvertin, Stuart-Prower factor and thromboplastin in the blood follow a pattern similar to that of true prothrombin.[6, 14, 20]

Values for activity of true prothrombin less than 10% of the mean values of normal adults have been encountered occasionally in infants without evidence of bleeding,[5] but such low values are usually associated with hemorrhagic disease of the newborn. The activity of proconvertin is generally more markedly reduced than that of prothrombin[2] and is primarily responsible for the prolonged one-stage prothrombin time.

Minimal Effective Dose for Prevention of Coagulation Abnormalities in the Newborn Infant

The minimal effective dose of vitamin K compounds for preventing coagulation abnormalities of the newborn infant is estimated to be 1 to 5 μg daily.[21-23] Although growth of bacteria in the intestinal tract can be demonstrated within a few hours after birth,[24] nothing is known about bacterial synthesis of vitamin K in the newborn period.

The breast-fed infant is at a particular disadvantage because of the lower volume of intake during the first few days of life and because of the even lower concentration of vitamin K in human milk (1.5 μg/100 ml) than in cow milk (6 μg/100 ml).[19] In this regard it has been shown[19, 25-27] that a greater prolongation of the one-stage "prothrombin time" occurs in the exclusively breast-fed infant than in the arti-

ficially fed infant or in the breast-fed infant who receives small supplements of cow milk beginning on the first day of life. Sells *et al.*[21] have demonstrated that oral administration of 5 to 10 gm of powdered whole milk (perhaps equivalent to 30 to 60 ml of liquid whole milk) on the third or fourth day of life resulted in significant decrease in one-stage prothrombin time.

The observations of Willi *et al.*[28] indicate that when a water-miscible preparation of vitamin K_1 is administered intramuscularly to the premature infant, 1 mg is as effective as 10 mg in preventing prolongation of "prothrombin time." *Oral* administration of 1 to 2 mg of this preparation has also been shown to be effective in preventing prolongation of prothrombin time.[29, 30]

Toxicity of Vitamin K

The biochemical and physiologic mechanisms involved in the development of hemolytic anemia, hyperbilirubinemia and kernicterus after parenteral administration of large doses of water-soluble vitamin K analogues are not well understood. Glutathione metabolism in erythrocytes of infants may be significantly affected by the presence of menadione sodium bisulfite,[31] and the conjugation of bilirubin to the glucuronide is inhibited by menadiol sodium diphosphate in an in vitro liver enzyme system.[32] Although this may explain the development of hyperbilirubinemia in the newborn infant, there is no evidence from in vivo studies to support this hypothesis. Other possible mechanisms for development of hyperbilirubinemia have been discussed by Lucey and Dolan.[33]

Vitamin K_1, the natural fat-soluble form of the vitamin, apparently does not elicit toxic symptoms or hyperbilirubinemia when given parenterally in doses of 10 to 25 mg.[28, 34, 35] There are no reports of toxicity after *oral* administration of vitamin K_1, of menadione sodium bisulfite or menadiol sodium diphosphate (Synkayvite) to newborn infants; menadione is not ordinarily administered orally because it causes vomiting.

Maturity is apparently an important factor in development of evidences of toxicity to vitamin K analogues, as full-term and larger premature infants demonstrate greater tolerance than do smaller premature infants.[35-37] Hemolytic anemia has been reported[38] in premature infants after parenteral administration of 5 to 10 mg daily of menadiol sodium diphosphate (Synkayvite). Laurance[39] reported death due to kernicterus in six premature infants given 10 mg of this preparation parenterally three times daily for 3 days. Allison,[40] Meyer and Angus[41] and Bound and Telfer[42] reported that administration of large doses produced increased concentrations of bilirubin in the serum and increased risk of kernicterus in premature and full-term infants. These and other reports have been reviewed by Dyggve.[36]

Administration of Vitamin K to Woman in Labor: Effectiveness and Toxicity with Respect to Infant

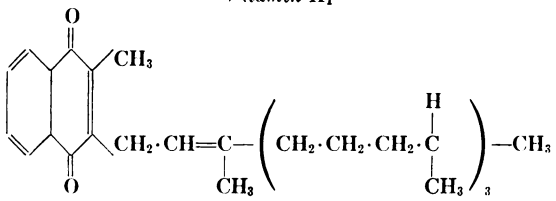
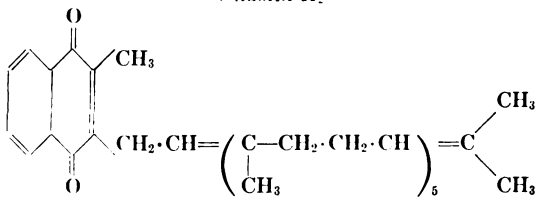
There is at present considerable difference of opinion concerning the effectiveness of administering vitamin K to the woman in labor in an attempt to prevent hypoprothrombinemia and the other coagulation abnormalities of the newborn. Vitamin K, radioactively labeled with C-14, has been shown to pass from the pregnant rat to the fetus,[41] and available data[43, 44] indicate that similar transfer occurs in the human. However, it seems impossible as yet to specify a maternal dose that will be both effective and safe for the newborn infant. Thus, although intravenous administration of 10 mg of menadiol sodium diphosphate to the mother modified the abnormality in activity of prothrombin and proconvertin in the newborn, this dosage was significantly less effective than was 50 mg.[43] The possibility that a dose of 50 mg may be hazardous, at least for some infants, has been suggested by Lucey and Dolan[33] concerning development of hyperbilirubinemia in seven premature infants born to mothers who had received another vitamin K analogue—menadione sodium bisulfite—in dosage of 72 mg.

It is not yet possible to specify a dose

TABLE I

STRUCTURE, CHARACTERISTICS AND ROUTES OF ADMINISTRATION OF NATURAL VITAMIN K COMPOUNDS AND SOME SYNTHETIC WATER-SOLUBLE ANALOGUES

A. Natural Vitamin K Compounds

	Vitamin K_1	*Vitamin K_2*
Structure		
Chemical term	2-methyl-3-phytyl-1,4-naphthoquinone	2-methyl-3-difarnesyl-1,4-naphthoquinone
Official term (U.S.P. XVI)	phytonadione	—
Solubility	fat	fat
Source	green plants	gastrointestinal micro-organisms
Preparations	phytonadione (U.S.P. XVI) and Mephyton are oily preparations; Aquamephyton and Konakion are clear aqueous colloidal suspensions	none available
Routes of administration	phytonadione and Mephyton: oral or intravenous; Aquamephyton and Konakion: oral, intramuscular, subcutaneous, intravenous	—

B. Water-Soluble Analogues of Vitamin K

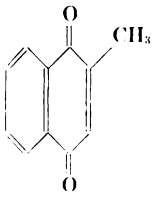
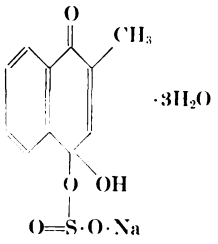
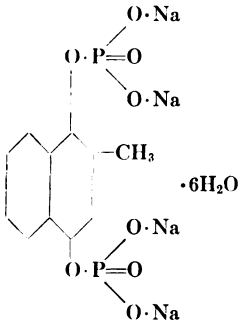
Structure			

TABLE I—(*continued*)

Chemical term	2-methyl-1,4 naphthoquinone	2-methyl-2-sodium bisulfite-3-dehydro-1,4-naphthoquinone	2-methyl-1, 4-naphalendiol tetrasodium diphosphate hexahydrate
Official term (U.S.P. XVI)	menadione	menadione sodium bisulfite	menadiol sodium diphosphate
Solubility	water	water	water
Preparations	menadione (U.S.P. XVI)	Hykinone and menadione sodium bisulfite (U.S.P. XVI)	Synkayvite and menadiol sodium diphosphate (U.S.P. XVI)
Routes of administration	intravenous or intramuscular	oral, intravenous, or intramuscular	oral, intravenous, or intramuscular

and route of administration of vitamin K for the woman in labor that will provide effective and safe prophylaxis for the infant.

RECOMMENDATIONS AND CONCLUSIONS

It is suggested that "hemorrhagic disease of the newborn" be defined as a hemorrhagic disorder of the first days of life caused by a deficiency of vitamin K and characterized by deficiency of prothrombin and proconvertin (stable factor, factor VII), and probably of other factors.

Vitamin K_1 and commonly employed synthetic vitamin K analogues (menadione, menadione sodium bisulfite and menadiol sodium diphosphate) are all probably safe and effective when administered to the infant in proper dosage for the prophylaxis and treatment of hypoprothrombinemia and spontaneous hemorrhage of premature and full-term infants. However, the margin of safety is almost certainly greatest with vitamin K_1 (phytonadione) and *vitamin K_1 is therefore considered the drug of choice. A single parenteral dose of 0.5 to 1.0 mg or oral dose of 1.0 to 2.0 mg is probably adequate for prophylaxis,* but it may at times be necessary to repeat this dosage for treatment, and larger doses will generally be necessary for treatment of infants whose mothers have received anticoagulant therapy. It may be noted that oral, intramuscular, subcutaneous or intravenous dosage of vitamin K_1 is feasible (Table 1).

Administration of large doses of the water-soluble vitamin K analogues to the woman in labor or to the newborn infant has been followed by hemolytic anemia, hyperbilirubinemia, kernicterus and death of the infant. Available data indicate that lesser doses of vitamin K analogues administered to the mother may frequently be ineffective in preventing the coagulation abnormalities of the infant.

For reasons mentioned, it is recommended that vitamin K prophylaxis be administered to the infant after birth rather than prenatally through administration to the mother.

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