From the Canadian Paediatric Society

The use of vitamin K in the perinatal period

Fetus and Newborn Committee,* Canadian Paediatric Society

The incidence of hemorrhagic disease of the newborn (HDNB) can be expected to increase in Canada as breast-feeding becomes more popular. There are three clinical patterns of hemorrhagic disease: early HDNB (usually related to maternal drug ingestion), classic HDNB (related to breast-feeding) and late hemorrhagic disease of infancy (related to the combination of breast-feeding and diseases that cause fat malabsorption). Despite the knowledge that the disease can virtually be prevented by the administration of vitamin K, not all newborns are being routinely considered for such treatment. The Canadian Paediatric Society has made several recommendations: (a) women who take drugs that interfere with vitamin K metabolism should receive oral doses of vitamin K_1 daily for a minimum of 2 weeks before expected delivery; (b) all healthy term infants should receive a single dose of vitamin K_1, orally or intramuscularly, within 6 hours after birth; (c) all other newborns, including preterm, low-birthweight and sick infants, should receive a single intramuscular dose of vitamin K_1 within 6 hours after birth; and (d) infants at high risk for secondary late-onset hemorrhagic disease due to fat malabsorption should receive vitamin K_1 orally every day or intramuscularly once a month.

La faveur grandissante avec laquelle, au Canada, on regarde l'allaitement au sein fait prévoir une survenue plus fréquente de maladie hémorragique du nouveau-né (MHNN). On reconnaît de celle-ci trois formes: précoce (ordinairement causée par des médicaments pris par la mère), classique (reliée à l'allaitement maternel) et retardée (reliée à la combinaison de l'allaitement maternel et de troubles de l'absorption des graisses). Bien qu'on sache que la vitamine K prévient presque toujours la MHNN, cette prophylaxie n'est pas offerte de façon systématique à tous les nouveau-nés. Voici ce que recommande la Société canadienne de pédiatrie: (a) aux mères traitées par des médicaments modifiant le métabolisme de la vitamine K on fera prendre une dose quotidienne de vitamine K_1 par la bouche pendant au moins 2 semaines avant la date prévue de l'accouchement; (b) tout enfant bien portant né à terme a besoin d'une dose unique de vitamine K_1, par la bouche ou en intramusculaire, dans les 6 heures après la naissance; (c) tous les autres enfants, y compris ceux qui sont prématurés, hypotrophiques ou malades, ont besoin d'une dose unique de vitamine K_1 par la voie intramusculaire dans les 6 heures après la naissance; et (d) on donnera la vitamine K_1 par la bouche tous les jours, ou en intramusculaire une fois par mois, à l'enfant souffrant de malabsorption des graisses, qui est à risque élevé de maladie hémorragique retardée.

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The term hemorrhagic disease of the newborn (HDNB) was first coined in 1894 by Townsend,[1] who described 50 infants in whom bleeding, commonly from the gastrointestinal tract, had begun typically 2 or 3 days after birth and had usually been self-limited. Vitamin K was discovered in 1929 by Dam,[2] who observed that spontaneous hemorrhage occurred in chickens fed a fat-free diet. Over the next 12 years the association between vitamin K deficiency and HDNB was established by means of demonstrating that the prothrombin level, characteristically low in

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healthy newborns,[3] could be increased with the use of vitamin K.[4-6] The decrease in the incidence of hemorrhage and the increase in the prothrombin level in response to vitamin K therapy have become recognized as important features of HDNB that distinguish it from other hemorrhagic disorders[7,8] and have suggested that vitamin K be used prophylactically.[9-11]

In 1961 the Committee on Nutrition of the American Academy of Pediatrics recommended that vitamin K_1, 0.5 to 1.0 mg, be administered intramuscularly to all newborns shortly after birth.[10] Other investigators preferred the oral route[9,11] and recommended that vitamin K_1, 0.5 to 2.0 mg, be given with the first clear-fluid feeding to all healthy newborns and that the intramuscular route be reserved for preterm, low-birthweight and sick newborns.[12,13] During the past 20 years considerable progress has been made in understanding vitamin K and the physiologic changes in the coagulation process that occur in relation to HDNB.[14] However, in some nurseries in Canada vitamin K has not been routinely given to all newborns,[15] and in another centre in Canada HDNB developed in several infants who did not receive vitamin K.[16]

The pertinent data concerned with vitamin K prophylaxis are reviewed here, and the recommendations for its use in the perinatal period are reassessed.

Hemorrhagic disease of the newborn (HDNB)

HDNB occurs during the first days or months after birth because of vitamin K deficiency and is characterized by low levels of the four known vitamin-K-dependent coagulation factors: II, VII, IX and X. A rapid response to vitamin K therapy confirms the diagnosis. The classic clinical syndrome is generally confined to otherwise healthy infants, most of whom are breast-fed and have not received supplemental vitamin K at birth. Hemorrhage due to birth trauma, such as superficial bleeding in the scalp, is excluded. Estimates of the incidence of severe hemorrhage among infants who have not received vitamin K vary from 1:200 to 1:1200.[17,18] Hypoprothrombinemia during the neonatal period serves as a common basis on which other factors may be superimposed to cause HDNB. Breast-feeding and the low level of vitamin K in human milk,[19] high-risk pregnancy,[20] maternal epilepsy treated with phenobarbital or phenytoin[21,22] and oral anticoagulant therapy[23] have been causally linked to HDNB. There are three clinical patterns: early and classic HDNB and late hemorrhagic disease of infancy.

Early HDNB

This form of HDNB develops within 24 hours after birth. Although some cases have occurred without apparent cause,[24,25] most have been associated with maternal ingestion of drugs that interfere with vitamin K metabolism (e.g., warfarin and anticonvulsants).[10,21,23] The extent of hemorrhage varies from mild bruising to severe intracranial hemorrhage.

Classic HDNB

Infants with this form of disease typically present between 2 and 5 days after birth with bruising or gastrointestinal hemorrhage. Classic HDNB occurs almost exclusively in breast-fed infants[26] and is virtually nonexistent in those given vitamin K at birth.[14] Intracranial hemorrhage is not common but may develop at 1 to 2 weeks of age if the disorder is not treated.

Late hemorrhagic disease of infancy

Over the past 10 to 15 years vitamin K deficiency has also been found to cause significant illness and death in infants more than 2 weeks of age. These infants usually present with pallor, severe abnormalities of the central nervous system due to acute intracranial hemorrhage and no history of hemorrhage. They are usually thought to have been healthy before the onset of the disease. Many of the infants with acute intracranial hemorrhage die, and those who survive often have neurologic damage. Another initial sign is widespread deep-skin ecchymoses or nodular purpura. Hemorrhage from the gastrointestinal tract and mucous membranes and excessive bleeding from surgical trauma or intramuscular injections are less common in late hemorrhagic disease of infancy than in early and classic HDNB.

Vitamin K deficiency may be the primary disorder, in which case it usually presents between 1 and 3 months after birth, or it may be secondary to an underlying disease and occur any time during the first year. Underlying diseases that must be considered are cystic fibrosis, chronic diarrhea, α_1-antitrypsin deficiency, hepatitis, biliary atresia, abetalipoproteinemia, celiac disease and illness due to chronic exposure to warfarin. Although these diseases aggravate late hemorrhagic disease of infancy, vitamin K deficiency seems to play a significant role because almost all reported cases have occurred in breast-fed infants who had not received vitamin K at birth.[14]

Vitamin K

Pharmacologic features

Vitamin K acquired its name after the discovery of a hemorrhagic disorder in chickens fed a fat-free diet. The factor in fat found to prevent hemorrhage, *Koagulation Vitamin*[2] or vitamin K, has been isolated in three forms: vitamin K_1 (phytonadione), which is found in green leafy vegetables; vitamin K_2 (menaquinone), which is synthesized by intestinal bacterial flora; and vitamin K_3 (menadione), which is a lipid-soluble qui-

none derivative that can be made water-soluble as the sodium bisulfite salt or the tetrasodium salt of the diphosphoric acid ester. Vitamin K_3 is not usually used in the neonatal period because in high doses it has caused hemolysis, excessive jaundice and kernicterus.[27,28]

Vitamin K is required for the post-translational carboxylation of glutamic acid residues of the vitamin K-dependent proteins: factors II (prothrombin), VII, IX and X, and protein C (an important inhibitor of coagulation). The conversion of glutamic acid to γ-carboxyglutamic acid creates effective calcium-binding sites and allows coagulation to proceed. Without vitamin K these proteins are present only in the functionally defective, noncarboxylated forms.

Although the half-life of vitamin K_1 in plasma may be as low as 3 hours in newborns[29] and is similar to that in adults, the clinical efficacy of a single parenteral dose appears to far outlast the vitamin's life span in the plasma. Adults have been found to show signs of vitamin K deficiency after 21 to 28 days of starvation and antibiotic therapy to limit the production of vitamin K by intestinal bacteria.[30]

Controversy over routine administration

The recommendation in 1961 of the Committee on Nutrition of the American Academy of Pediatrics[10] resulted in the widespread acceptance of routine vitamin K prophylaxis in the United States. However, the principle that vitamin K should be given to all newborns has not been generally accepted in many other countries. This scepticism has spread because recent studies have failed to show vitamin K deficiency at birth through attempting either to measure the level of vitamin K in cord plasma[31] or to detect protein induced by vitamin K's absence (PIVKA).[32] However, the relation of vitamin K levels in cord blood at birth to a disease process that occurs 2 to 5 days later may not be valid.

In a controlled study Motohara and associates[33] showed that noncarboxylated prothrombin (PIVKA-II) could be detected at 5 days of age in the blood of 62% of infants who had not been given vitamin K at birth, as compared with 11% of those who had been given 5 mg of vitamin K_1 6 to 12 hours after birth. The presence of PIVKA-II in the first group strongly suggests vitamin K deficiency. Aballi[34] reviewed a great deal of information and found that the low levels of vitamin-K-dependent factors in many newborns respond dramatically to the administration of vitamin K. In centres where vitamin K was routinely given only to infants at high risk for HDNB the overall incidence of the disease had sharply increased, from 1 in 20 000 to 1 in 1200 deliveries;[18] this was thought to be due to the increased incidence of breast-feeding and the decreased supplementation with cow's milk formula.

HDNB clearly results from inadequate vitamin K intake during the first days or months after birth and can be prevented if sufficient amounts of vitamin K are given to the mother before delivery and to the newborn at birth and during the first several months.

Optimal dosage and administration

The single 1-mg intramuscular dose of vitamin K_1 recommended by the Committee on Nutrition of the American Academy of Pediatrics has been found to be effective in markedly decreasing the incidence of HDNB in the United States.[14] Aballi and de Lamercus[8] showed that 25 μg of vitamin K_3 was the minimal effective dose required to correct abnormal prothrombin times in term newborns. Infants with extremely low birthweights (500 to 999 g) may receive between 140 and 280 times the minimal dose. Because vitamin K_1 has recently been found to enhance the production of oxygen free radicals,[35] and because low-birthweight infants are prone to eye and lung damage from oxygen therapy, the recommended dose for such infants may have to be revised.

Only a fraction of the actual dose is needed to acquire protection against HDNB, and vitamins K_1 and K_3 have been shown to be absorbed well from the gastrointestinal tract;[6,9,31,36,37] therefore, the oral route is apparently as effective as and is much less expensive and traumatic than the intramuscular route. The oral administration of vitamin K_1 or K_3 has been used in healthy term infants for a number of years in three institutions (Southmead Hospital, Bristol, England;[12] Royal Victoria Hospital, Montreal [Robert H. Usher: personal communication]; and Grace Maternity Hospital, Halifax [Alexander C. Allen: personal observations]), each hospital delivering more than 3000 infants annually. Two cases of HDNB developed in a total aggregate population of 200 000 infants. A commercially available oral preparation of vitamin K_1, in 2.0-mg doses, is required to facilitate administration and to decrease still further the cost of prophylaxis.[12]

Prevention of early HDNB

The administration of vitamin K_1, 20 mg/d orally for 2 weeks before delivery, to epileptic mothers who were taking phenobarbital or phenytoin resulted in normal prothrombin levels (70% to 110%) in all of the infants, as compared with fewer than 20% of the infants whose epileptic mothers did not receive vitamin K.[22] In another study the prothrombin levels were found to be higher in infants whose mothers had been given a single 20-mg oral dose of vitamin K_1 between 4 and 24 hours before delivery than in those whose mothers did not receive vitamin K_1.[9]

Breast-feeding and late hemorrhagic disease of infancy

The vitamin K content of human milk is low

and thus predisposes breast-fed infants to hemorrhagic disease.[19] The administration of vitamin K_1, 20 mg/d orally, to the mother may significantly increase the vitamin K content of her milk[30] and may prevent late hemorrhagic disease of infancy. Further research is required to determine how the vitamin K content of human milk can be increased to meet the needs of infants during the first year after birth.

Recommendations

- Mothers who take drugs that impair vitamin K metabolism (e.g., anticonvulsants [specifically phenobarbital and phenytoin], rifampin, isoniazid and coumarin anticoagulants) should be given vitamin K_1, 20 mg/d orally, for at least 2 weeks before the expected time of delivery.
- All healthy term infants should receive a single dose of vitamin K_1, either 1.0 mg intramuscularly or 2.0 mg orally, within 6 hours after birth. The oral dose should be given with the first clear-fluid feeding, before milk is given. All preterm, low-birthweight and sick infants should receive 1.0 mg of vitamin K_1 intramuscularly within 6 hours after birth. Because of the risk of an overdose with orally administered vitamin K_3, an oral preparation of vitamin K_1 is preferred.
- Infants at high risk for secondary late hemorrhagic disease due to cystic fibrosis, chronic diarrhea, α_1-antitrypsin deficiency, hepatitis, biliary atresia, abetalipoproteinemia, celiac disease or long-term exposure to warfarin should be given vitamin K_1, 50 to 100 μg/d orally or 1 mg intramuscularly once a month.[14]

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