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Vitamin K for the Prevention of Bleeding in Newborns

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The prevention of vitamin K-deficiency bleeding (VKDB) in infancy remains a worldwide concern. The condition was initially termed "hemorrhagic disease of the newborn" by Townsend in 1894 to describe 50 infants he observed with bleeding within the first two weeks of life. The relationship between bleeding in early infancy and vitamin K deficiency, however, was not established until much later. In their 1952 landmark study of over 33,000 infants, Dam and colleagues showed that vitamin K administered in the perinatal period could prevent hypoprothrombinemia. Determination of the optimal method for administering vitamin K took several additional years.[1,2] In 1961, the American Academy of Pediatrics began recommending routine prophylaxis with 0.5 to 1 mg dose of vitamin K given intramuscularly (IM) as a single dose within an hour of delivery to prevent VKDB.[3] That initial recommendation remains unchanged forty years later.

Classification

VKDB, the term adopted by the Committee of the International Society on Thrombosis and Hemostasis in 1999, is defined as an acquired coagulopathy secondary to reduced levels of vitamin K-dependent coagulation factors II (prothrombin), VII, IX, and X. Vitamin K is necessary in the hepatic post-translational carboxylation of glutamic acid residues on these factors. The conversion of glutamic acid to gamma-carboxyglutamic acid creates functional calcium binding sites on the proteins, allowing them to interact with phospholipid surfaces and rendering them active. Vitamin K is also essential in the synthesis of the anticoagulant proteins C and S.[1,4-6]

VKDB can be classified according to patient age at onset: early (within the first day of life), classic (within the first week), and late (from the second week to six months of age). Early VKDB is rare and almost exclusively related to placental transfer of drugs which inhibit vitamin K activity, such as carbamazepine, phenytoin, rifampin, or warfarin. Classic VKDB is the most common form, occurring in 0.25 to 1.5% of newborns without prophylaxis. This form is typically associated with inadequate vitamin K intake, resulting from a delay in feeding or consumption of an inadequate volume of breastmilk or formula. Late VKDB is also rare, occurring in 5 to 7 of every 100,000 live births without prophylaxis. The development of late VKDB suggests long-standing inadequacy of vitamin K intake, malabsorption, or impaired utilization. While rare, late VKDB is a cause of significant morbidity and mortality. Intracranial hemorrhage occurs in up to 60% of affected infants.[1,4-6]

Rationale for current practice

At birth, all neonates are vitamin K deficient because of limited transfer across the placenta. Serum vitamin K concentrations in newborns are only 30 to 60% of those in adults, but steadily rise within the first weeks of life. While often having undetectable levels at birth, most healthy, breastfed infants will achieve serum concentrations close to an average adult value of 0.4 ng/ml within six weeks. Infants fed with standard vitamin-fortified formulas have much higher vitamin K concentrations, often as much as 10 fold higher, within days after birth.

Administration of vitamin K in the immediate postnatal period provides a rapid increase in serum concentrations and vitamin K-dependent

clotting factors. While administration of a single dose by any route appears to be adequate for the prevention of classic VKDB, the current standard of practice in the United States is to give as phytonadione, a lipid-soluble synthetic vitamin K_1 analog (AquaMEPHYTON®; Merck), by the intramuscular (IM) route. IM administration produces very high vitamin K concentrations initially, with a gradual decline over several months, providing protection against the development of late VKDB. When compared at 4 weeks of age, infants given IM vitamin K were found to have serum concentrations 1.5 times greater than breastfed infants given no prophylaxis.[1]

With the rarity of VKDB, demonstrating a statistically significant reduction in incidence has been difficult; however, two studies have documented a significant decrease in the incidence of neonatal bleeding.[7,8] Several other clinical trials have demonstrated the efficacy of IM vitamin K by secondary endpoints, such as increasing prothrombin index and reducing serum concentrations of nonfunctional clotting factor precursors, also referred to as proteins induced in vitamin K absence (PIVKA).[9-11]

The controversial link to cancer

In the early 1990s, Golding and colleagues from Southwestern England first suggested that IM vitamin K administration might be associated with an increased risk of childhood cancer.[12,13] In their retrospective study, a group of 180 children with cancer were evaluated with a cohort of 507 healthy children.[13] The odds ratio was 2.65 (98% confidence interval 1.34 to 5.24) for acute lymphocytic leukemia and 1.97 (confidence interval 1.04 to 2.84) for all forms of cancer. The mechanism for this association was suggested from *in vitro* studies where the presence of IM vitamin K induced single and double-strand DNA breaks, increasing sister chromatid exchanges, and the knowledge that IM administration often leads to initial serum concentrations 10,000 times higher than endogenous levels.

Several papers have challenged this association. The Golding study was limited by its small sample size and lack of consistent methods for vitamin K administration. In a larger cohort study, Ekelund and colleagues evaluated over 1 million infants born in Sweden between 1973 and 1989.[14] In this study, 2,354 children were diagnosed with cancer. Analysis of the patients revealed no difference in cancer rates between children receiving IM and oral vitamin K. The odds ratio was 0.90 (95% confidence interval 0.70 to 1.16) for leukemia and 1.01 (confidence interval 0.88 to 1.17) for all cancers.

In September 1993, Klebanoff and coworkers from the National Institutes of Health published the results of their nested cohort study using prospective controls.[15] This trial identified 48 cases of childhood cancer among 54,795 children in the Collaborative Perinatal Project from 1959 through 1966. Vitamin K had been administered to 68% of the 44 cases available for evaluation and in 71% of the 228 matched controls. The odds ratio was 0.47 (95% confidence interval 0.14 to 155) for leukemia and 1.08 (confidence interval 0.45 to 2.61) for all cancers. The authors concluded that there was no clear association between IM vitamin K administration and childhood cancer, although a slight increase in risk could not be ruled out. When weighing the benefits of preventing VKDB versus this risk, they suggested that routine prophylaxis not be abandoned.

Several other studies have also refuted the link between IM vitamin K and cancer. In a review of the evidence available to date, Ross and Davies evaluated ten case-controlled studies, seven of which found no relationship and three that found only a weak relationship between the use of parenteral vitamin K and leukemia.[16] In addition, a small *in vivo* study of infants given vitamin K found no increase in sister chromatid exchanges.[17] While this information has provided a degree of assurance for the safety of IM administration, concerns over the potential risk remained. Publication of the Golding papers has led some practitioners to abandon the IM preparation and institute oral dosing regimens for vitamin K prophylaxis.

Oral vitamin K as an alternative

Oral vitamin K administration would appear to offer several advantages for routine VKDB prophylaxis. In addition to the concerns raised about a link with childhood cancer, other disadvantages with IM administration include the trauma and complications associated with this route of administration (hematoma, vessel or nerve injury, abscess, or osteomyelitis) and the higher cost of therapy.[1,2,4-6]

It is clear that oral administration of vitamin K produces adequate serum concentrations for the prevention of classic VKDB.[11,18] While no oral liquid preparation is available in the United States, the injectable product has been found to be safe and effective when given by the oral route.[19,20] In a retrospective review of 23,228 infants at the University of Missouri given a

single dose of vitamin K via nasogastric tube after birth, no cases of classic VKDB were identified over the period from 1967 to 1993.[20]

Unfortunately, the rise in the use of oral vitamin K prophylaxis has led to an increase in reports of late VKDB. A single oral dose does not typically provide the sustained elevation in serum vitamin K concentrations needed to prevent late bleeding. While most infants are receiving adequate vitamin K through breastmilk or formula after a week of life, some still have relatively low stores due to inadequate intake or hepatic dysfunction. A multidose regimen, typically three 1 or 2 mg doses given over the first two months, is used in many countries to provide prophylaxis against late VKDB.[1,2,4-6,18]

Several countries currently use an alternative mixed micellar preparation of vitamin K (Konakion MM®; Roche) for multidose oral prophylaxis. This formulation appears to provide greater absorption than traditional preparations and may make oral administration more effective. It is currently under investigation in the United States. In 1998, Greer and colleagues compared 2 mg doses of Konakion MM® given at birth and repeated at 7 and 30 days of life in 79 infants with standard IM dosing (a single 1 mg injection at birth) in 77 infants at two Wisconsin hospitals.[21] At three months, patients receiving the oral preparation had significantly higher serum vitamin K concentrations than the patients receiving the IM dose. No patients in either group experienced late VKDB. There were no significant differences in prothrombin times (INR values) between the groups. Uncarboxylated prothrombin (PIVKA II) values were elevated in three of the 77 IM patients at 56 days, but none of the 79 infants given the new oral product. The authors concluded that the mixed micellar preparation is a safe and effective alternative to traditional IM vitamin K administration. It should be noted, however, that this product is currently administered in the United Kingdom by health care providers, rather than parents, making it a considerably more expensive alternative.

Although there have been several studies which support the efficacy of oral three-dose regimens in controlled settings, there is now a significant number of reports of treatment failures in clinical practice.[22-24] Zipursky recently summarized a number of large scale surveillance studies highlighting a growing incidence of late VKDB in infants treated with oral vitamin K.[25] von Kries, Hachmeister, and Gobel recently reported treatment failures in Germany, with late VKDB occurring at a rate of 1.8 per 100,000 live births despite the use of three 2 mg doses of the mixed micellar preparation.[23,26] A similar failure rate was reported in Australia, where the recommendation for prophylaxis subsequently returned to IM administration. Switzerland reported the highest failure rate with 3.6 cases per 100,000 live births, using only two doses of the mixed micellar preparation.[23]

In the United States, the American Academy of Pediatrics formed a task force to examine the data regarding oral versus IM vitamin K dosing.[27] Based on the rise in treatment failures in countries switching to oral prophylaxis, the participants concluded that IM administration should remain the treatment of choice for VKDB prevention. It should be kept in mind, however, that no method of prevention is without fail. Although new surveillance data from Australia, where IM dosing is once again standard, and Denmark have not identified any late VKDB,[18,23] there has recently been a report following IM dosing in Italy.[28]

It has been suggested that longer regimens of oral vitamin K would prevent late VKDB while avoiding the concerns with IM use.[24] In 1992, The Netherlands adopted a regimen of 1 mg oral vitamin K at birth, followed by daily doses of 25 mcg from 1 week to 3 months of age in breastfed infants.[29] Surveillance data collected on infants receiving this regimen have revealed no cases of late VKDB.[23] Another alternative regimen now used in Switzerland consists of weekly 1 mg oral doses for two or three months with the Konakion MM® preparation.[30] The primary disadvantages of these methods are the reliance on parent compliance and the increased cost. In addition, oral administration is still hindered by unreliable intake in infants and poor absorption in infants with undiagnosed cholestasis.[1]

Summary

Intramuscular administration of vitamin K at delivery remains the cornerstone of VKDB prevention in the United States. This treatment appears to be both safe and effective for most neonates; however, concerns over the practicality and potential carcinogenicity of this regimen remain. Work continues on developing effective alternatives for the prevention of VKDB in infancy.

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Pharmacology Literature Review

Therapy review for PDA

The authors of this review focus on the use of traditional nonsteroidal anti-inflammatory agents (ie, indomethacin and ibuprofen) for closure of patent ductus arteriosus (PDA). Much of the review is devoted to a discussion of methods to reduce the renal toxicity associated with these agents. The authors also include a brief discussion of potential new therapies, such as the selective COX-2 inhibitors and nitric oxide inhibitors. Hammerman C, Kaplan M. Comparative tolerability of pharmacologic treatments for patent ductus arteriosus. **Drug Safety 2001;24:537-51.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/28/01:

1. The restriction on polyethylene glycol 3350, NF (Miralax®) was amended to allow prescribing by physicians on all pediatric services.

2. Iron sucrose (Venofer®) was added to the Formulary for patients intolerant of treatment with parenteral iron dextran. Sodium ferric gluconate complex (Ferrlecit®) was deleted.

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