New Aspects of Vitamin K Prophylaxis

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ABSTRACT

Vitamin K-deficiency bleeding (VKDB) is rare, unpredictable, and life-threatening. Warning signs such as minimal bleeds, evidence of cholestasis, and failure to thrive often are present but overlooked. Therefore VK prophylaxis is necessary, at least for breast-fed infants. Most effective is the intramuscular application, which unfortunately has real disadvantages (trauma, poor acceptance by parents) and potential risks due to very high VK levels, since VK affects not only coagulation but all processes associated with carboxylation.

Three oral doses of VK protect many babies (2-mg doses giving better protection than 1 mg) but the prevention of VKDB is not assured even with the mixed-micelle preparation. Use of small VK doses either daily or weekly seems to give effective prophylaxis without the adverse effects of intramuscular VK application.

The risks of VKDB are minimized if prophylaxis recommendations are followed and if warning signs are recognized and promptly acted upon. The next goal is the search for methods of identifying early the few infants destined to bleed so that targeted prophylaxis can replace the current "prophylaxis for all."

KEYWORDS: Vitamin K deficiency bleeding, hemorrhagic disease of the newborn, Vitamin K prophylaxis

Objectives: Upon completion of this article the reader should be able to (1) list clinical features of vitamin K-deficiency bleeding and (2) state the optimal conditions for vitamin K prophylaxis to prevent these bleedings.

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When we were asked to prepare a position paper on vitamin K (VK) in infancy on behalf of the Pediatric/Perinatal Subcommittee of the International Society of Thrombosis and Hemostasis (ISTH), we faced a major problem. The most effective prophylaxis, using intramuscular VK, stood accused of doubling the risk of childhood cancer. Fortunately, as I worked on that paper and struggled to find a solution, Maureen Andrew came to Freiburg. Within days she reviewed all the available data and was able to offer a way forward.[1] Now when new aspects are discussed we can concentrate on "fine tuning," using new data to make further progress. A chronological review will show how far we have come and help to identify areas for further endeavor.

HISTORY OF VITAMIN K

In 1894 Charles Townsend from Boston described "the hemorrhagic disease of the newborn" (HDN) in 50 neonates, of whom 31 died. Thirty-five years later Henrik

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Dam, a young Danish biochemist, suggested the existence of a fat soluble "koagulation factor" (he used the German spelling) which he later isolated and named vitamin K. For this work he justly received the Nobel Prize, because VK saved the lives of thousands of newborns by preventing and treating HDN. Prophylactic use of VK, either orally or intramuscularly, proved very effective in preventing neonatal life-threatening bleeding but its routine use suffered a setback in the early 1950s when large doses (30 mg or more was sometimes used) of water-soluble, synthetic VK_3 were found to cause hemolysis, leading to kernicterus in many neonates. The problem was solved when synkavit [editor's note: no longer on the market] was replaced by low-dose (1 mg) VK_1 (phytomenadion, Roche, Grenzach, Germany), but confidence was shaken. In the 1980s numerous cases of "late HDN," in which bleeding began after the first week of life, caused new problems. A survey in Germany including 100 infants with "late HDN" revealed that breastfed infants were predominantly at risk, boys more than girls; over 50% had intracranial bleeding and many of them died. In Germany the incidence of late HDN was 10 in 100,000 births per year, in Japan almost twice as many.[2] Single-dose intramuscular VK seemed protective but many cases occurred after one oral dose of prophylaxis. The reintroduction of intramuscular VK prophylaxis for all babies seemed the obvious solution but then, in 1992, suspicions were raised that intramuscular VK might double the risk of childhood cancer.[3] As a consequence, intramuscular VK prophylaxis was replaced in many countries by multiple oral dose prophylaxis but cases of late HDN with cerebral hemorrhage continued to occur. All the confusion did, however, provoked one immediate step forward: a consensus that the term "hemorrhagic disease of the newborn" should be gracefully retired after 100 years of faithful service. In its place came "vitamin K-deficiency bleeding" (VKDB), a term which accurately describes the pathology, does not (as did its predecessor) sound confusingly like "hemolytic disease of the newborn," and does not misleadingly imply a condition limited to the newborn period.

The dilemmas surrounding VK prophylaxis in the early 1990s can be summarized in a few questions: Is intramuscular VK (known to give effective prophylaxis) truly dangerous, as suggested? Can oral prophylaxis be made more effective by using different regimens or preparations (such as the "mixed micelle" formulation, said to be better absorbed than other formulations despite cholestasis, which is a common cause of VK deficiency)? Can oral prophylaxis be regarded as safe? At the 1997 annual general meeting of the Royal Institute of Midwives it was even debated whether routine VK prophylaxis should be abandoned altogether.[4]

How can progress be made? A key is the physiological state of VK in infants and its alteration by different modes of prophylaxis.

VITAMIN K IN INFANTS

Breastfed Infants

VK is poorly transmitted across the placental barrier. At birth VK levels are often below the detection limit of 0.02 ng/mL, yet hemostasis is good and the vast majority of newborns do not bleed. In breastfed babies given no VK supplement, measurable levels are normally found about 12 hours after birth and adult levels of 0.4 ng/mL by day 4.[5] Bleeding occurs if the VK level is far below normal, as may occur with insufficient supply (for instance, if onset of feeding is long delayed) or if absorption is deficient. The incidence of late VKDB in developed countries is about 7 to 10 per 100,000 newborns; most affected infants are breastfed and many are found to have cholestasis.[1,6]

Oral Vitamin K Prophylaxis

Formula-fed infants achieve VK levels approximately 10 times higher than those in exclusively breastfed infants[7] and, with some exceptions, are protected against both classical and late VKDB.

A single oral prophylactic dose of 1 mg VK at birth causes a significant increase in plasma levels of VK[8] and protects newborns from the classical form of VKDB. However, due to the fact that the body has an extremely limited capacity to store VK, blood levels fall again very rapidly. By 2 weeks, in normal breastfed infants given 1 mg VK_1 orally at birth, VK levels are approximately 0.8 ng/mL and later fall to unsupplemented levels.[7]

In the most vulnerable babies VKDB may occur if gaps between oral VK doses are too long, which may explain the recurrence of late VKDB after VK prophylaxis was changed from intramuscular to three oral VK (1 mg) doses at intervals of up to 5 weeks.[9] Better protection was obtained by increasing the dose from 1 to 2 mg.[10] More continuous protection is provided by weekly oral doses of 1 mg VK[11] or by daily oral doses of 25 to 50 μg (mimicking the daily VK intake of a baby fed a VK-supplemented formula milk) for 3 months.[12] This approach transfers the responsibility of VK prophylaxis to the parents which may not be appropriate if compliance cannot be assured.

Intramuscular Vitamin K Prophylaxis

Four hours after 1 mg of intramuscular VK is administered, mean plasma levels of VK are several thousand times higher than age-dependent normal levels.[5,8] By 2 weeks, VK levels are still 4 times, and by 4 weeks approximately 1.5 times the normal level in breastfed infants given no prophylaxis.[6] These sustained high levels of VK explain the longer protection afforded by intramuscular VK compared with that from single oral prophylaxis. The effect is most likely due to a "depot" function at the injection site from which VK is slowly released over many weeks.[13]

Efficacy of Different Regimens

Without prophylaxis about 7 to 10 per 100,000 newborns suffer from the late form of VKDB. VK is definitely protective. A single oral dose of VK reduces the incidence to 1.42 per 100,000,[6,15] while 3 doses reduce it to 1.29 per 100,000.[15] The dose plays an important role, since doubling the dose to 2 mg reduces the incidence to 0.44 per 100,000 births.[10] For breastfed infants a single oral dose of 1 mg at birth followed by a daily dose of 25 μg VK is highly protective, as is a weekly dose of 1 mg.[11,14] (See Table 1).

EXPLORING THE QUESTIONS

With these data in mind the following questions can be answered more precisely.

Is Vitamin K Prophylaxis Necessary?

The answer is a clear Yes. Without prophylaxis in Germany about 60 to 80 infants per year would suffer from the late form of VKDB. When VK was given according to the recommendations (1 mg at birth, 1 mg on discharge from hospital, 1 mg between 4 and 6 weeks after birth), there were 8 cases of VKDB in 1994 (an incidence of 1/100,000 births), when three doses of 1 mg oral VK were routinely given.[16] Subsequently each dose was increased to 2 mg and the annual incidence fell to 3 to 5 cases. Unfortunately there was no further reduction when, from 1997 on, the mixed micelle preparation became more widely used. It should be noted that a majority of late VKDB cases had received less VK prophylaxis than recommended or none at all. Among babies receiving the prophylaxis as recommended, the incidence is between 0.4 and 0.7 per 100,000 newborns per year. Despite the improvements, complete prevention has not yet been attained.

VK administered to women before delivering a very premature infant has not been shown to protect against subsequent periventricular hemorrhage.[17]

Is Intramuscular Vitamin K Dangerous?

There is now professional confidence that any increased risk of cancer is substantially less than the twofold increase suggested by Golding and associates[3] but even a 10% increase in the risk of cancer would adversely affect more children than would benefit from the complete prevention of VKDB.[4] Recent conclusions are that while small effects cannot be entirely ruled out there is no convincing evidence that intramuscular VK increases the risk of childhood leukemia.[18]

The main disadvantages of intramuscular VK prophylaxis are local trauma, poor acceptance by parents, and relatively high cost. In Japan intramuscular injections are avoided in children for fear of legal consequences. After intramuscular VK, rare complications such as injury to vessels and nerves, abscesses, osteomyelitis, and massive hemorrhage in infants with bleeding disorders have been reported.[6] In addition, severe complications have occurred when babies have mistakenly been injected with ephedrine, oxytoxin, and adrenaline instead of VK[19]; presumably any risk would be smaller when the mistake involved oral medication. Consideration should be given to the potential for unforeseen consequences of high VK levels following intramuscular application.[20]

How Can the Gap between Effective Protection and Low Risk Be Bridged?

Colleagues from the Netherlands[14] and Denmark,[11] learning from the physiological data on VK in infants, have used (after an initial oral dose of 1 mg VK) oral doses of only 25 μg VK daily or of 1 mg weekly. These regimens seem to be as protective against VKDB as intramuscular prophylaxis but the extremely high VK blood levels of the latter are avoided. An oral fat-soluble preparation combining vitamin D with VK could integrate two protective measures. Maureen Andrew again led the way by recommending an oral VK combination (ADEK) as a daily supplement to children with cystic fibrosis, improving their levels of PIVKA-II (an inactive precursor of prothrombin and useful indicator of VK deficiency).[21]

Table 1 Prophylaxis Failure (Complete Prophylaxis)

		Oral					
Vitamin K Prophylaxis	**Intramuscular**	**Single (1–2 mg)**	**Triple (1 mg)**	**Triple (2 mg)**	**Daily (25 μg)**	**Weekly (1 mg)**	**None**
Population $\times 10^3$	325	140	1,400	3,200	439	396	139
Incidence of VKDB per 10^5 live births	0	1.42	1.29	0.44	0	0	10
References	Zipursky[22]	von Kries, Göbel[15]	von Kries, Göbel[15]	von Kries et al[10]	Cornelisson[14]	Hansen et al[11]	von Kries, Göbel[15]

DEDICATION

In memory of Maureen Andrew, who gave so much to children, doctors, and scientists.

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