

Scientific and Standardization Committee Communications

Vitamin K Deficiency Bleeding (VKDB) in Infancy*

On behalf of the ISTH Pediatric/Perinatal Subcommittee

Anton H. Sutor[1], Rüdiger von Kries[2], E. A. Marlies Cornelissen[3], Andrew W. McNinch[4], Maureen Andrew[5]

From the [1]Universitäts-Kinderklinik, Freiburg, Germany; [2]Institut für Soziale Pädiatrie und Jugendmedizin, München, Germany; [3]University Children's Hospital, Nijmegen, The Netherlands; [4]Department of Child Health, Royal Devon and Exeter Hospital, Exeter, United Kingdom; [5]Hamilton Civic Hospital Research Centre, Henderson General Division, Hamilton, Ontario, Canada

Summary

Terminology. Replace the term "Hemorrhagic Disease of the Newborn" (HDN) by "Vitamin K Deficiency Bleeding" (VKDB), as neonatal bleeding is often not due to VK-deficiency and VKDB may occur after the 4-week neonatal period. *Definition.* VKDB is bleeding due to inadequate activity of VK-dependent coagulation factors (II, VII, IX, X), correctable by VK replacement. *Diagnosis.* In a bleeding infant a prolonged PT together with a normal fibrinogen level and platelet count is almost diagnostic of VKDB; rapid correction of the PT and/or cessation of bleeding after VK administration are confirmative. *Warning signs.* The incidence of intracranial VKDB can be reduced by early recognition of the signs of predisposing conditions (prolonged jaundice, failure to thrive) and by prompt investigation of "warning bleeds". *Classification.* VKDB can be classified by age of onset into early (<24 h), classical (days 1-7) and late (>1 week <6 months), and by etiology into idiopathic and secondary. In secondary VKDB, in addition to breast feeding, other predisposing factors are apparent, such as poor intake or absorption of VK. *VK-Prophylaxis: Benefits.* Oral and intramuscular VK (one dose of 1 mg) protect equally well against classical VKDB but intramuscular VK is more effective in preventing late VKDB. The efficacy of oral prophylaxis is increased with a triple rather than single dose and by using doses of 2 mg vitamin K rather than 1 mg. Protection from oral doses repeated daily or weekly may be as high as from i.m. VK. *VK-Prophylaxis: Risks.* VK is involved in carboxylation of both the coagulation proteins and a variety of other proteins. Because of potential risks associated with extremely high levels of VK and the possibility of injection injury, intramuscular VK has been questioned as the routine prophylaxis of choice. Protection against bleeding should be achievable with lower peak VK levels by using repeated (daily or weekly) small oral doses rather than by using one i.m. dose. *Breast feeding mothers taking coumarins.* Breast feeding should not be denied. Supervision by pediatrician is prudent. Weekly oral supplement of 1 mg VK to the infant and occasional monitoring of PT are advisable. *Conclusion.* VKDB as defined is a rare but serious bleeding disorder (high incidence of intracranial bleeding) which can be prevented by either one i.m. or multiple oral VK doses.

Introduction

Vitamin K deficiency bleeding (VKDB) in infancy is an acquired coagulopathy secondary to reduction of vitamin K (VK)-dependent coagulation factors below hemostatic levels; 30-60% of cases are associated with intracranial haemorrhage (55). Intramuscular (i.m.) administration of VK at birth seems the most effective form of prophylaxis. A reported link between i.m. VK and childhood cancer (20) prompted a number of epidemiological studies which have yielded inconsistent results; whilst most have been reassuring, the possibility of a small risk remains (46).

The Perinatal/Pediatric Subcommittee on Haemostasis of the ISTH approved an update on the following topics: 1. Terminology, definition, diagnosis and classification of VKDB; 2. VK in the neonate; 3. I.m. VK and cancer; 4. Risk-benefit analysis of VK prophylaxis; 5. Therapy; 6. Vitamin K in babies of breast feeding mothers taking oral anticoagulants.

Terminology, Definition, Diagnosis, and Classification of VKDB

Terminology

The term "Haemorrhagic Disease of the Newborn" (HDN) was coined by Charles Townsend in 1894 to describe bleeding in the early days of life which was not caused by traumatic delivery or hemophilia (60). The different causes of such bleeding were then unknown. HDN later came to mean bleeding due to VK deficiency but still implied a condition confined to neonates. The specific term "Vitamin K Deficiency Bleeding" (VKDB) should be adopted, being more informative and appropriate; neonatal bleeding is often not due to VK deficiency and VKDB often occurs after the 4-week neonatal period (54).

Definition

VKDB is defined as bleeding due to inadequate activities of VK-dependent coagulation factors (II, VII, IX, X), correctable by VK replacement.

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Correspondence to: Dr. A. H. Sutor, Univ.-Kinderklinik, Albert Ludwigs University, Mathildenstraße 1, D-79106 Freiburg, Germany – Tel.: +49 761 270 43 63; FAX Number: +49 761 270 44 81; E-mail: sutor@kkl200.ukl.uni.freiburg.de

Diagnosis

Inclusion criteria are hemorrhage and coagulation defects due to VKD.

Hemorrhage. VKDB includes bleeding at any site and whether spontaneous or iatrogenic. Common sites for spontaneous bleeding are mucus membranes, skin, umbilicus, retroperitoneum and intracranial hemorrhage, urinary and gastrointestinal tracts. Iatrogenic causes are those in which the abnormal bleeding is precipitated by venepuncture or surgery. *Coagulation defects.* There is decreased activity of the VK-dependent coagulation factors (II, VII, IX, X) while VK-independent factors are normal for age. Circulating acarboxy proteins (PIVKA = Protein Induced in Vitamin K Absence) are present. In practice, a clearly prolonged prothrombin time (PT) [International Normalized Ratio (INR) >3.5] or low Quick-value (<20%) in the presence of normal fibrinogen concentration and platelet count is highly suggestive of VKD (56). Rapid normalization (within 30-120 min) of these values after administration of VK is diagnostic (53). The so-called "near-miss" cases, in which diagnostic laboratory results are fortuitously noted (for example on pre-operative screen) before bleeding has occurred, should be recorded separately. *Exclusion criteria.* A normal PT for age (2) excludes the diagnosis of VKDB. If PT is prolonged, then coagulopathies due to impaired production must be excluded. Children with liver disease may have deficiencies of VK-independent factors, for instance of fibrinogen, from hepatocellular dysfunction. Unlike VK deficiency, consumption coagulopathies generally show not only a prolonged PT but also feature reduced fibrinogen, antithrombin (AT) and platelet count. The extremely rare hereditary deficiencies of factors V, VII, or X may need to be excluded by analysis of single factors (e.g. isolated factor VII deficiency has a normal PTT). In contrast to all other conditions requiring exclusion, only in VKDB is administration of VK followed by significant shortening of PT and cessation of bleeding.

Classification

VKDB can be classified by etiology and age of onset.

Etiology. The etiology may be considered either idiopathic or secondary. In idiopathic VKDB no cause other than breast-feeding can be demonstrated. The vast majority of breast fed infants have an adequate, albeit marginal, VK supply and do not bleed even if given no prophylactic VK. Presumably an additional risk factor is required to further lower the VK-dependent factors and cause bleeding (56) but if none other than breast feeding is identified the VKDB is termed idiopathic. In secondary VKDB additional factors impairing VK effect are diagnosed (55), such as poor intake of milk, malabsorption of VK (because of liver or bowel disease) or antagonism of VK by drugs (31). Among 108 German cases of VKDB more than 60% had previously undiagnosed hepatobiliary disease, predominantly cholestasis (56). The proportion of cases deemed idiopathic declines with increasing thoroughness of investigation.

Age at onset. VKDB can be classificied into early, classical and late VKDB with different pathogenic mechanisms and implications for VK-prophylaxis.

Early VKDB (onset <24 h of age) is rare. It is due almost exclusively to placental transfer of maternal drugs which inhibit VK-activity in the baby. The drugs include anticonvulsants (carbamazepine, phenytoin and barbiturates, but not valproic acid), antibiotics (cephalosporins), tuberculostatic agents (rifampicin, isoniazid) and VK antagonists (phenprocoumon, warfarin) (8, 9). The incidence of VKDB in newborns of mothers taking these drugs without VK supplementation varies from 6 to 12% (14, 40, 58).

Classical VKDB as described by Townsend (60) begins in the first week excluding the first 24 h, usually between days 3 and 5 and in babies with delayed or inadequate feeding. Estimates of the frequency vary from 0.25% to 1.5% in older reviews (Amer Acad Pediatr 1961) and 0-0.44% in recent reviews (30, 42). Bleeding is usually from the umbilicus, the gastrointestinal tract and skin punctures and may cause significant blood loss. Surgical procedures such as circumcision unmask subclinical cases of VKD (52). Intracranial hemorrhage (ICH) is rare but can cause significant morbidity or death.

Late VKDB begins on or after day 8, most often between weeks 2 and 8 and rarely after 3 months (5, 21, 39, 56). In co-operative studies the upper age limit was set arbitrarily at the end of week 12 (33); but infants presenting with VKDB between weeks 13 and 26 should also be reported (62). Late VKDB occurs almost exclusively in breast-fed infants, more often in boys than girls (56); its incidence ranges widely (Table 1) for reasons which may include racial variation (including maternal diet), different VK prophylaxis regimens and compliance. In early reports intracranial bleeding (ICH) was observed in 65-100% (25), but in more recent reports in 30-60% (56). Babies with late VKDB often have signs of predisposing disease (for example, prolonged jaundice with pale stools and dark urine implying cholestasis, or failure to thrive sug-

Table 1 Forms of vitamin K deficiency bleeding (VKDB) in infancy (from Sutor 1995, with kind permission of Schattauer Verlag)

	Early VKDB	Classical VKDB	Late VKDB
Age	less than 24 hours	Days 1-7 (mostly 3-5)	Week 2 to 6 months (mostly weeks 2-8)
Causes and risk factors	Drugs taken during pregnancy (some anticonvulsants, oral anticoagulants, tuberculostatics and antibiotics).	Marginal VK content in breast milk. Inadequate milk intake for any reason, including late onset of feeding.	Marginal VK content of breast milk (idiopathic). Malabsorption of VK (liver or bowel disease). Commoner in boys than girls and in summer than winter.
Location in order of frequency	Cephalhematoma, umbilicus, intracranial, intraabdominal, intrathoracic, gastrointestinal	Gastrointestinal tract, umbilicus, nose, needle-prick sites, circumcision, intracranial	Intracranial (30-60%), skin, nose, gastrointestinal tract, needle-prick sites, umbilicus, urogenital tract, intrathoracic
Frequency without VK prophylaxis	Less than 5% in high-risk groups (see causes and risk factors)	0.01% - 1.5%; wide variations due to different feeding patterns and risk factors	4 - 10 per 100,000 births (more common in South East Asia)
Avoidance measures	Stop or replace offending drugs. Give VK prophylaxis to the mother during pregnancy.	Adequate VK supply by early and adequate breast-feeding, VK prophylaxis (oral is as effective as IM)	VK prophylaxis (single IM or repeated oral). Early recognition of predisposing conditions (prolonged jaundice, failure to thrive) and prompt investigation of "warning bleeds".

gesting malabsorption) long before bleeding begins. Some even have "warning bleeds" such as mild bruises, nose bleeds or umbilical oozing as the first manifestation of VKDB, followed (sometimes days later) by intracranial hemorrhage. Earlier recognition of diseases predisposing to VKDB, and immediate investigation/treatment of "warning bleeds", help prevent the worst consequences of VKDB; too often is VKDB the presenting feature of a serious underlying disease which could have been recognized earlier (4, 42).

Vitamin K in the Neonate

Breast-fed and Formula-fed Neonates

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. Measurable levels are normally found about 12 h after birth and adult levels of 0.4 ng/ml by day 4, this is in breast-fed babies given no VK supplement (50).

Formula-fed infants achieve VK levels approximately 10 times higher than those in exclusively breast-fed infants (10) and, with some exceptions, are protected against both classical and late VKDB. The marginal supply of VK in exclusively breast-fed infants is reflected in lower VK levels and more frequent demonstration of PIVKA than in the formula-fed (64), but not in any difference in activity of the VK-dependent coagulation factors (50). Infants fed non-VK-supplemented soy-based formulas may have a higher risk of VKDB (16).

Oral Vitamin K Prophylaxis

A single oral prophylactic dose of 1 mg VK at birth causes a significant increase in plasma levels of VK (41) and protects newborns from the classical form of VKDB (30). Due to the short biological half-life, levels of VK decrease very rapidly. By 2 weeks VK levels in normal breast-fed infants given 1 mg VK_1 orally at birth are approximately 0.8 ng/ml, and subsequently 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 i.m. to three oral VK (1 mg) doses at intervals of up to 5 weeks (36). More continuous protection is provided by weekly oral doses of 1 mg VK or by daily oral doses of 25-50 μg for 3 months (7, 10-12, 23, 48, 88). This approach transfers the responsibility of VK prophylaxis to the parents which may not be appropriate if compliance cannot be assured.

Prophylaxis may be improved by using mixed micellar preparations of VK (26, 49, 61). More reliable absorption, even despite cholestasis, may necessitate use of lower doses than current preparations allow if excessive peak levels of VK are to be avoided.

Intramuscular Vitamin K Prophylaxis

I.m. VK (1 mg) results in mean plasma levels of VK at 4 h 20,000 times greater than age-dependent normal levels (41, 50). By 2 weeks VK levels are still 4 times, and by 4 weeks approximately 1.5 times the normal level in breast-fed infants given no prophylaxis (55). These sustained high levels of VK explain the longer protection afforded by i.m. VK compared to that from single oral prophylaxis.

High blood levels of VK following i.m. VK are reflected in the liver stores of VK. At birth the concentration of VK_1 in the liver is 1 ng/g (about one fifth of adult levels), giving a total liver store of only 0.1 μg. In adults 90% of the total store consists of VK_2, whereas the neonate stores only VK_1 up to the second week and then gradually accumulates VK_2, not reaching adult storage concentrations for more than one month. For several days following i.m. VK liver concentrations remain a thousand times higher than in infants not given prophylaxis (51). It is unknown whether there is any risk of exposing the blood and the liver to such high concentrations of VK.

Risk-benefit Analysis of VK Prophylaxis

Efficacy of VK Prophylaxis for the Different Forms of VKDB

Early VKDB. Prevention of early VKDB is by stopping or replacing the offending medication during pregnancy if possible, or, more commonly, by VK prophylaxis to the mother during pregnancy (9, 14, 58).

Classical VKDB. Classical VKDB is preventable by a single postnatal dose of VK. Clinical and laboratory studies have shown that an oral dose is as effective as i.m. in preventing VKDB in the first week (13, 30).

Late VKDB. Late VKDB can also be prevented by VK prophylaxis. In one study single oral prophylaxis was found to reduce the incidence 3- to 5-fold (56) whilst von Kries and Göbel (32) found a risk ratio of 5.1 with a 95% confidence interval from 1.1 to 23.1. Surveys from Japan found that triple oral prophylaxis using doses of 2 mg vitamin K_2 reduced the incidence 15- to 30-fold (22, 57), but others reported failures of prophylaxis after three doses of 1 mg VK_1 (13, 36). However, these figures must be interpreted with caution because of differences between the studies in population characteristics and in details such as intervals between VK doses. The decision to revert from triple oral to i.m. VK prophylaxis in Australia emphasises the efficacy of i.m. prophylaxis (13). Daily oral prophylaxis, as practised in the Netherlands by a daily supplement of 25 μg VK_1 in breast-fed babies in addition to an oral dose of 1 mg VK_1 at birth, seems as effective as i.m. prophylaxis (13). Intramuscular prophylaxis may form a depot of VK at the injection site and so protect for many weeks (39), increasing the chances of detecting underlying pathology before bleeding occurs. In Sweden and the USA, i.m. VK prophylaxis has almost eliminated VKDB of infancy (18, 24). Studies from the UK (42), Sweden (18), Germany (32, 56), and Switzerland (59) show that i.m. VK protects more reliably than a single oral dose. Intravenous VK does not have the depot effect of i.m. VK and so may not give the same prolonged protection (39).

Risks and Disadvantages of Different Forms of VK Prophylaxis

Comparison of oral and parenteral VK prophylaxis. The main disadvantages of oral VK prophylaxis are the unreliable intake, poor absorption in unsuspected cholestasis and short duration of effect of each dose. Wide variation in plasma VK levels occurs after oral prophylaxis (41). One dose of oral VK does not protect all babies against late VKDB (32, 42, 56, 59).

The main disadvantages of i.m. VK prophylaxis are local trauma, poor acceptance by parents, and relatively high cost (30). In Japan i.m. injections are avoided in children for fear of legal consequences. After i.m. VK rare complications such as injury to vessels and nerves, abscesses, osteomyelitis, and massive hemorrhage in infants with bleeding disorders have been reported (55). A potential problem with i.m. VK is that the extremely high blood levels may adversely affect VK activity in other proteins and organs (51). The risk of cancer will be discussed in the next section.

Intramuscular Vitamin K and the Risk of Cancer in Childhood

Theoretical Background

The recently described role of VK-dependent Gla proteins as ligands for receptor tyrosine kinases, establishes the role of VK in cell growth and transformation (28). High concentrations of VK_1 increase sister chromatid exchange in lymphocyte suspensions and produce other forms of mutagenic activity in animals. It has been postulated that the low levels of VK normally found in the fetus and neonate may protect against potentially toxic, mutagenic and carcinogenic metabolites (27). Nevertheless Cornelissen et al. (6) found that intramuscular administration of 1 mg VK_1 to six neonates did not lead to any increase in sister chromatid exchange or to chromosome aberrations. They emphasize, however, that the effect of high VK concentrations on tissues other than peripheral lymphocytes must also be considered. Presently there is no conclusive experimental evidence that VK is carcinogenic in humans (65).

Epidemiologic Studies in Children

In 1992 Golding et al. suggested from epidemiological data that the risk of childhood cancer may be doubled by i.m. but not by oral VK prophylaxis. Studies from Sweden, USA and Denmark (17, 29, 44) did not support Goldings's findings but were not directly comparable to her studies. Two later case-control studies were more comparable, avoided some flaws of the earlier work and so provided more compelling evidence (3, 37): The first included 272 children with leukemia or cancer and 334 controls matched for age and sex; the second included 109 infants with leukemia and 218 controls matched for age, sex, and hospital of birth. Records of VK administration in the neonatal period were critically assessed, avoiding shortcomings of previous studies in which, for some cases, details of VK administration had to be inferred from hospital policies. These studies (3, 37) and one more recent by McKinney et al. (40a) failed to confirm an increased risk of cancer associated with i.m. prophylaxis. Subgroup analyses in the study by von Kries et al. did show an increased risk for leukemia in the 1- to 6-year age group when compared to local but not to state controls, which was attributed to chance and multiple testing. However, the studies of Parker et al. (45a) and Passmore et al. (46) made similar observations and the latter concluded that although "the risk, if any, attributable to the use of VK cannot be large … the possibility that there is some risk cannot be excluded". The editorial by von Kries (38) summarizes the current uncertainty.

Therapy

Rapid and effective therapy is essential since VKDB carries a high risk of ICH. Vitamin K should be given, either intravenously or subcutaneously, to any bleeding infant suspected of having VKDB, even before laboratory results confirm the diagnosis (see Diagnosis). Intramuscular injection should be avoided in this circumstance since it may cause serious intramuscular bleeding. Intravenous VK should be given slowly because of the small theoretical risk of anaphylaxis. Although the effect of parenteral VK is rapid, in very severe bleeding additional therapy with whole blood, plasma, fresh frozen plasma or prothrombin complexes may be indicated.

Vitamin K in Babies of Breast-feeding Mothers Taking Oral Anticoagulants (Coumarins)

The transfer of oral anticoagulants such as warfarin, acenocoumarine and phenprocoumon into human milk is minimal (19, 34, 45); we are not aware of any report of VKDB being attributed to anticoagulant ingestion via mother's milk and firmly believe that babies should not be denied breast-feeding, which is so advantageous, because of maternal anticoagulation. Nevertheless, in theory a tiny amount of anticoagulant in breast milk might precipiate VKDB in a baby whose vitamin K status is already precarious so supervision by a pediatrician would be prudent; a weekly oral supplement of 1 mg vitamin K to the infant and occasional monitoring of PT are advisable.

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