Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject	: Advisory letter *Vitamin K supplementation in infants*	
Your reference	: VGP/VC 2989978	
Our reference	: I 429/09/RW/db/862-B	Publication no. 2010/11E
Enclosure(s)	: 2	
Date	: June 29, 2010	

Dear Minister,

In November 2009, the Dutch Association for Paediatric Medicine approached you about their proposal for a new directive on vitamin K administration to full-term infants in order to prevent bleedings as a result of vitamin K deficiency, the so-called vitamin K deficiency bleedings (Annex A). Under the current prophylaxis regime, approximately five infants develop such a bleeding every year.[1,2] In order to decrease this number, according to the new proposed directive, the dosage for vitamin K prophylaxis should be significantly higher than the current prophylaxis.

Following your request (Annex A), I am advising you about the health effects of the new proposed directive.

Method and composition of letter

This advisory letter was created based on literature study and consultations with experts (Annex B). In addition to this, Dr. M.J. Shearer of the St Thomas' Hospital in London – an internationally recognised expert in the field of vitamin K – has commented on the advice. The advice was reviewed by the standing committees on Medicine and Nutrition of the Health Council of the Netherlands.

The advisory letter has been set out as follows: first the role of vitamin K in the body and in vitamin K deficiency bleeding is explained. Factors that increase the risk of these bleedings are also discussed. The advice then concentrates on the current Dutch prophylaxis policy. Next, the new proposal from the Dutch Association for Paediatric Medicine is discussed. The advice concludes with a response to your questions and some considerations associated with this.

P.O. Box 16052
NL-2500 BB The Hague
Telephone +31 (70) 340 70 18
Telefax +31 (70) 340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 VX The Hague
The Netherlands
www.healthcouncil.nl

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Vitamin K: sources, physiological significance and consequences of too little and too much

Vitamin K is a fat-soluble vitamin. There are two main forms of vitamin K: vitamin K_1 and vitamin K_2. Vitamin K_1 (phylloquinone) is produced by plants. Good sources of vitamin K_1 are leafy green vegetables and certain vegetable oils; supplements also contain vitamin K_1. Vitamin K_2 is the collective name for a number of different menaquinones that are synthesised by certain bacteria. This synthesis occurs in the large intestine among others. Vitamin K_2 is found in fermented products.[3]

Breast milk contains 1 to 2 micrograms of vitamin K per litre and formula milk approximately 60 micrograms per litre. The higher level in formula milk is based on the level of vitamin K that occurs naturally in cows' milk.[4,5]

The extent to which vitamin K is absorbed from breast milk and formula milk and is available in the body to be used or stored, the bio-availability, has not been studied. There are estimates that approximately 80 percent of the unbound vitamin K in a supplement, is absorbed.[6,7]

Vitamin K is important for coagulation, but also plays a role in processes in the bones, vascular walls and the brain. Think of processes such as bone construction, cell differentiation and apoptosis, inflammatory reactions, oxidative processes and the synthesis of so-called sphingolipids, a type of fat found in the brain.[4,8-10] However, not enough is known about these processes to be able to determine a daily requirement of vitamin K based on these processes. Instead, the daily requirement is derived from the median intake of vitamin K. For infants, the daily requirement has been set at 2 micrograms per day.[11,12]

Vitamin K deficiency[a] in neonates can result in bleedings.[2,4,13] There are three types of vitamin K deficiency bleedings: early, classic and late. Early bleeding occurs within 24 hours after the birth and occurs mainly due to specific medication use by the mother. These are medicines that affect vitamin K metabolism, including anticoagulant medication, medication to combat seizures and medication to treat tuberculosis. Classic bleeding occurs between 24 hours and 7 days after birth. Late vitamin K deficiency bleeding occurs between 1 and 12 weeks after birth and a cerebral bleeding occurs in 50 percent of the late vitamin K deficiency bleedings.[4,14]

[a] A vitamin K deficiency is defined as a prothrombin ratio greater than 1.5 in combination with a normal number of thrombocytes.[2,13]

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

Very little research has been performed on the potential detrimental health effects associated with (excessively) high vitamin K intake. Only the protective effect of high vitamin K intake on the risk of cerebral bleedings in infants has been examined, any other effects were not examined. There has also been very little research into a high intake of vitamin K in adults. These limited studies provide no indications for harmful effects with an intake of up to 10 milligrams of vitamin K per day for no more than one month.[15] We cannot state with certainty that these findings in adults will translate to children. However, these data were supported by data from animal experimental studies on rats in which no harmful effects were observed after daily administration of 2,000 milligrams vitamin K per kilogram of body weight for 30 days.[15]

The limited availability of research into potential harmful effects of vitamin K in the short term and long term does not provide hard evidence that these effects do not exist. However, vitamin K prophylaxis has been implemented for some time in various administration forms and doses and in various countries without tangible indications of harmful effects.

However, it cannot be excluded completely that intramuscular administration of vitamin K in infants increases the risk of acute lymphoblastic leukaemia, even though the evidence for this is very weak.[4,16,17]

Factors that increase the risk of a late vitamin K deficiency bleeding under the current prophylaxis policy

Since 1990, all full-term neonates in the Netherlands receive 1 milligram of vitamin K orally after birth in order to prevent early and classic vitamin K deficiency bleedings. In addition, parents and carers are advised to give breastfed infants 25 micrograms of vitamin K daily from day 8 until they are three months old in order to prevent late vitamin K deficiency bleeding.[18,19] This advice does not apply to formula-fed infants, as formula milk contains sufficient vitamin K.

This prophylaxis offers healthy, breastfed infants adequate protection against vitamin K deficiency bleedings. However, breastfed infants with fat malabsorption are not adequately protected.[1,2] Vitamin K is less well absorbed as a result of the fat malabsorption. The fat malabsorption is usually caused by cholestasis, a condition in which bile is not transported from the liver to the intestines. Cholestasis occurs in approximately 1 in 20,000 infants.[b] [20,21] The cholestasis can be mild and temporary, but it can also be severe as a result of – for example – complete biliary atresia, in which the bile duct is blocked or absent.[4,9]

[b] In 2008 there were 184,634 live births.[20]

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

Only a portion of the infants with fat malabsorption can be traced at an early stage due to jaundice (yellowing of the skin), peri-umbilical warning bleedings, a nosebleed or blood in the faeces, and/or lighter faeces and (dark) yellow urine. There are currently no other options for early forms of diagnosis.

Formula milk and vitamin K deficiency bleedings

Compared to the current prophylaxis policy for breastfed infants, formula milk does offer infants with fat malabsorption good protection against late vitamin K deficiency bleedings.[4,24,25] In the period 1991-2003, 25 of the 30 breast-fed infants with biliary atresia developed a vitamin K deficiency bleeding and only 1 of the 93 formula-fed infants with biliary atresia. This could be due to:

- The higher dose of 50 micrograms of vitamin K that they receive spread throughout the day;[4]
- Improved bio-availability[c] of vitamin K from the formula milk compared to a supplement (drops). Possibly due to the longer bowel passage time of formula milk[26], or because the supplement is not administered simultaneously with the feed;
- and/or a greater production of vitamin K_2 by bacteria in the large intestine of formula-fed infants compared to breast-fed infants.[4,27]

As it is not know exactly why formula milk offers better protection, the level of vitamin K in formula milk was not taken as the starting point for determining the desired level of supplementation.

Efficacy of the current vitamin K prophylaxis policy

An evaluation of the current Dutch prophylaxis policy between 1992 and 1994 revealed an incidence of 0.5 infants with a late vitamin K deficiency bleeding per 100,000 infants (95 percent confidence interval runs from 0.1 to 1.6).[14]

Due to reports of late bleedings in the interim period, the policy was re-evaluated between 1 January and 31 December 2005. This evaluation revealed a higher incidence of 3.2 infants per 100,000 (95 percent confidence interval runs from 1.2 to 6.9).[1] Early and classic vitamin K

[c] Bio-availability is the extent to which a substance is absorbed by and available to the body to be used or stored.

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

deficiency bleedings did not occur in either study.[1,14] A possible reason for the higher incidence in 2005 is that, in the 1990s, breastfed infants with jaundice were switched to formula milk and as has been mentioned above, formula milk offers better protection against late vitamin K deficiency bleedings.[28] Another possible reason for the difference in incidence is that a study spanning one year is probably too short to obtain a thorough insight into the incidence of vitamin K deficiency bleedings. It is also possible that, by pure coincidence, more infants with fat malabsorption were born in 2005. Finally, the registration in 2005 may have been more complete than in the period between 1992 and 1994.[1]

A study of Dutch infants with biliary atresia confirms that the current supplementation policy does not offer sufficient protection for this group. In the period from 1991 up to and including 2003, 25 of the 30 breastfed infants with biliary atresia developed a vitamin K deficiency bleeding (this was a cerebral bleeding in 13 cases), despite the fact that all 30 infants received 25 micrograms of vitamin K per day.[2]

Efficacy of the vitamin K prophylaxis proposal by the Dutch Association for Paediatric Medicine

According to the newly proposed directive from the Dutch Association for Paediatric Medicine, all infants should be given 2 milligrams of vitamin K orally after birth. The proposal also suggests that breastfed infants should receive 1 milligram of vitamin K orally each week from day 8 until they are three months old or until their daily intake contains 500 millilitres of formula milk (Annex A). Comments were made concerning these recommendations by the Dutch Association for Paediatric Medicine about when extra vitamin K should not be given or should be given in another way: for example, what should be done in the case of infants who are known to have fat malabsorption and what should be done in situations where the supplement is regurgitated or when a breast milk fortifier is used (a supplement that is added to expressed breast milk).

The proposal by the Dutch Association for Paediatric Medicine is based on infants with abnormal fat absorption due to biliary atresia. This study shows that the risk of late vitamin K deficiency bleedings in infants in the Netherlands was significantly higher than in Denmark.[2] As previously mentioned, in the Netherlands, 25 of the 30 breastfed infants with biliary atresia developed a vitamin K deficiency bleeding under the current prophylaxis policy. In Denmark this was one out of 13 infants after oral administration of 2 milligrams vitamin K after birth followed by a weekly dose of 1 milligram vitamin K. The bleeding in these infants was less severe than in

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

the Dutch infants. This finding should be interpreted cautiously, due to the small number of infants in the study. In addition, the Danish policy also does not offer complete protection. Approximately 40 percent of the Danish breastfed infants with biliary atresia in the study were vitamin K deficient and thus had an increased risk of vitamin K deficiency bleedings. This applied to 100 percent of the Dutch infants with biliary atresia.[2]

Research based on information from paediatric departments in hospitals and a national patient register in Denmark confirmed the abovementioned finding. There were no cases of late vitamin K deficiency bleedings found in 396,000 infants born during the Danish oral prophylaxis policy between 1992 and 2000 (95 percent confidence interval runs from 0 to 0.9).[29] As previously described, the incidence in the Netherlands in 2005 was 3.2 infants per 100,000 (95 percent confidence interval runs from 1.2 to 6.9).[1]

In the Danish study it also became apparent that approximately 90 percent of the infants had received all the weekly vitamin K doses.[29] The therapy compliance for the preceding week was requested in The Netherlands: 85 percent of the parents/carers reported that they had given their infants all the daily doses of vitamin K; 10 percent had given five to six doses; and 3 percent had given three or four of the daily doses.[28]

The Danish prophylaxis policy appears to offer better protection against vitamin K deficiency bleedings in breastfed infants with fat malabsorption than the current Dutch prophylaxis policy. The extent of protection is similar to that of intramuscular vitamin K prophylaxis.[2]

Other forms of vitamin K prophylaxis

In addition to the current Dutch prophylaxis policy and the new proposal from the Dutch Association for Paediatric Medicine, there are other forms of vitamin K prophylaxis, in which vitamin K is administered orally or intramuscularly (Annex A, Table 1). These other forms of oral prophylaxis do not offer adequate protection against late vitamin K deficiency bleedings.[4,25,30] Intramuscular prophylaxis does offer adequate protection, but does carry a risk of the medicines intended for the mother being mixed up with the vitamin K for the infant. This applies specifically to endometrin, which could be fatal for the infant.[31,32] When a supplement became available in the Netherlands during the 1980s for oral administration, the risk of medication switches was the most important reason for changing to oral prophylaxis. In addition, intramuscular administration can lead to localised injuries and rare complications such as an abscess or infection of bone marrow or

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

bone tissue or severe intramuscular bleeding (the latter only in children with abnormal blood clotting).[31]

One of the reasons for the existence of different types of vitamin K prophylaxis is the lack of a systematic study on the best method for preventing vitamin K deficiency bleedings.[4,25,30] The policy is also affected by the availability of vitamin K preparations.[24]

Responses to your questions

The current prophylaxis policy does not sufficiently protect breastfed infants with fat malabsorption against late vitamin K deficiency bleedings. A higher dose of vitamin K could improve this situation, but exposes healthy infants to higher plasma concentrations of vitamin K. The question "how much higher should this dosage be?" cannot be answered with certainty. No systematic research has been conducted on the efficacy of various levels of oral vitamin K prophylaxis. There is also no information about any favourable or unfavourable effects of higher dosages of vitamin K on bone quality, vascular wall function or brain function in healthy infants.

Hereby the responses:

What are the health effects of an increase in the intake from 1 milligram to 2 milligrams of vitamin K immediately after birth?

The health effects of an increase in intake from 1 milligram to 2 milligrams of vitamin K immediately after birth have not been specifically researched. It is known that a single dose of 1 milligram oral administration protects just as well against classic bleeding as 1 milligram intramuscular administration.[22] It is not known whether a dose of 2 milligrams vitamin K soon after birth offers better protection against late vitamin K deficiency bleedings. It is known that, in the Netherlands, there have been no cases of vitamin K deficiency bleedings that occurred during the first two weeks of life under the current prophylaxis regime.[1,2,13,14] It is also known that vitamin K rapidly leaves the blood.[8]

An increase in the intake from 1 milligram to 2 milligrams of vitamin K immediately after birth in all likelihood does not result in an extra health benefit during the first two weeks after birth.

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

What are the health effects of increasing the current vitamin K prophylaxis from 25 micrograms per day to 150 micrograms per day?

The effects of 150 micrograms of vitamin K per day have not been researched, but the effects of 1 milligram per week have. If we assume that these two are equally effective, it appears that an increase in the current vitamin K prophylaxis from 25 micrograms per day to 150 micrograms per day would offer infants with fat malabsorption better protection against late vitamin K deficiency bleedings.[2]

What are the health effects if vitamin K is administered weekly instead of daily, i.e. 1 milligram/week versus 150 microgram/day?

The health effects when vitamin K is given daily instead of weekly have not been studied. Ensuring therapy compliance will have a large impact on the efficacy of the oral prophylaxis. Daily oral administration best matches the current prophylaxis policy for vitamin D and K. In addition, the increase in the plasma concentration of vitamin K with a daily administration would be less great than for weekly administration, even though the health effects of this are not known.

Weekly administration of vitamin K instead of daily may result in lower therapy compliance. In addition, the consequences of (repeatedly) forgetting a dose would probably be greater.

To conclude: I recommend that the current dose of 1 milligram of vitamin K that is administered immediately after birth be maintained and the dosage from week 1 (day 8) to 3 months for breastfed infants be increased from 25 to 150 micrograms per day. As bile is required for the absorption of vitamin K in the intestines[4], which is secreted when fatty food reaches the intestines, it is recommended that the vitamin K drops be administered during breastfeeding. In addition, the comments by the Dutch Association for Paediatric Medicine remain in force for these recommendations with exceptions (see page 5 of this advisory letter).

Finally

There is not enough scientific information to make a well-informed statement about the best level of vitamin K prophylaxis. As the answers and recommendations in this advice are based on expert opinion, monitoring of the effects of the vitamin K prophylaxis is essential. The monitoring should

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

Gezondheidsraad
Health Council of the Netherlands

be aimed particularly at determining the efficacy of preventing vitamin K deficiency bleedings in infants with fat malabsorption and at possible side effects.

In addition, a number of other study questions concerning vitamin K deficiency, vitamin K supplementation and formula milk still remain. It would be desirable to perform research on the optimum dose of vitamin K for the prevention of vitamin K deficiency bleedings in infants with fat malabsorption. Particular attention should be paid to the bio-availability of vitamin K from formula milk and supplements. Research into this could possibly contribute to the development of an optimum dose or different composition of vitamin K supplements with better bio-availability for infants with fat malabsorption and/or that increases the synthesis of vitamin K in the intestines. It is also desirable to perform research on indicators of fat malabsorption, so that infants with fat malabsorption can be detected at an early stage.

Finally, the availability of the required vitamin K drops should also be considered. Currently, the 25 microgram per day oral supplement is available in the form of drops. It is technically feasible to concentrate the current drops.

With this advice, the Health Council has responded to your questions about the health effects of a new directive from the Dutch Association for Paediatric Medicine for the administration of vitamin K in full-term infants in the Netherlands. In this response, the Health Council has expanded on the proposed directive. I trust that you will be able to make a well-informed decision about the measures required to protect infants with fat malabsorption as best as possible in a very early and very vulnerable phase of life, without unnecessarily exposing other infants to very high doses.

Yours sincerely,

(signed)
Prof. D. Kromhout
Acting President

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

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P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

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P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

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P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 70 18
Telefax +31 (070)340 75 23
E-mail: rianne.weggemans@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.healthcouncil.nl

Annex **A**

Request for advice

On 8 March 2010 the chairman of the Council received a request from the Minister for Health, Welfare and Sport to advise about vitamin K. The minister wrote (letter no. VGP/VC 2989978):

In November last year I was approached by the Dutch Association for Paediatric Medicine (NVK) concerning their “new directive for vitamin K administration to full-term neonates in the Netherlands” (see appendix). When it comes to the advice on vitamin K prophylaxis in neonates, this directive clearly deviates from the current standard based on an advice from the study group on Infant Feeding from the National Cross Society, the Nutrition Information Bureau and the Dutch Association for Paediatric Medicine that was endorsed by the Food Council in 1991.

The NVK has provisionally published its new directive, but the directive has not come into force yet. The field and the various professional groups involved are familiar with the possible significant changes to the vitamin K prophylaxis policy, but cannot yet include these changes in the advice given to their patients.

The abovementioned has resulted in an unclear and undesirable situation, combined with the fact that this does affect a very vulnerable group in Dutch society. As a result of all this, I am of the opinion that this situation should be resolved as soon as possible. Due to the consequences of any changes to the current standard for vitamin K, I would like to reinforce my decision with scientific evidence. Therefore, I am asking the Health Council to implement their expertise in this matter. I have made capacity available for this via the knowledge questions at the RIVM (National Institute for Public Health and the Environment).

Request for advice

- What are the health effects of an increase in intake from 1 mg to 2 mg of vitamin K immediately after birth?
- What are the health effects of increasing the current vitamin K prophylaxis from 25 µg per day to 150 µg per day?
- What are the health effects if vitamin K is given weekly instead of daily, i.e. 1 mg/week versus 150 micrograms/day?

Appendix to the request for advice

A new directive for vitamin K administration to full-term neonates in the Netherlands, September 2009

This directive has not come into force yet. This will happen following approval by the Ministry for Health, Welfare and Sport and the Health Council. The implementation of the new directive will be announced at a national level, among others via a press release from the NVK.

Definitions and purpose of the directive

Vitamin K deficiency in neonates and infants can cause bleedings during the first few hours and up to several months after birth. This phenomenon was originally called haemorrhagic disease in neonates. The terminology was recently changed to "vitamin K deficiency bleedings" (VKDB), as a neonatal bleeding is not always the result of a vitamin K deficiency and VKDB can also occur after the neonatal period. VKDB can be divided into three categories: early (first hours after birth), classic (first week after birth) and late (between the 2nd and 12th week of life). Neonates have a limited liver supply of vitamin K. A shortage can occur particularly in breastfed infants, which can lead to a haemorrhagic complication. The recommended daily intake of 1.5 µg/kg/day is rarely achieved with breast milk. In addition, breastfed infants have a different intestinal flora compared to formula-fed children. As a result, the breastfed infant does not produce vitamin K2 (menaquinone) and these infants are at a greater risk of VKDB.

The current Dutch directive for prophylaxis with vitamin K was implemented in 1990. This has resulted in a significant decrease in the incidence of early and classic bleedings caused by vitamin K deficiency, but late bleedings still occur in the Netherlands. These late bleedings were almost exclusively described in breastfed infants with undiagnosed cholestatic liver disease.

International vitamin K directives (Table 1)

A single intramuscular administration of 1 mg vitamin K is administered after birth in many Anglo-Saxon countries (UK, USA, Canada, Australia). In the UK, parents are offered the choice of intramuscular or oral administration. Oral administration of 2 mg vitamin K is prescribed mainly in European countries (Ger-

many, Switzerland, Belgium). The subsequent maintenance dose varies: repeat of 2 mg vitamin K oral at 4-7 days and 1 month after birth (Germany, Switzerland, UK) or weekly 2 mg vitamin K oral administration for 6 months (France). In Denmark, infants were initially given 2 mg vitamin K orally at birth and for the first 3 months. All children are now given 2 mg vitamin K intramuscular.

As far as the late form of VKDB in children with malabsorption problems, the Netherlands scores differently for incidence with complete prophylaxis than Germany, Switzerland, Australia and New Zealand (data up to and including 2000). The raised prevalence of the late form of VKDB in the Netherlands could be a result of the published standpoints concerning the method of administration – oral and not intramuscular in the Netherlands – and/or the dosage – the Netherlands uses a lower dose than the surrounding countries.

Table 1 Overview of Vitamin K policy for full-term infants and available incidence figures per 100,000 live births of late bleedings in various countries.

Country	Dose immediately after birth	Dose with breastfeeding	Duration of prophylaxis	Incidence (per 100,000)
Germany	2 mg p.o.	2 mg p.o. between day 4-6 2 mg p.o. between week 4-6	N/A	0.44 (95% CI 0.2-0.9)
France	2 mg p.o.	2 mg p.o. weekly	6 months	No data
Switzerland	2 mg p.o.	2 mg p.o. day 4 2 mg p.o. week 4	N/A	No data
The Netherlands	1 mg p.o.	From 8th day 25 micrograms/day	3 months	3.2 (95% CI 1.2-6.9)
Denmark	2 mg p.o. or 2 mg i.m.	1 mg p.o. weekly	3 months	0.0 (95% CI 0-0.9)
UK	1 mg i.m. or 2 mg p.o.[a]	2 mg p.o. after 1 and 4 weeks	N/A	0.1 [26] 0.43 [26]
Australia	0.5 - 1 mg i.m. or 2 mg p.o.[a]	None or 2 mg p.o. day 3-7 and 2 mg after 6 weeks	N/A	0.2 [28] 4.1 [28]
USA[1]	1 mg i.m.	none	N/A	No data
Canada	1 mg i.m.	none	N/A	0.37 [31]

[a] If parents state that they do not want intramuscular administration; i.m.: intramuscular; p.o.: per os;
N/A: no maintenance prophylaxis is advised besides the dose immediately after birth and the doses with breastfeeding.

The dose and method of administration of vitamin K immediately after birth

An oral dose of 1 mg is sufficient for preventing the classic form of VKDB, but not for preventing the late form of VKDB in infants with malabsorption. Comparison with two prophylactic regimes in Denmark shows that the protection of this subcategory of infants can be improved significantly. Whilst ~80% of exclusively breastfed infants with biliary atresia in the Netherlands presented with a VKDB, the incidence of a VKDB in these infants in Denmark was 1/13 and 1/10 respectively, for oral administration of 2 mg at birth followed by a weekly dose of 1 mg vitamin K orally or a single administration of 2 mg intramuscular at birth. The severity of these bleedings under the Danish regimes was also mild. The higher average age upon presentation in Denmark provides further support for the robustness of the protection offered.

The pharmacokinetics of oral administration results in a lower plasma concentration after 2 weeks when compared to the intramuscular administration. A single intramuscular administration of vitamin K immediately post-partum acts as a depot and can almost entirely prevent late bleedings in infants. Oral administration of 1 mg will offer less protection against late bleedings to the neonate than 1 mg intramuscular. In order to offer the same protection, the oral dose of vitamin K immediately post-partum must be increased. This policy was included in the new directive.

The maintenance dose of vitamin K for breastfed neonates

No maintenance dose has been agreed on in the countries where vitamin K is administered as an intramuscular injection after birth, in contrast to the countries where vitamin K is given per os after birth (Table 1). The current maintenance dose in the Netherlands of 25 micrograms/day does cause an elevation of vitamin K plasma levels, but does result in significantly lower plasma levels than those achieved with formula milk. In a recent article by Van Hasselt *et al.*, the current Dutch prophylaxis schedule was compared to the Danish prophylaxis schedule (post-partum 2 mg oral, then 1 mg per week oral or post-partum 2 mg i.m.) for breastfed infants with biliary atresia. This demonstrated that the relative risk of a bleeding for these Dutch infants is many times greater than for the Danish infants (RR 77.5 for 25 µg per day oral, RR 7.2 for 1 mg per week oral, and RR 9.3 for 2 mg i.m. post-partum; compared only to formula-fed children). A daily maintenance dose of 25 µg per day orally clearly does not provide sufficient protection for the infant with cholestatic liver disease. This difference cannot be explained by differences in therapy compliance.

Maintaining a daily prophylaxis schedule offers benefits when it comes to continuity and thus compliance to the new directive. However, there is currently no proven effective regime based on daily prophylaxis. Elevation of the daily dose would “only” be a “category D recommendation” (expert opinion), a lower evidence level than either of the Danish prophylactic regimes. In theory, the consequences of repeatedly skipping, “forgetting” and/or regurgitating one administration of vitamin K in the case of weekly administration are greater, but in practice (in Denmark) this did not result in a higher incidence of VKDB. Intravenous administration of vitamin K is not advised as a prophylaxis against late bleedings.

Safety

The literature lists the disadvantages of intramuscular administration as localised trauma, relatively higher costs, risk of switching with maternal medication (particularly ergometrin), lack of acceptance by parents and rare complications after administration (abscess, osteomyelitis and intramuscular bleedings). The benefits of oral administration over parenteral administration relate mainly to the non-invasive nature, the relatively low costs, possibly greater acceptance by parents and the fact that this does not require trained medical staff. Another benefit is that "forgetting" a dose is associated with less severe consequences and that the fluctuations in vitamin K serum concentrations are smaller. Disadvantages of oral administration include problems with therapy compliance and the unpredictable absorption in the case of intestinal and liver diseases or unnoticed regurgitation. Golding *et al.* suggested that there was an increased incidence of leukaemia and other malignancies in children who had received intramuscular vitamin K. This study result caused a decrease in the intramuscular administration of vitamin K since 1990 in Sweden, Germany, the UK and Australia and this was reserved for neonates with a high risk of late VKDB. However, since then, no evidence has been found for the suggested relationship between parenteral vitamin K administration and cancer in children (summarised in a review by Ross and Davies). Roman *et al.* were also not able to demonstrate a relationship between the occurrence of solid tumours and intramuscular vitamin K administration in a study of more than 2500 children with a malignancy. As far as children who are born prematurely are concerned, it has been described that vitamin K2,3 epoxide accumulation can occur if an excessively high dose of vitamin K is administered in an infant with a relatively immature liver. It was also demonstrated that vitamin K1 has an effect on the biosynthesis of sphingolipids, which play an important role in the brain. Therefore, further scientific research on the safety of vitamin K1 is essential.

Pharmacological aspects

Vitamin K is a fat-soluble vitamin, meaning that its absorption from the gastro-intestinal tract depends greatly on the presence of conjugated bile salts. A pharmaceutical preparation of vitamin K1 has been marketed in Europe and North America for more than 50 years. The absorption of this preparation is moderate in children with cholestasis, which means that these children are most at risk of a late VKDB. The mixed micellar preparation, developed in the 1990s, was expected to enable better absorption. However, epidemiological research did not demonstrate improved efficacy in this group of children. In addition to modification of the amount of daily prophylaxis, another (hydrophilic) form of the preparation, as already exists for vitamin AD, will probably contribute to the prevention of late bleedings in children with cholestasis.

The recommendation

From this inventory, it can be concluded that the national directive from 1990 is no longer adequate in view of new insights and the surveyed practical experience. This formed the reason for developing a new directive (Table 2).

Table 2 New directive on vitamin K administration to neonates and infants.

Child	Dose immediately after birth	Dose to be started with breastfeeding on day 8 (weekly)	Duration of prophylaxis
Healthy full-term neonate	2 mg p.o.	1 mg p.o.	3 months
Full-term neonate with risk factors	One-off 1 mg i.m.	No prophylaxis	N/A

We advise the selection of a proven effective oral prophylaxis: 2 mg oral at birth, followed by a weekly oral dose of 1 mg. The crucial reason for selecting oral prophylaxis is that oral administration is just as effective as intramuscular administration on the one hand, whilst on the other hand it has neither the potential disadvantages of double protection of formula-fed children nor an (anticipated) increased chance of rejection by parents. In addition, there is also a practical consideration. In view of the large number of home births in the Netherlands, all involved midwives would have to administer intramuscular injections to neonates. A definitive recommendation has not yet been formulated for the dosage for premature babies, pending the new Cochrane review that is due. The change in the Dutch directive for the prevention of late VKDB should be accompanied by a good information campaign about the implementation of this directive for professionals and non-professionals with cooperation between the JGZ (Child Health Care), midwives, general practitioners and paediatricians.

Comments

- Risk factors: only if the oral route cannot be used or if certain medicines have been used by the mother during pregnancy and lactation, such as phenobarbital, phenytoin, rifampicin, isoniazid, phenylbutazone and vitamin K antagonists.
- Stop prophylaxis if daily feed contains more than 500 ml of formula milk.
- The same dose should be administered again if the baby regurgitates within 1 hour.
- Children who are eventually diagnosed with malabsorption should be given an adequately high dose of vitamin K.
- Extra vitamin K prophylaxis is not necessary if breast milk fortifier (BMF) is given.

This directive was composed by the authors following a request from the Dutch Association for Paediatric Medicine. The advice has been approved by the Board and by the committee on Nutrition of the NVK.

Composition of the working group:

- Dr. J.P. de Winter, paediatrician, Paediatric Medicine department, Spaarne Hospital, Hoofddorp
- Dr. K.F.M. Joosten, paediatrician-intensivist, Erasmus MC/Sophia Children's Hospital, Rotterdam, on behalf of the section Nutrition of the Dutch Association for Paediatric Medicine
- Dr. P.M. van Hasselt, paediatrician metabolic diseases, Paediatric Medicine department, Wilhelmina Children's Hospital UMC, Utrecht

- Ms. W.M. IJland, paediatrician, Paediatric Intensive Care Unit, University Medical Centre St Radboud, Nijmegen
- Prof. H.J. Verkade, paediatrician-gastro-enterologist, Paediatric Medicine department, Beatrix Children's Hospital UMCG, Groningen
- Prof. M. Offringa, paediatrician-epidemiologist, Paediatric Medicine department, Emma Children's Hospital AMC, Amsterdam

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- Dr R.H.J. Houwen
- Dr. E.A.M. Cornelissen
- Dr. J. Uitentuis
- Dr. J.A. Taminiau

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Annex **B**

Participants working conference

The experts listed below were initially consulted individually about the proposal for a new directive on vitamin K supplementation for breastfed infants. The working conference about the concept advice from the Health Council was held on 19 May 2010 and was chaired by Prof. D. Kromhout, Acting Presidient of the Health Council, with secretarial support by F.L. Büchner and Dr. R.M. Weggemans, scientific secretaries for the Health Council.

- Dr. H. Van den Berg
  Nutritionist, Nutrition Centre, The Hague
- Dr. K. Fischer
  Paediatric haematologist, University Medical Center Utrecht
- Dr. J.M. Geleijnse
  Senior lecturer, Wageningen University and Research Centre
- Dr. P. van Hasselt
  Paediatrician, University Medical Center Utrecht
- Prof. H.S.A. Heijmans
  Professor of paediatric medicine, Amsterdam Medical Center (not present at the working conference; written comments)
- Prof. L.A.H. Monnens
  Emeritus Professor paediatric nephrology, University Medical Center St Radboud Nijmegen

- Dr. F.J.M. van der Meer
  Haematologist, Leiden University Medical Center
- Prof. P.J.J. Sauer
  Professor of paediatric medicine, University Medical Center Groningen
- Prof. R.P.M. Steegers-Theunissen
  Professor of gynaecology, Erasmus Medical Center Rotterdam

The Health Council and interests

Members of Health Council Committees – which also include the members of the Advisory Council on Health Research (RGO) since 1 February 2008 – are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.