
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 8 th 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 K_{2,3} 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.

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