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Oral Versus Intramuscular Phytomenadione

Safety and Efficacy Compared

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Abstract

Oral and intramuscular phytomenadione (vitamin K1) prophylaxis became an issue following the report of a potential carcinogenic effect of intramuscular but not oral phytomenadione prophylaxis. There is increasing evidence, however, that oral phytomenadione prophylaxis is less effective for the prevention of late vitamin K deficiency bleeding (VKDB) than intramuscular prophylaxis.

Following a report of an increased cancer risk after intramuscular phytomenadione, a series of papers on this issue appeared. Although an increased risk for solid tumours could almost certainly be excluded, a potential risk for acute lymphatic leukaemia in childhood could not be ruled out definitively.

Almost all cases of late VKDB are preventable with intramuscular phytomenadione prophylaxis administered once at birth, whereas a single oral dose given at birth is much less effective. Repeated oral phytomenadione doses given to breast-fed infants either weekly (1mg) or daily (25μg) seem to be as effective as intramuscular phytomenadione prophylaxis. The efficacy of 3 oral 2mg doses with the new mixed micellar preparation ('Konakion MM') remains to be established.

Although a number of studies have failed to confirm a cancer risk with phytomenadione, these studies have been unable to rule out a risk definitely because absence of evidence is not evidence of absence. A meta-analysis of the available studies might provide 95% confidence intervals narrow enough to exclude even a small cancer risk with some certainty. Oral prophylaxis will probably be as safe as the intramuscular prophylaxis if given daily (25μg) or weekly (1mg).

Phytomenadione (vitamin K1) deficiency can account for serious bleeding in the neonatal period and in early infancy. In the neonatal period early vitamin K deficiency bleeding (VKDB) within the first 24 hours after birth and classical VKDB between day 1 and 7 have been differentiated, because of different aetiologies and outcomes.[1] Late VKDB is observed after the first week of life up to 6 months.[2]

Classical VKDB was recognised more than a hundred years ago and was originally called haemorrhagic disease of the newborn. Late VKDB was recognised in Europe in the early 1980s and has since then been given much attention because of its severity.[3]

About half of the infants with late VKDB present with intracranial haemorrhage. The condition is almost always confined to infants who are exclu-

sively breast fed, with an incidence peak between week 2 to 6 following birth and underlying cholestatic disease is often recognised after the bleeding episode.[1] Without phytomenadione prophylaxis the incidence of late VKDB in Europe was estimated to be in the range of 40 to 100 per million live births, whereas in Asia the condition appeared to be considerably more common.[4]

Almost all cases of VKDB can be prevented by intramuscular phytomenadione prophylaxis given at birth. Clinical observations[5] and laboratory investigations[6] have clearly shown that a single oral dose of phytomenadione protects against classical VKDB but is less effective for the prevention of late VKDB.[4]

Oral prophylaxis is nevertheless appealing, however, because the risk of trauma and infection associated with all intramuscular injections can be avoided. For intramuscular phytomenadione prophylaxis there is an additional risk in the setting of the delivery room: accidental administration of ergometrine in adult dosage to the newborn infant instead of phytomenadione. This risk is a real one, as shown in a recent paper on 7 cases observed over a 25-year period in 1 hospital.[7] The features of the acute toxicity syndrome (encephalopathy, seizures and peripheral vascular disturbances) are dramatic, although the long term outcome appears to be good in most infants.[7]

For the risks of intramuscular phytomenadione prophylaxis to outweigh the benefits, a presumed cancer risk,[8] if it were real, would be even more relevant.

1. Is Oral Prophylaxis as Effective as Intramuscular Prophylaxis?

The first hint that phytomenadione prophylaxis administered at birth might be protective with regard to late VKDB came from observational studies in the UK and Germany[9,10] which clearly demonstrated a dramatically reduced risk of late VKDB for intramuscular as compared with no phytomenadione prophylaxis. These observations additionally suggested that oral phytomenadione prophylaxis given as a single dose at birth was less effective than intramuscular administration. Similar observations were reported from Sweden[11] and Switzerland.[12] The respective figures illustrating these effects are shown in table I. The efficacy of single oral versus intramuscular phytomenadione prophylaxis was reviewed in the consensus statement of the Scientific and Standardization Subcommittee on Perinatal Haemostasis and confirmed the clearly higher efficacy of intramuscular prophylaxis (table I).[4]

The higher efficacy for prevention of late VKDB of intramuscular as compared with a single oral dose of phytomenadione prophylaxis could be a result of poor absorption of phytomenadione administered orally.[13] Recently, a depot effect at the site of injection was suggested as another possible

Table I. Number of cases of late vitamin K deficiency bleeding (VKDB) in relation to phytomenadione (vitamin K) prophylaxis: no prophylaxis versus intramuscular (IM) or oral single doses

Country	Year	Prophylaxis	No. of infants with late VKDB	Rate/100 000 infants	95% CI
UK[9]	1991	Nil	9	4.4	02.0 to 8.4
		Oral phytomenadione 1-2mg	7	1.5	0.6 to 3.2
		IM phytomenadione 1mg	0	0	0.0 to 0.4
Sweden[11]a	1991	Oral phytomenadione 1-2mg	16	6	3.7 to 9.8
		IM phytomenadione 1mg	0	0	0.0 to 5.6
Switzerland[12]	1986	Oral phytomenadione 1-3mg	7	6.4	2.5 to 13.1
		IM phytomenadione 1mg	0	0	0.0 to 5.3
Germany[10]	1992	Nil	10	7.2	3.5 to 13.3
		Oral phytomenadione 1-2mg	2	1.4	0.2 to 5.2
		IM or SC phytomenadione 1mg	1	0.25	0.01 to 1.32

a The original publication includes a case of bleeding with a prothrombin activity of 24%, which was omitted in this table.

CI = confidence interval; **SC** = subcutaneous.

explanation for the higher efficacy of intramuscular phytomenadione prophylaxis.[14]

Recommendations for oral phytomenadione prophylaxis had already been in place in some European countries (e.g. Sweden, Switzerland and The Netherlands) before the publication of a study that indicated a possibly increased cancer risk in children given intramuscular phytomenadione prophylaxis[8] at birth which triggered a shift to oral phytomenadione prophylaxis with multiple dose schedules in several countries (e.g. Australia, Germany and the UK). Different multiple dose schedules were used in different countries, because data on the most effective dose schedule were lacking.

The optimal approach to identify the most effective dose schedule would be a randomised controlled trial with late VKDB as an end-point. Because of the very low incidence of late VKDB (about 7 per 100 000 infants)[4] such a trial, however, would be virtually impossible because of high costs and logistical problems. Additionally, such a trial would have to confirm the null hypothesis (equal efficacy of multiple oral and intramuscular prophylaxis), which is almost impossible because most statistical tests are set up to refute rather than to confirm the null hypothesis.

Surrogate markers have therefore been used to assess the effect of different oral phytomenadione schedules. The rationale for such studies was the observation that infants who are exclusively breast fed have considerably lower plasma vitamin K levels than children receiving infant formula which is supplemented with phytomenadione.[15] Additionally, PIVKA II (proteins induced by vitamin K absence or antagonists–II), a sensitive marker for subclinical vitamin K deficiency, is never detectable in formula-fed infants aged 1 to 3 months as compared with up to 10% of children of the same age who are fully breast fed.[16]

The most systematic studies in this field were performed by Marlies Cornelissen and colleagues in The Netherlands.[16-18] These studies revealed the absence of PIVKA II in fully breast fed, 1- to 3-month-old infants who were given oral phytomenadione either daily at a dose of 0.025mg or weekly at a dose of 1mg.[17,18] No such studies have been performed for other multiple dose schedules, with doses given at birth, on day 4 to 10 and in week 4 to 6 with doses in the range of 0.5 to 2mg each.

Since late VKDB is a very rare condition there are limitations for such studies based on surrogate markers. Even if all surrogate markers are negative in several hundred children, it is still possible that bleeding might occur in the very next child. Although such studies can be used to find out which oral schedules are very likely to be ineffective and those which are promising, they cannot prove efficacy. Systematic surveillance studies on late VKDB in different countries applying different oral vitamin prophylaxis strategies are more likely to identify the most effective multiple, oral dose prophylaxis schedule.

Such a systematic comparison of the VKDB bleeding rates in 4 countries assessed with identical case definitions and similar strategies for case finding was published recently.[19] The main results of this study are summarised in table II, which also includes data from observations on late VKDB from Denmark[20] and additional data from Germany.[21] These data confirm the high efficacy of intramuscular phytomenadione prophylaxis. The main conclusions regarding multiple, oral phytomenadione regimen to be drawn from these studies are:

- 3×1mg oral phytomenadione with the cremophor preparation is less effective than intramuscular prophylaxis;
- a dose increase to 3×2mg oral phytomenadione with the cremophor preparation appears to increase the efficacy, but not to the extent of intramuscular phytomenadione;
- whether substitution of the cremophor preparation in such 3×2mg dose schedules by a new mixed micellar preparation, which is better absorbed in newborns[22] and in children with cholestasis,[23] increases the efficacy of such dose schedules remains to be established;
- daily supplements of oral phytomenadione 0.025mg or weekly supplementation of oral

Table II. Incidence of late vitamin K deficiency bleeding (VKDB) in different countries with oral phytomenadione (vitamin K) prophylaxis. The 95% confidence interval is shown in parentheses

Country	Oral doses of phytomenadione	Observation period	Birth population	Incidence/10^5 all cases[a]	Cases given the recommended prophylaxis
The Netherlands	1mg at birth + 25μg daily for wks 1-13 (breast-fed infants only)	10/92 to 12/94	439 000	0.5 (0.1 to 1.6)	0 (0 to 0.7)
Germany	3 × 1mg on days 1, 4-10 and 28-42	04/93 to 09/94	1 200 000	2.6 (1.8 to 3.7)	1.8 (1.1 to 2.8)
	3 × 2mg days 1, 4-10 and 28-42	01/95 to 12/95	800 000	0.9 (0.35 to 1.8)	0.5 (0.14 to 1.28)
Australia	3 × 1mg days 1, 3-5 and 21-28	01/93 to 03/94	325 000	2.5 (1.1 to 4.8)	1.5 (0.5 to 3.6)
Denmark	1mg (once)	04/90 to 11/92	134 500[b]	4.5 (1.6 to 10.3)	4.5 (1.6 to 10.3)
	2mg at birth + 1mg weekly for as long as breast feeding constituted >50% of the infant's nutrition	12/92 to 01/96	163 000[b]	0 (0 to 1.96)	0 (0 to 1.96)
Switzerland	2 × 2mg days 1 and 4[c]	01/95 to 12/95	83 000	4.7 (1.3 to 11.9)	1.2 (0 to 6.5)

a Infants with late VKDB in weeks 2 to 12 and no underlying condition known before the bleeding.

b Estimated number exposed.

c Mixed micellar phytomenadione preparation available and widely used.

phytomenadione 1mg appear to be as effective as intramuscular phytomenadione prophylaxis.

Based on these data it is difficult to give firm and uniform recommendations for the 'optimal phytomenadione prophylaxis' worldwide, because we simply do not know it.

2. Phytomenadione and Cancer Risk in Children

The first report about a potential association between phytomenadione prophylaxis and the risk for childhood cancer appeared in 1990.[24] This unexpected finding could not be ignored since the plasma vitamin K levels after intramuscular administration of phytomenadione 1mg exceed endogenous levels by a factor of up to 10 000.[13] The question of whether such high uptake of phytomenadione might be harmful needed rapid clarification.

The subsequent case-control study by Golding et al.[8] confirmed the presumed risk of intramuscular phytomenadione for all cancers and for leukaemia in particular. A series of ecological[25] and analytical epidemiological[26-28] studies followed which failed to confirm an increased cancer risk for intramuscular phytomenadione. In a 1996 editorial on neonatal phytomenadione, Zipursky[29] therefore suggested that it was time to abandon worries about a potential cancer risk with intramuscular phytomenadione prophylaxis.[29]

In January 1998, 4 new studies on phytomenadione and cancer were published, 3 case-control studies and 1 ecological study. Two of these studies are reassuring. The strengths of the population-based case-control study by McKinney et al.[30] are the representativeness for the population studied and the standardised and refined protocol for the abstraction of the phytomenadione exposure. The odds ratios for CNS and other solid tumours were 1.0 or below, and those for leukaemia, including acute lymphoblastic leukaemia, never exceeded 1.3 with 95% confidence intervals including 1.

Similarly reassuring are the results of the ecological study by Passmore et al.[31] From these data a cancer or leukaemia risk of the magnitude suggested the data of Golding et al.[8] appears unlikely, but a smaller, 20 to 30% increase in the cancer risk, cannot be excluded because of the methodologic limitations of this type of study.

The results from the study by Parker et al.[32] are less reassuring. Although a cancer risk with respect to solid tumours was almost certainly excluded, a 'significant' 2-fold risk for acute lymphoblastic in a subgroup of children aged 1 to 6 years was reported. There are, however, several possible biases in the design of this study – only about half of the

eligible cases were included, the exposure was not ascertained with blinding to the case-control status and no adjustment for multiple testing was made in the analyses.

Even less reassuring are the results of the case-control study by Passmore et al.[33] The most remarkable findings in this study are: a borderline significant risk for all cancers (odds ratio 1.44, 95% confidence interval 1.00 to 2.08), which was mainly caused by an increased risk for acute lymphoblastic leukaemias. This risk could partly be accounted for by abnormal delivery. Abnormal delivery, however, cannot simply be considered as a confounder, because abnormal delivery has not been identified as a risk factor for childhood cancer in previous studies. Surprisingly the cancer risk (mainly leukaemia) associated with abnormal delivery in this study was only detectable for children born in hospitals with selective intramuscular phytomenadione prophylaxis policies (administration based on specific clinical criteria including abnormal delivery) but not in those hospitals with non-selective policies (i.e. intramuscular phytomenadione prophylaxis given to all newborns or none).

In the paper of Passmore et al.,[33] a good summary of the results of all published studies on intramuscular phytomenadione and childhood cancer is given. Based on the results from these 4 recent and the previous studies, a risk for solid tumours can almost definitely be ruled out. A small risk for leukaemia cannot be excluded. A specific risk for acute lymphoblastic leukaemia in the 1- to 6-year age subgroup, as suggested by Parker et al.,[32] could not be confirmed by the data of Passmore et al.[33] and McKinney et al.[30]

One of the lessons to learn from all these studies on intramuscular phytomenadione prophylaxis and childhood cancer is that exposure to phytomenadione is very difficult to measure because phytomenadione prophylaxis is not well documented in the records. Additionally, the exposure to phytomenadione is often associated with operative delivery or other perinatal problems. Whether or not there is an unidentified risk factor for leukaemia which might account both for operative delivery or other perinatal problems and the administration of intramuscular phytomenadione prophylaxis needs further study.

3. Conclusions for Practical Decision Making

3.1 The Case for Intramuscular Prophylaxis

Almost all cases of late VKDB are preventable with intramuscular phytomenadione prophylaxis. A potential risk for acute lymphatic leukaemia in childhood cannot be ruled out definitively. Exclusion of such a risk, however, is a difficult task: the absence of evidence for a cancer risk even in several independent studies is not necessarily evidence of absence of such a cancer risk. Most statistical tests are designed to falsify the null hypothesis of no risk. Failure to falsify the null hypothesis does not mean, that the null hypothesis has to be true. Meta-analysis of the available studies on this issue might help to narrow the uncertainty further.

3.2 The Case for Multiple Oral Phytomenadione Prophylaxis

Repeated oral phytomenadione doses given to breast-fed infants either weekly at a dose of 1mg or daily at a dose of 25μg seem to be as effective as intramuscular phytomenadione prophylaxis. The evidence for such an efficacy, however, is so far based on observations in relatively small populations. Confirmation of these findings in populations of a larger size would be reassuring.

The efficacy of 3 oral 2mg doses of the new mixed micellar preparation ('Konakion MM') remains to be established.

If oral phytomenadione is used, the doses should be high if only 3 doses are given, whereas much smaller doses appear to be effective with more frequent administration.

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