Effects of oral and intramuscular vitamin K prophylaxis on vitamin K₁, PIVKA-II, and clotting factors in breast fed infants

E A M Cornelissen, L A A Kollée, R A De Abreu, J M van Baal, K Motohara, B Verbruggen, L A H Monnens

Abstract
A randomised clinical trial was conducted to establish the effects of oral and intramuscular administration of vitamin K at birth on plasma concentrations of vitamin K₁, proteins induced by vitamin K absence (PIVKA-II), and clotting factors. Two groups of about 165 healthy breast fed infants who received at random 1 mg vitamin K₁ orally or intramuscularly after birth were studied at 2 weeks and 1 and 3 months of age. Although vitamin K₁ concentrations were statistically significantly higher in the intramuscular group, blood coagulability, activities of factors VII and X and PIVKA-II concentrations did not reveal any difference between the two groups. At 2 weeks of age vitamin K₁ concentrations were raised compared with reported unsupplemented concentrations and no PIVKA-II was detectable. At 3 months vitamin K₁ concentrations were back at unsupplemented values and PIVKA-II was detectable in 11-5% of infants. Therefore, a repeated oral prophylaxis will be necessary to completely prevent (biochemical) vitamin K deficiency beyond the age of 1 month.

(Vit K deficiency is associated with haemorrhagic disease of the newborn. Three patterns of bleeding have been differentiated: early haemorrhagic disease of the newborn within 24 hours after birth, classical on days 1 to 7, and late after the first week of life. Late disease is often intracranial. These haemorrhages may be fatal or cause serious morbidity. Breast feeding has an important role in the pathogenesis of classical and late disease. Many countries recommend vitamin K prophylaxis after birth to prevent this hazard of vitamin K deficiency. Nevertheless, there are still controversies concerning the best way of providing effective prophylaxis, resulting in different policies. The safety of oral and parenteral vitamin K prophylaxis in the prevention of classical haemorrhagic disease of the newborn has been established, whereas the relationship between a single vitamin K dose at birth and late haemorrhagic disease of the newborn has not been clearly determined. Several studies have indicated that oral prophylaxis might be as effective as intramuscular administration, but these studies lack follow up beyond the first week of life. Epidemiologically, intramuscular vitamin K prophylaxis appears to have a lower incidence of failure probably because of the more reliable absorption. Oral administration has the appealing characteristics that an injection is avoided and that administration is simple, resulting in better parental acceptance.

The aim of this study was to evaluate whether oral administration of vitamin K is as effective as intramuscular administration in the prevention of vitamin K deficiency beyond the first week of life in breast fed infants. Determination of proteins induced by vitamin K absence (PIVKA-II) was used to detect biochemical vitamin K deficiency. Vitamin K is necessary for production in the liver of coagulation factors II, VII, IX, and X. The vitamin K dependent carboxylation of glutamic acid residues to γ-carboxyglutamic acid residues promotes calcium binding to these proteins which is essential for effective haemostatic function. When carboxylation is impaired because of deficiency or antagonism of vitamin K, inert precursors of prothrombin (factor II) are detected in the blood. These are known as PIVKA-II. In formula fed infants and adults PIVKA-II is not detectable, but it is found relatively frequently in breast fed infants without vitamin K prophylaxis at birth. Although biochemical markers of vitamin K deficiency are only of limited value in assessing clinical relevance, they provide a most sensitive way to determine which group of infants is at risk for haemorrhagic disease of the newborn.

Subjects and methods
A total of 331 infants, delivered spontaneously vaginally, in the University Hospital of Nijmegen or at home under midwife guidance, were enrolled. Inclusion criteria were: gestational age of 37 weeks or more, birth weight over the 2-3rd centile, and Apгар score of 7 or more at 5 minutes. The mother had to be healthy and not be taking vitamin K, anticoagulants, antibiotics, or antiepileptic drugs. All mothers intended to breast feed their child. After the parents had given informed consent the neonates received vitamin K prophylaxis on the first or second day of life. The newborns were randomly allocated to one of the two treatment groups. One group (n=165) received 1 mg vitamin K₁ orally (1 mg/ml phytomenadione, Konakion, Hoffman-La Roche). The other group (n=166) received 1 mg vitamin K₁ intramuscularly (Konakion 2 mg/ml). Some characteristics of the infants are represented in table 1. No feature was significantly different between the groups at the beginning or at other times during the study (χ² and Student’s t test).
Results of PIVKA-II determination are represented in table 2. Two weeks after birth PIVKA-II could not be demonstrated in any of the 285 infants studied. At 1 month PIVKA-II was detectable in four out of 262 infants: one in
the intramuscular group (0-8%) and three in the oral group (2-2%). PIVKA-II concentrations ranged from 0-10 to 0-47 AU/ml. The difference in percentages of positive samples after oral compared with intramuscular administration is not statistically significant (χ², p=0-34). The 95% confidence intervals of the difference were −1-5 to 4-3%. At 3 months of age PIVKA-II could be detected in 15 out of 131 infants: seven in the oral group (10-3%) and eight in the intramuscular group (12-7%). The 95% confidence interval of the difference between the oral and intramuscular group was −13-3 to 8-5% (p=0-67). PIVKA-II concentrations ranged from 0-10 to 0-32 AU/ml.

Vitamin K₁ plasma concentrations decreased significantly during follow up in both groups (Wilcoxon, p<0-001; fig 2). At 2 weeks of age the mean (SD) concentration of 1608 (873) pg/ml in the intramuscular group (n=64) was significantly higher than that of 815 (414) pg/ml in the oral group (n=74) (Mann-Whitney, p<0-0001). At 1 month of age the concentration was still significantly higher in the former group: 615 (272) pg/ml (n=84) vs 391 (207) pg/ml (n=94); p<0-0001. Remarkably, at 3 months of age concentrations were still slightly different: 329 (186) pg/ml (n=57) vs 268 (174) pg/ml (n=62); p=0-03. Plasma concentrations of vitamin K₁ did not correlate with sex, gestational age, birth weight, Apgar score, or arterial cord blood pH, nor with blood coagulability, activities of factor VII or X, or PIVKA-II concentration.

In table 3 individual results of PIVKA-II, blood coagulability, factors VII and X, vitamin K₁, and alanine aminotransferase determinations are shown for the infants positive for PIVKA-II. Values for blood coagulability and factors VII and X were not different from infants negative for PIVKA-II. Similarly, vitamin K₁ concentrations were not extremely low. At 3 months of age mean (SD) vitamin K₁ concentration in the infants positive for PIVKA-II was 221 (74) pg/ml compared with 312 (191) pg/ml in the infants negative for PIVKA-II (Mann-Whitney, p=0-16). Results of the alanine aminotransferase determinations indicate that liver dysfunction is not a major cause for the appearance of PIVKA-II. No relevant correlations between the concentration of PIVKA-II and other parameters could be detected.

### Discussion

Concentrations of vitamin K₁ in blood vary widely, according to the diet of the subject and the method used. The reference range reported for fasting adults, measured by a technique comparable with ours, ranges from 62–980 pg/ml. The reference range for neonates and infants is still unknown. Mean plasma concentrations in healthy breast fed infants of 3 months of age without vitamin K prophylaxis are reported to be 500–700 pg/ml. 10 15 Formula fed infants have much higher concentrations of

**Table 2** Presence of PIVKA-II (≥0-10 AU/ml) in breast fed infants of different ages after either oral or intramuscular vitamin K prophylaxis at birth

<table>
<thead>
<tr>
<th>Time after birth</th>
<th>Oral group</th>
<th>Intramuscular group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>0 (n=145)</td>
<td>0 (n=140)</td>
</tr>
<tr>
<td>1 month</td>
<td>3 (n=135)</td>
<td>1 (n=127)</td>
</tr>
<tr>
<td>3 months</td>
<td>7 (n=68)</td>
<td>8 (n=65)</td>
</tr>
</tbody>
</table>

**Figure 2** Mean (SD) vitamin K₁ plasma concentrations in breast fed infants at 2 weeks, 1 month, and 3 months of age after either oral or intramuscular vitamin K prophylaxis at birth.

**Table 3** Results of PIVKA-II, blood coagulability clotting factors VII and X, vitamin K₁, and alanine aminotransferase in PIVKA-II positive infants

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (months)</th>
<th>PIVKA-II (AU/ml)</th>
<th>Blood coagulability* (%)</th>
<th>Factor VII⁺ (%)</th>
<th>Factor X⁺ (%)</th>
<th>Vitamin K₁ (pg/ml)</th>
<th>Alanine aminotransferase⁺ (UI/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>1</td>
<td>0-47</td>
<td>90</td>
<td>44</td>
<td>57</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0-16</td>
<td>700</td>
<td>47</td>
<td>189</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Oral</td>
<td>1</td>
<td>0-12</td>
<td>&gt;100</td>
<td>60</td>
<td>43</td>
<td>243</td>
<td>6</td>
</tr>
<tr>
<td>IM</td>
<td>1</td>
<td>0-10</td>
<td>&gt;100</td>
<td>51</td>
<td>43</td>
<td>436</td>
<td>23</td>
</tr>
<tr>
<td>IM</td>
<td>3</td>
<td>0-32</td>
<td>&gt;100</td>
<td>99</td>
<td>52</td>
<td>190</td>
<td>20</td>
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<tr>
<td>IM</td>
<td>3</td>
<td>0-31</td>
<td>100</td>
<td>85</td>
<td>61</td>
<td>220</td>
<td>58</td>
</tr>
<tr>
<td>IM</td>
<td>3</td>
<td>0-29</td>
<td>&gt;100</td>
<td>61</td>
<td>52</td>
<td>238</td>
<td>31</td>
</tr>
<tr>
<td>IM</td>
<td>3</td>
<td>0-28</td>
<td>&gt;100</td>
<td>70</td>
<td>47</td>
<td>140</td>
<td>16</td>
</tr>
<tr>
<td>IM</td>
<td>3</td>
<td>0-22</td>
<td>&gt;100</td>
<td>66</td>
<td>51</td>
<td>125</td>
<td>13</td>
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<tr>
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<td>0-19</td>
<td>&gt;100</td>
<td>95</td>
<td>74</td>
<td>328</td>
<td>17</td>
</tr>
<tr>
<td>IM</td>
<td>3</td>
<td>0-14</td>
<td>655</td>
<td>78</td>
<td>48</td>
<td>357</td>
<td>26</td>
</tr>
<tr>
<td>IM</td>
<td>3</td>
<td>0-14</td>
<td>&gt;100</td>
<td>62</td>
<td>48</td>
<td>235</td>
<td>8</td>
</tr>
<tr>
<td>Oral</td>
<td>3</td>
<td>0-13</td>
<td>705</td>
<td>48</td>
<td>48</td>
<td>126</td>
<td>20</td>
</tr>
<tr>
<td>IM</td>
<td>3</td>
<td>0-12</td>
<td>757</td>
<td>66</td>
<td>49</td>
<td>251</td>
<td>12</td>
</tr>
<tr>
<td>IM</td>
<td>3</td>
<td>0-11</td>
<td>&gt;100</td>
<td>89</td>
<td>43</td>
<td>424</td>
<td>44</td>
</tr>
<tr>
<td>IM</td>
<td>3</td>
<td>0-11</td>
<td>&gt;100</td>
<td>72</td>
<td>67</td>
<td>77</td>
<td>51</td>
</tr>
<tr>
<td>Oral</td>
<td>3</td>
<td>0-10</td>
<td>&gt;100</td>
<td>89</td>
<td>46</td>
<td>184</td>
<td>11</td>
</tr>
<tr>
<td>Oral</td>
<td>3</td>
<td>0-10</td>
<td>&gt;100</td>
<td>67</td>
<td>63</td>
<td>357</td>
<td>18</td>
</tr>
</tbody>
</table>

*Blood coagulability and factors VII and X are expressed as a percentage of normal adult pooled plasma.

⁺Alanine aminotransferase: normal value<40 UI/l.

⁺⁺Missing value due to insufficient volume of serum.

⁺⁺⁺Activity less than mean −2 SD of PIVKA-II negative infants of that age.

IM=intramuscular.
3000–4500 pg/ml, because of the relatively high concentration of vitamin K₁ in formula (60 μg/l) compared with human milk (2 μg/l). 10 15 McNinch et al reported vitamin K₁ plasma concentrations in breast fed infants after 1 mg vitamin K₁ orally or intramuscularly at birth. 4 In the oral group the peak median concentration occurred earlier and higher in the intramuscular group, and vitamin K₁ concentrations declined rapidly, after 24 hours the mean was 23 ng/ml in the oral group and 444 ng/ml in the intramuscular group. The present study demonstrates that at 2 weeks of age vitamin K₁ concentrations are still raised; concentrations of about 1600 pg/ml after intramuscular injection and of 800 pg/ml after oral administration were found. At 1 month of age concentrations declined to about 600 and 400 pg/ml, respectively. Other reports confirm that four to six weeks after an intramuscular injection of 1 mg vitamin K₁, plasma concentrations are back at unsupplemented values. 10 16 Nevertheless, at all ages vitamin K₁ concentrations were lower after oral administration. To our knowledge, vitamin K₁ concentrations beyond the first week of life after a single oral dose were not reported before. To determine whether the lower vitamin K₁ plasma concentration after oral administration also entails a worse protection against vitamin K deficiency, we have to compare coagulation parameters.

Blood coagulability and activities of clotting factors VII and X showed no difference between the two groups. However, these coagulation tests are not sensitive enough to detect biochemical vitamin K deficiency. 17 Accordingly, blood coagulability and factors VII and X were not different in PIVKA-II positive infants compared with those who were PIVKA-II negative. In contrast to vitamin K₁ plasma concentrations and activities of clotting factors, PIVKA-II detection is a more direct reflection of vitamin K dependent carboxylation of clotting factors in the liver. As mentioned previously, detection of PIVKA-II in vitamin K deficient neonates is a sensitive, albeit not specific, method. PIVKA-II has no clinical consequences, but it does indicate whether enough vitamin K has been available to carboxylate all vitamin K dependent proteins. Prolongation of low vitamin K intake may lead to serious complications.

In cord blood, using the same method as we did, Motohara et al detected PIVKA-II in 21–5% of 102 samples. 18 At 3 to 5 days of age 50 to 60% of infants were PIVKA-II positive if they were breast fed and had not received vitamin K prophylaxis at birth. 18 At the age of 1 month 12–3% were positive. 19 Biochemical vitamin K deficiency occurs frequently in unsupplemented breast fed infants. Widdershoven et al compared PIVKA-II concentrations in breast fed and formula fed infants. 10 At 4 days of age about 10% of both groups had PIVKA-II in their blood. At 1 month of age PIVKA-II was not detected in any formula fed infant, compared with 5–5% of breast fed infants. At 3 months of age no formula fed infant was positive, compared with 7–5% of breast fed infants. Thus, formula feeding seems an effective way to prevent the appearance of PIVKA-II in the blood of young infants, probably due to the high intake of vitamin K₁.

PIVKA-II was not detectable in any of our infants at 2 weeks of age. This corresponds with the raised vitamin K₁ concentrations in both groups. Surprisingly, in four 1 month old infants PIVKA-II was detected. However, the concentration in the only positive infant of the intramuscular group was at the limit of detectability. In both groups, PIVKA-II was undetectable at any 1 month old infant had PIVKA-II detectable, while it was detectable in a few in the oral group. Exact comparison of our PIVKA-II results with those of Motohara et al 10 and Widdershoven et al 10 is hampered by the fact that our method is more sensitive. Their detection limit amounted to 0·13 compared with 0·10 AU/ml in our study. If we applied their detection limit as a selection criterion just two 1 month old infants would remain positive, thus strengthening the clinically relevant difference in PIVKA-II detectability between our supplemented and their unsupplemented 1 month old breast fed infants (χ², p<0·01). Even without correction, PIVKA-II was less frequently detected in our intramuscular group than in the unsupplemented infants of Widdershoven et al 1/(1/27 7 v 4/73, p<0·05). 10 Our oral group did not differ significantly from the unsupplemented infants of Widdershoven et al (3/135 v 4/73, p=0·21). This demonstrates that intramuscular vitamin K seems still effective at the age of 1 month, while oral vitamin K is not.

At the age of 3 months a high percentage of children in both our oral and intramuscular groups had PIVKA-II detectable, indicating that neither route was completely effective by that age. Vitamin K₁ concentrations declined to values of 300 pg/ml. Although vitamin K₁ concentrations in the intramuscular group were slightly higher than in the oral group, both concentrations seem insufficient to prevent biochemical evidence of vitamin K deficiency in all infants. Other reports confirm the reappearance of PIVKA-II after a single oral dose of vitamin K₁ administration at birth. Motohara et al reported a decrease in PIVKA-II detectability on the third and fifth day of life after a single oral dose of 5 mg vitamin K₁ at birth. 18 At 1 month of age, however, no significant reduction in PIVKA-II detectability was demonstrated unless a second oral dose was administered at 14 days of age. 19 Widdershoven et al detected PIVKA-II in none of 48 infants of 1 month old, in one of 29 infants of 2 months old, and in one of 23 infants of 3 months old after the administration of 1 mg vitamin K₁ intramuscularly at birth. 10 10

We failed to detect an association between PIVKA-II and vitamin K₁ plasma concentrations. Vitamin K₁ concentrations were not different in PIVKA-II positive children compared with PIVKA-II negative infants. This may be caused by the fact that PIVKA-II has a half life of about 70 hours and hence can still be present in plasma even when the vitamin K deficiency has been corrected. 19 Moreover, due to frequent feeds, plasma concentrations of vitamin K₁ in infants vary widely. The plasma half life of tritiated vitamin K₁ has been reported to be 120–150 minutes. 20 Information about hepatic vitamin K stores in infants is
limited. Shearer et al reported that in un-supple-
mented term neonates hepatic vitamin K1 con-
centrations were no more than about 1 ng/g liver
(fresh weight).21 Total liver stores amounted to
0.1μg. In adults a much higher mean concen-
tration of 5-5 ng/g was measured, resulting in
total stores of 8 μg. When the newborn had been
exposed to an intramuscular injection of vitamin
K1 (0.5-1 mg in 1 ml) endogenous hepatic values
remained raised for at least one week. Besides
vitamin K1 different forms of vitamin K2
(menaquinones 6 to 12) could be detected in the
liver.21 In adults menaquinones even accounted
for some 75-97% of total hepatic stores of
vitamin K on a molar basis. In the neonate,
however, menaquinones were not detectable
until about 14 days postpartum. Thereafter a
gradual build up was indicated and adult concen-
trations were attained about one month
after birth.21 However, the extent of vitamin K2 utili-
ation remains controversial. Nevertheless,
besides vitamin K1, vitamin K2 has to be
considered when assessing vitamin K status.
Altogether, the plasma vitamin K1 concentration
may not adequately represent the total amount
of vitamin K that is available as a cofactor
for the carboxylase enzyme in the liver.

Wallin has reported evidence to maturation of
the vitamin K dependent carboxylation system
in fetal-neonatal rats.22 At 7 days of neonatal age
d values of carboxylase activity were
reached. But activities of the two pathways that
provide carboxylase with reduced vitamin K2
cofactor (vitamin K epoxide reductase and
vitamin K reductase) were never as high as in
adult liver. In other words, it might be possible
that an increased requirement of vitamin K
exists in early infancy, due to immature reutili-
sation of vitamin K epoxide. The vitamin K1
reference range for fasting adults can not be
applied automatically to non-fasting young
infants. Moreover, individual difference in
efficiency maturation and therefore individual
difference in vitamin K requirement could
exist.

To summarise, single oral or intramuscular
administration of 1 mg vitamin K1 postnatally
may not offer complete protection against late
biochemical vitamin K deficiency. Correspond-
ingly, except for one infant with classical
haemorrhagic disease of the newborn,23 most
case reports of failures of vitamin K prophylaxis
concern late disease.19,24 Epidemiologically,
intrasutural vitamin K prophylaxis appears to
have a lower incidence of failure.25 In a recent
survey in the British Isles, 27 cases of haemorr-
hagic disease of the newborn were recorded.18
Seven of them occurred in spite of oral vitamin
K prophylaxis at birth. No failures were recorded
after intramuscular administration, although
there was uncertainty about intramuscular
vitamin K in one case. The relative risk for
babies who had received oral vitamin K com-
pared with babies who had received intra-
muscular vitamin K was 13:1. The relative risk
without prophylaxis was 81:1. A schedule of
repeated oral doses was considered.25 Taking
our results as well as epidemiological evidence
into account, we suggest that for complete
protection of breast fed infants against late
haemorrhagic disease of the newborn, vitamin K
administration should be repeated. Whether a
monthly, weekly, or daily administered oral
dose should be considered deserves further
investigation.

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