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Acarboxyprothrombin activity after oral prophylactic vitamin K

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SUMMARY The effect of prophylaxis with oral vitamin K (1 mg vitamin K_1 given with the first feed) on the rate of detection of acarboxyprothrombin (PIVKA II) and factor II clotting activity were analysed. Introducing such prophylaxis reduced the rates of detection of PIVKA II activity on day 5 from 48% to zero. None of the babies given prophylaxis had factor II clotting activity below 40%, compared with 34 of 95 babies not given prophylaxis. This study has important implications in the prophylaxis of both classical and late onset haemorrhagic disease of the newborn.

The need for prophylaxis with vitamin K has recently been reaffirmed.[1] There is, however, controversy as to how the vitamin should be given. Several authors have argued that oral instead of parenteral administration would spare babies the discomfort and potential risk of intramuscular or subcutaneous injections.[2 3] Fairly good absorption of vitamin K_1 given orally to healthy neonates has recently been reported.[3] Variation between subjects, however, was considerable, and the safety of oral vitamin K prophylaxis has therefore been questioned.[4]

In this study we assessed the effect of prophylaxis with oral vitamin K on the vitamin K supply of the neonate by analysing acarboxyprothrombin (PIVKA II) activity, a marker for vitamin K deficiency; we also used a coagulation test for factor II.

Patients and methods

PIVKA II and clotting analyses were performed in healthy 5 day old full term infants. We first looked at the detection rates of PIVKA II and factor II clotting activity in 95 neonates not given vitamin K prophylaxis from May to September 1985. We then compared the effect of oral prophylaxis (1 mg vitamin K_1 with first feed) on these measurements in a further 95 babies from May to September 1986. The influence of potential seasonal changes could be excluded as both groups were studied during the same months of the year. The Table shows that there were no significant differences in mean birth weights or methods of feeding (breast, formula, or mixed) between the two groups. Blood samples for measurement of PIVKA II activity and factor II clotting analysis were taken from a heel prick on day 5, at the same time as the compulsory blood sampling for screening tests for inherited disorders of metabolism and hypothyroidism.

PIVKA II activity was determined with crossed immunoelectrophoresis as described previously.[5] A whole blood clotting assay was used for factor II analysis.[6]

All mothers had given informed consent both to the blood sampling and to the vitamin K regimen.

Table 1 *Comparison of two groups of healthy full term infants*

Group	*Mean (SD) birth weight (g)*	*No breast fed*	*No breast and formula fed*	*No formula fed only*
A (no prophylaxis)	3370 (399)	66	23	8
B (1 mg vitamin K_1 orally with first feed)	3380 (403)	66	21	9

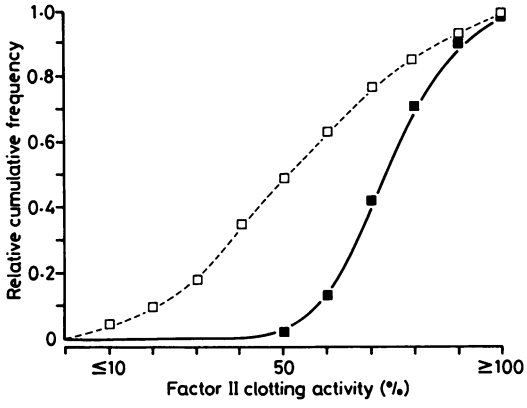

Figure *Association between factor II clotting activities in 5 day old healthy neonates and oral prophylaxis with vitamin K_1. □ no vitamin K prophylaxis, ■ 1 mg vitamin K_1 with first feed.*

The study was approved by the local ethical committee.

Results

Of 95 healthy babies not given vitamin K prophylaxis, 47 showed PIVKA II activity; none of the 95 babies given oral vitamin K did.

The cumulative distribution patterns of factor II clotting activity in babies who had and had not been given prophylactic vitamin K are shown in the Figure. None of the babies given vitamin K had factor II clotting activity below 40%, compared with 34 of the 95 babies not given vitamin K. Five of these babies, all exclusively breast fed, had severe hypoprothrombinaemia with factor II clotting activity of less than 10%.

Discussion

High detection rates of PIVKA II activity in healthy 5 and 6 day old neonates not given vitamin K prophylaxis at birth have been reported.[7] Apart from confirming these results, our data additionally give clear evidence of severe hypoprothrombinaemia in several of the babies with PIVKA II activity. This prompted us to introduce vitamin K prophylaxis and to evaluate the effect of an oral regimen.

Oral and intramuscular vitamin K prophylaxis have been shown to have similar effects on clotting factors dependent on vitamin K.[8] Using a more sensitive marker for vitamin K deficiency (PIVKA II activity), however, Motohara *et al* reported a detection rate of PIVKA II activity of 11·4% in babies given 5 mg vitamin K_2 orally at birth.[9] This prompted us to evaluate the effect of prophylaxis with oral vitamin K by giving a 1 mg dose of vitamin K_1, the only vitamin K preparation available in Europe. In our study all 95 babies given 1 mg vitamin K_1 with the first feed had no PIVKA II activity detectable on the fifth day of life and had normal factor II clotting activity. Though the blood sample may have been taken after the nadir of clotting factors dependent on vitamin K, vitamin K deficiency on previous days would not have escaped detection as PIVKA II has a 50% disappearance rate of about 50 hours.[10] These data therefore suggest that oral vitamin K_1 given as a 1 mg dose with the first feed protects against vitamin K deficiency in the neonatal period.

Several explanations might account for the high detection rates of PIVKA II activity in the series reported by Motohara *et al.*[9] Firstly, the method might not be specific enough to differentiate between neonatal prothrombin and PIVKA II activity. Secondly, some of the PIVKA II results on day 5 might arise from intrauterine vitamin K deficiency, as PIVKA II activity was found in 19·2% of the corresponding samples of cord blood with the enzyme linked immunosorbent assay used by Motohara *et al.*[9] With our method PIVKA II activity was not detectable in cord blood and interference with PIVKA II activity indicating anamnestic vitamin K deficiency therefore was unlikely.[7] Finally, the absorption and metabolism of vitamin K_2 might be different from that of vitamin K_1.

Even for vitamin K_1, however, the absorption in healthy babies varied widely,[3] but this does not seem to matter for the supply of vitamin K in the neonatal period. It might, however, be relevant to late onset vitamin K deficiency, a bleeding disorder that often presents with intracranial haemorrhage in 4–8 week old infants. Three observations (below) related to five cases of bleeding due to late onset vitamin K deficiency in this hospital cast doubt on the ability of prophylaxis with oral vitamin K to prevent late onset vitamin K deficiency.

Massive bleeding after a sample of venous blood had been taken was diagnosed in a 25 day old boy who had received 2 mg vitamin K orally with the first feed. Partial thromboplastin time and prothrombin time were prolonged, and vitamin K deficiency was proved when these measurements returned to normal within four hours of subcutaneous injection of 1 mg vitamin K_1. This boy had been fed on a formula not supplemented with vitamin K. He showed no clinical symptoms of malabsorption and had not received any antibiotics. At the time the late onset vitamin K deficiency was diagnosed he had mild cholestasis with slightly abnormal liver function test results, which could not

be attributed to bile duct atresia, viral hepatitis, cystic fibrosis, or α-1-antitrypsin deficiency.

Intracranial haemorrhage due to late onset vitamin K deficiency was diagnosed in a 45 day old boy who had been given 3 mg vitamin K_1 orally 24 days before the life threatening bleeding occurred.[11] The boy, who had not been given vitamin K prophylaxis at birth, first presented with bleeding from an insect bite when 21 days old. Coagulation studies initially showed prolonged prothrombin and partial thromboplastin times, but these returned to normal after treatment with oral vitamin K and were still normal one week later. On the forty fifth day, however, he had an intracranial haemorrhage due to vitamin K deficiency. The boy, who had been exclusively breast fed, had mild symptoms of liver disease and abnormal liver function test results due to α-1-antitrypsin deficiency. Although oral vitamin K had not been given at birth, it seems unlikely that a smaller prophylactic dose given three weeks earlier would have been effective in preventing the intracranial haemorrhage.

Massive umbilical bleeding due to vitamin K deficiency was diagnosed in a 13 day old, breast fed girl. Hypoprothrombinaemia responded promptly to oral treatment with 2 mg vitamin K_1. Vitamin K deficiency, however, recurred four times despite treatment with oral vitamin K after each episode. Although no prophylactic oral vitamin K had been given before the initial bleeding, it seems unlikely that prophylaxis at birth would have been effective in preventing the bleeding as recurrent vitamin K deficiency after oral vitamin K prophylaxis could be due to malabsorption of the vitamin.[12]

Parenteral vitamin K was safe and provided the babies with a high dose of vitamin K[3]: this might account for the fact that late onset vitamin K deficiency is rarely observed in babies given intramuscular prophylaxis, and it is certainly wiser to continue parenteral prophylaxis until the equivalent dose of oral vitamin K has been established to prevent late onset vitamin K deficiency.

The data presented in this paper encourage further studies to evaluate an appropriate dose regimen for oral vitamin K prophylaxis. Pharmacological studies[3] and clinical experience, however, suggest that much higher or repeated oral doses are required to protect against late onset vitamin K deficiency.

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