

ORIGINAL ARTICLE

Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding

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Arch Dis Child Fetal Neonatal Ed 2003;**88**:F109–F112

Objective: To determine whether the use of mixed micellar vitamin K improves the efficacy of the 3 × 2 mg oral vitamin K prophylaxis schedule.

Design: Nationwide active surveillance for vitamin K deficiency bleeding (VKDB) complemented with two surveys on the use of the mixed micellar preparation in hospitals and by paediatricians.

Setting and patients: Infants in Germany in 1997–2000.

Intervention: Prophylaxis with three oral doses of 2 mg mixed micellar vitamin K.

Main outcome measure: Confirmed VKDB between day 8 and week 12 and no condition requiring specific vitamin K supplementation known before the onset of bleeding.

Results: Twenty nine reports met the case definition: seven had not received any vitamin K prophylaxis; for three, vitamin K prophylaxis was unknown; two had insufficient vitamin K prophylaxis for their age; 17 had been given the recommended doses. The mixed micellar preparation had been given to seven, other preparations to nine, and one had been given both. These cases did not differ with respect to the site of bleeding and cholestasis detected at bleeding. Estimates of the use of the mixed micellar preparation in birth hospitals and by paediatricians yielded 1 817 769 newborns exposed to the mixed micellar preparation and 1 320 926 newborns exposed to other preparations. The rate of late VKDB was 0.44/100 000 (95% confidence interval (CI) 0.19 to 0.87) in children given mixed micellar vitamin K compared with 0.76/100 000 (95% CI 0.36 to 1.39) in children given other preparations.

Conclusion: Mixed micellar vitamin K did not significantly improve the efficacy of the 3 × 2 mg oral vitamin K prophylaxis schedule.

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Accepted 6 July 2002

Intramuscular vitamin K prophylaxis is effective in preventing classical and late vitamin K deficiency bleeding (VKDB)¹ (formerly called haemorrhagic disease of the newborn). However, there is still reluctance to recommend it for all newborns² because of concern about a potential carcinogenic effect,³ although this effect has neither been confirmed nor definitely excluded.⁴

The most efficacious oral vitamin K regimen for prevention of late VKDB remains to be established. Experience from small populations suggests that 0.025 mg given daily, as in the Netherlands,⁵ or 1 mg doses given weekly, as in Denmark,⁶ may be almost as effective as 1 mg given intramuscularly at birth, but the confidence intervals around the estimates of the incidence in these countries are wide, precluding definite conclusions about the efficacy of these approaches.⁷

Three oral doses of 2 mg vitamin K have been given to a substantial population of newborns under surveillance for late VKDB. The incidence of VKDB in these children was 0.56 (95% confidence interval (CI) 0.33 to 0.89)/100 000 live births, suggesting that this regimen is quite effective. Most of the infants who did not respond to prophylaxis had cholestatic disease.⁷ A further reduction in the incidence appeared to be possible by replacing the old cremophor vitamin K preparation with the mixed micellar oral preparation, for which good absorption, even in children with cholestatic disease, has been demonstrated.⁸ In a recent randomised controlled trial comparing breast fed infants given either 1 mg vitamin K₁ intramuscularly or 2 mg mixed micellar preparation orally at birth, on day 7, and day 30, good or even higher plasma vitamin K₁ concentrations up to the eighth week of life were observed in children on the oral regimen.⁹ Average plasma vitamin K concentrations, however, may not allow prediction of the occurrence of a rare event such as VKDB.

Does the use of the mixed micellar vitamin K preparation improve the efficacy of the 3 × 2 mg oral vitamin K prophylaxis

regimen? Active surveillance data on late VKDB collected over four years in Germany and survey data on the vitamin K preparations used were analysed.

METHODS

Surveillance for late VKDB

The heads of all paediatric hospital units in Germany receive monthly postcards which ask for the number of cases of VKDB and 11 other conditions observed in the previous month. A "nothing to report" option is included. The return rates of these postcards to Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland (German pediatric surveillance unit) (ESPED) were 94% in 1997, 95% in 1998, 94% in 1999, and 98% in 2000.

Reported cases were validated with a questionnaire asking for the location of the bleeding, the age at bleeding, type of vitamin K prophylaxis, associated disease, and the criteria required for the following case definition for late VKDB: any infant between 8 days and the end of week 12, with bruising/bleeding or intracranial haemorrhage associated with a grossly prolonged prothrombin assay, not due to an inherited coagulopathy or disseminated intravascular coagulation.

An established case definition for vitamin K deficiency as the cause of the coagulopathy was applied.¹⁰ Idiopathic and secondary cases, in which an underlying condition such as cholestasis could be identified after the bleeding, were included but not cases requiring additional vitamin K administration that were known before the bleeding.¹⁰

Abbreviations: VKDB, vitamin K deficiency bleeding; ESPED, Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland (German pediatric surveillance unit)

Information on the oral prophylactic vitamin K doses given was obtained from hospital records, the well baby booklet, or the parents' report. The recommendations for vitamin K prophylaxis in Germany for healthy babies since 1995 are 2 mg at birth, 2 mg on day 3–10, and 2 mg in week 4–6. Vitamin K prophylaxis was considered to be "as recommended" when two doses had been given until day 42 (age at bleeding up to 42 days) and three doses with an age at bleeding > 42 days. Fewer doses were considered to be "insufficient for age". The cremophor (Konaktion) and polysorbat 80 (Kanavit) preparations were the only vitamin K preparations licensed in Germany until July 1996. In August 1996, a mixed micellar preparation was launched.

Estimation of the use of different vitamin K preparations in Germany

A random sample of 100 paediatricians and 100 obstetric hospitals was analysed. The sampling frame for the paediatricians was provided by the board of German paediatricians in private practice. Paediatricians in private practice perform about 80% of all well baby visits in Germany. The third dose of vitamin K is given as part of the third well baby visit. The obstetric hospitals were sampled from a list of all obstetric hospitals in Germany provided by Nestlé.

Informative questionnaires were obtained from 88 paediatricians/94 hospitals. No information was obtained from 12 paediatricians: seven had closed their practice or did not see children in this age group anymore, and five could not be traced by mail or telephone. No information was obtained from six obstetric wards: five had been closed, and one refused to provide the information.

We asked whether vitamin K prophylaxis was given to all, at risk children only, the route of vitamin K prophylaxis (intramuscular, subcutaneous, or oral), the number and doses of oral prophylaxis, and the preparation used. If different schedules were used for at risk children, we asked for them to be specified. To assess how long the present oral vitamin K prophylaxis regimen had been practised, we asked for changes in vitamin K prophylaxis in previous years (1997, 1998, 1999) or in the course of 2000. If there had been changes in the prophylaxis regimen, we asked for details.

Statistical analysis

The populations exposed to oral prophylaxis with different preparations (mixed micellar, cremophor, or others) were estimated from the use in hospitals and private practice according to the following algorithm: for each year (1997, 1998, 1999, 2000) the proportions were estimated by the mean of the respective estimates in hospitals and from paediatricians, and the number of exposed children each year was estimated from the birth rate. Comparison of the incidence of late VKDB with three oral doses of 2 mg vitamin K given as mixed micellar preparation with other preparations was calculated by the number of cases in which the respective preparation was given and the estimated numbers exposed in Epi Info version 5.00 (χ^2 , Mantel Haenszel). The 95% CI around the incidence estimates was estimated from the Poisson distribution. The 95% CI around the prevalence estimates for the exposure to mixed micellar preparation was estimated using the exact method of Pearson-Clopper.^{10a}

RESULTS

The number of reports made to ESPED from January 1997 to December 2000 was 105. The questionnaires for 103/105 (98%) reports were returned (including 14 double reports and four false reports). There were two reports of no bleeding, 38 reports of bleeding in the first week of life most of which were not associated with vitamin K deficiency (34/38 cases), and 45 reports of bleeding in children older than 1 week. Four of the latter cases were in children aged 13–35 weeks, three were

caused by failure of management (underlying disease associated with fat malabsorption known before the bleeding but no adequate supplementation given), and there were nine cases in which the diagnosis of VKDB was not confirmed. Twenty nine cases of late VKDB in children aged 8 days to 12 completed weeks were observed. In all of these cases in which prophylaxis failed, the prothrombin clotting time was at least four times as long as in healthy controls, and vitamin K deficiency was confirmed by a documented prothrombin time normalisation after administration of vitamin K. Twenty eight of these children had been exclusively breast fed (breast + formula in one case), and 20/29 had intracranial haemorrhage. Skin, nose, and the gastrointestinal tract were other sites of bleeding (8/29). In one case, excessive bleeding after a diagnostic venepuncture for work up of suspected hyperbilirubinaemia was observed. In 21/29 cases, cholestasis was detected after the bleeding episode. In 11 of these, the cause of cholestasis was unclear at the time of reporting. There were three cases of confirmed bile duct atresia and bile duct hypoplasia. There were two cases of homozygous α_1 antitrypsin deficiency, and one case of Byler's disease and sclerosing cholangitis.

The information on vitamin K prophylaxis had been documented in the birth records or in the well baby check up booklet in all but three children with bleeding. For two of the seven children who did not receive oral vitamin K prophylaxis, the parents had explicitly refused the treatment, but in the remaining five cases the reason for the lack of treatment was not known. In 17 cases, the recommended prophylactic doses of vitamin K according to age had been given. Ten of these children had been given 3×2 mg (age at bleeding 37–71 days), and in seven cases the children had received 2×2 mg (age at bleeding 15–41 days) (table 1).

The annual total number of cases according to the case definition with vitamin K prophylaxis as recommended was in the range three to six. The number of cases in which the new mixed micellar preparation had been given increased from one in 1997 and 1998 to three in 1999 and 2000 (table 1). The number of patients with late VKDB with prophylaxis as recommended given the mixed micellar preparation did not differ from those who received the other preparations: intracerebral bleeding (5/7 v 6/10), breast feeding (7/7 v 10/10), cholestasis (6/7 v 8/10) for children given the mixed micellar preparation or other preparations respectively.

An increase in the use of the mixed micellar preparation in relation to all oral vitamin K preparations was observed during the observation period both in obstetric hospitals (from 48.9% (95% CI 38.5% to 59.5%) in 1997 to 76.6% (95% CI 66.7% to 84.7%) in 2000) and by paediatricians (40.9% (95% CI 30.5% to 51.9%) in 1997 to 62.5 (95% CI 51.5% to 72.6%) in 2000). The other two oral vitamin K preparations used during the observation period were the cremophor preparation in the

Table 1 Late vitamin K deficiency bleeding (day 8–week 12) in Germany 1997–2000

Prophylaxis	1997	1998	1999	2000
Unknown	1	0	0	2
None	1	1	3	2
Insufficient for age				
Mixed micellar	0	1	0	0
Cremophor	1	0	0	0
As recommended				
Mixed micellar	1	1	2	3
Cremophor	3	2	1	2
Polysorbat 80	0	0	0	1
Cremophor+mixed micellar	0	0	1	0
Total	7	5	7	10

Table 2 Number of cases and children exposed to different oral vitamin K proportion in 3×2 mg dose regimen in Germany 1997–2000

Preparation	Cases with oral prophylaxis	Estimated number of children exposed	Rate per 10000 (95% CI)
Mixed micellar	8	1817769	0.44 (0.19 to 0.87)
Other*	10	1320926	0.76 (0.36 to 1.39)

*Cremophor, polysorbat 80.

range decreased 36.1–6.4% in hospitals and 47.7–21.6% by paediatricians, and the polysorbat 80 preparation in the range of 10.6–14.9% in hospitals and 9.1–13.6% by paediatricians. For two hospitals (2.1%) there were missing data for year of change, and two different preparations were used by two paediatricians (2.3%).

For table 2 we attempted to estimate the proportion of children born in Germany during the observation period who were exposed to oral vitamin K prophylaxis with the mixed micellar or other vitamin K preparations, and to relate this to the number of infants given mixed micellar or other oral vitamin K prophylaxis. The case in which both the mixed micellar and the cremophor preparation were given was counted in both groups. The respective rates were slightly but not significantly lower in children given the mixed micellar preparation. The relative risk was 0.58 (95% CI 0.23 to 1.47).

DISCUSSION

The expectations about the potential of the mixed micellar preparation to prevent almost all cases of late VKDB with a 3 × 2 mg oral schedule were high. The few cases observed with this oral prophylaxis regimen were almost completely confined to children with cholestasis.⁷ The plasma concentrations up to 8 weeks of age in 63 breast fed babies on this regimen were at least as good as in the reference group given 1 mg vitamin K intramuscularly.⁹ In three children with bile duct atresia, a 20 mg dose of mixed micellar preparation was excellently absorbed.⁸

The efficacy of the mixed micellar preparation in the field, however, was less convincing. Since the introduction of this preparation in Germany, there has been no decrease in the rate of late VKDB. Compared with children given the old vitamin K preparations, the rate was only slightly lower. The proportion of children with cholestasis in prophylaxis failure cases given the mixed micellar preparation was as high as in the cases given the other preparations.

Some possible limitations of this study are discussed in the following. Surveillance was based on one data source only: clinical ESPED surveillance. We know from capture recapture studies of conditions under surveillance with ESPED that the ascertainment is in the range 40–80%.¹¹ Dramatic conditions are more likely to be in the 70–80% range of the scale¹¹; intracranial bleeding is undoubtedly a dramatic condition. In addition, there is some awareness of the vitamin K issue because of the discussion on vitamin K and cancer and the dramatic increase in the number of cases since abandonment of intramuscular/subcutaneous prophylaxis, with almost no cases in favour of a 3 × 1 mg regimen in 1993 and 13 cases in 1994.¹² Selective reporting or under-reporting of cases in which the mixed micellar prophylaxis was given does not appear likely either as there was constant reporting of cases that did not meet the case definition and cases in which no vitamin K prophylaxis was given at all.

We asked the reporting doctors to check three sources with regard to vitamin K prophylaxis: hospital records, the well baby booklet, and the parents' report. In most cases the information on administration and the preparation were based on the well baby booklet. Misclassification of the exposure therefore appears unlikely.

The exposure to vitamin K prophylaxis in the population was assessed by two surveys on random samples of sufficient size to produce estimates of reasonable precision. Most non-responses were due to closure of obstetric units or retirement of paediatricians and were therefore unrelated to the exposure of interest.

However, the estimate of the number of children exposed to mixed micellar or other vitamin K preparations is not precise. As in previous publications, we related exposure to oral vitamin K to all live births,^{5,13} although about 10% may have been considered at risk and given intramuscular or subcutaneous vitamin K prophylaxis (one third of the delivery hospitals reported that they gave different vitamin K prophylaxis to newborns considered at risk; the proportion of newborns born by caesarian section, or who are premature, or are referred to neonatal intensive care units is below 30% in German perinatal surveys (Dr Wolff, personal communication)), and we do not know the number of children given no vitamin K prophylaxis or who missed doses. The proportion of exclusively breast fed children constituting the population at risk for late VKDB was 60% on day 14 and 42% after two months according to the most recent German survey.¹⁴ Most children receive their first two vitamin K doses in hospital and the third from their paediatrician. We only know the proportion of obstetric hospitals and paediatricians giving the mixed micellar preparation, and there may be mixing of the preparations, with hospitals giving mixed micellar and paediatricians giving other preparations and vice versa. Estimation of the numbers exposed from the birth rates and a calculated average between hospitals and paediatricians by year only is crude. Although there are some limitations in the study design, none appear to invalidate the results and conclusions.

Because of the excellent absorption of a 20 mg dose of vitamin K reported in children with bile duct atresia given the mixed micellar preparation,⁸ we had expected a reduction in the incidence of late VKDB with this preparation of up to 90%, because most oral prophylaxis failures had been observed in children with cholestasis.⁷ No such reduction was observed, however. In addition, the proportion of patients with cholestasis given the mixed micellar preparation was as high as for children given other preparations.

Swiss data on a 2 × 2 mg regimen suggested a trend to higher efficacy for the mixed micellar compared with the cremophor preparation, although the difference was not significant and there are some methodological constraints (comparison with a historical group) with that study.¹⁵

Our data on the 3 × 2 mg regimen did not show a significant improvement in the efficacy of oral vitamin K prophylaxis with the mixed micellar preparation. A switch from "old vitamin K" preparations to the expensive new mixed micellar preparation for oral vitamin K prophylaxis is therefore not warranted.

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Conflict of interest: This work was supported by Roche Germany.

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