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Weekly oral vitamin K prophylaxis in Denmark

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Aim: To evaluate oral vitamin K prophylaxis at birth by giving 2 mg phytomenadione, followed by weekly oral vitamin K prophylaxis; 1 mg was administered by the parents until 3 mo of age. *Methods:* A total of 507 850 live babies were born in Denmark during the study period, November 1992 to June 2000. Of these infants, 78% and 22% received oral and intra-muscular prophylaxis, respectively; i.e. about 396 000 neonates received oral prophylaxis at birth. Weekly oral prophylaxis was recommended for all infants as long as they were mainly breastfed. A survey of possible cases of vitamin K deficiency bleeding (VKDB) was carried out by repeated questionnaires to all Danish paediatric departments and by checking the National Patient Register. *Results:* No cases of VKDB were revealed, i.e. the incidence was 0–0.9:100 000 (95% CI). The questionnaires were used to evaluate compliance with the regimen. Parents of 274 infants participated. A dose of vitamin K was regarded as having been given if the infant received a drop of vitamin K or was mostly formula-fed that week, and the prophylaxis was regarded as completed if the infant had received at least 9 doses. Compliance was good, with 94% of the infants completing the course of prophylaxis.

Conclusion: Weekly oral vitamin K supplementation during the first 3 mo of life was an efficient prophylaxis against VKBD. Parental compliance with the regimen was good.

Key words: *Haemorrhagic disease of the newborn, vitamin K deficiency bleeding, vitamin K prophylaxis*

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Vitamin K deficiency bleeding (VKDB), although a rare disorder, is a serious disease that carries a high mortality and a high frequency of neurological sequelae in surviving children. Traditional intra-muscular (i.m.) prophylaxis gives almost complete protection. Oral prophylaxis given once at birth, as used in many Western European countries in the past two decades, has now been abandoned because of unsatisfactory protection from late VKDB. Therefore, many Western countries reverted to i.m. prophylaxis or to giving a few repeated oral doses.

Only two nations recommended continuous prophylaxis, i.e. The Netherlands and Denmark. In Denmark, weekly oral prophylaxis has been practised since November 1992 to June 2000. At that time, Roche withdrew the currently used Konakion® multidose dropper bottle preparation (phytomenadione, the original cremaphor preparation) from the Danish market, without any explanation. At present, no licensed oral preparation is available in Denmark.

The aim of this study was to present the results of the Danish VKDB survey and to report on parental compliance.

Methods

Vitamin K deficiency bleeding study

We considered VKDB to be established by the following criteria: age 0–6 mo (late VKDB age 1 wk–6 mo), bleeding from any source stopped by vitamin K administration, initial very low vitamin K-dependent parameters that are normalized after vitamin K administration, matching the international consensus definition (1).

Since 1991, consultants at the 21 Danish paediatric departments have currently reported cases of possible VKDB to the Danish surveillance group (i.e. the first and third authors) and have answered an annual questionnaire. To ensure that the data were complete, they were checked against The National Patient Register, a database containing information about all discharges from Danish hospitals. We searched the diagnoses for neonatal and acquired VKDB, classified according to the Danish versions of the ICD (International Classification of Diseases) 8 and 10 and examined the retrieved discharge reports.

From November 1992 to June 2000, the oral vitamin

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K prophylactic recommendation according to the National Health authorities was 2 mg (2 drops) phytomenadione, multidose dropper bottle, Konakion®, at birth, administered by midwives, followed by 1 mg (1 drop) weekly, administered by the parents until 3 mo of age as long as the babies were more than 50% breastfed. In accordance with the guidelines, a very limited "at risk" group was recommended i.m. prophylaxis, 1 mg phytomenadione (Konakion®) at birth, also followed by weekly oral prophylaxis, as outlined above. The "risk" group included infants with a gestational age <33 wk, difficult delivery or asphyxia requiring resuscitation and infants of mothers receiving antiepileptic drugs. To calculate the number of infants given oral prophylaxis at birth, we used the annual birth-rate in Denmark, and questionnaires were sent to all 43 Danish maternity units in 1995 and in March 2000. The maternity units were asked about their vitamin K policy at birth, i.e. their indications for administering i.m. and oral prophylaxis, the fraction of neonates given i.m. prophylaxis and the annual birth-rate. Departments that did not respond to the questionnaires, despite a reminder, were interviewed by telephone.

Compliance study

All 401 general practitioners in North Jutland and Viborg counties were invited to participate in the study, resulting in an acceptance rate of 36% (144). The study period lasted from 1 April to 31 May 2000.

The Danish child vaccination schedule starts with diphtheria, tetanus, pertussis and polio vaccination at 3 mo of age. Parents visiting practitioners for their baby's first vaccination and who were willing to participate in the study completed a questionnaire immediately, during the visit. In the questionnaire they could mark "yes", "no" or "don't remember" to a question about having given vitamin K in each of the first 12 wk of life. Furthermore, they were asked to say how long the baby had been mainly breastfed.

We regarded a dose as having been given if the infant had received a drop of vitamin K or was mainly formula-fed during that week. If the parents could not remember whether a dose had been given, we considered this as not given. We regarded the prophylaxis to have been completed if an infant had received at least 9 doses.

Results

Vitamin K deficiency bleeding study

All maternity units used only the recommended vitamin K preparations, and oral prophylaxis in the majority of cases. They also administered i.m. prophylaxis to "at risk" babies. The perception of "at risk" babies varied considerably, and i.m. prophylaxis was given to a more extended population than was recommended by the health authorities. The estimated proportion of neonates given i.m. prophylaxis, based on the maternity unit survey, was unexpectedly high, at 22%. The main reason for this was that infants born by caesarean section were given i.m. prophylaxis by most maternity units and that a quarter of the centres gave i.m. prophylaxis to all premature infants with a gestational age of <37 wk, as recommended in previous Danish guidelines.

A total of 507 850 live babies were born during the period of weekly prophylaxis in Denmark. Thus, about 396 000 newborns had received oral prophylaxis at birth.

No cases with VKDB were found by either method. The incidence of VKDB after weekly oral prophylaxis was 0–0.9:100 000, 95% CI.

Compliance study

The parents of 309 children were asked to participate in the study. Nine (3%) refused. Of the 300 questionnaires that were returned to us, 26 had not been correctly filled in. Thus, the study population was reduced to 274 infants.

A total of 192 infants were exclusively breastfed during the specified 3 mo; 79 infants, mainly formula-fed for a shorter or longer time-span in the period were given prophylaxis as drops, formula or both. The numbers of infants given 0, 1, 2. 12 doses of phytomenadione were 1, 0, 0, 2, 3, 2, 1, 4, 4, 4, 13, 40 and 200, respectively. The course of prophylaxis was completed by 257 (93.8%) of the children. If we include the 26 incorrectly completed questionnaires, and perform a sensitivity analysis in the form of a best/worst case analysis, the best-case compliance would be 283/300 = 94.3%, and the worst-case compliance 257/300 = 85.6%.

Discussion

The incidence of late VKDB without prophylaxis in large-scale studies is 4–10 cases per 100 000 newborns (2–3). One milligram vitamin K i.m affords almost complete protection (2–4). The effect on late VKDB of one oral dose at birth is limited (2–3, 5). A few repeated doses offer better, but still inadequate protection (2, 6–9).

Konakion MM®, a mixed micellar product, somewhat superior to the original cremaphor preparation in absorption studies, has not proved to be significantly more effective in late VKDB surveillance studies (4, 6, and von Kries, in press). Konakion MM® is marketed in 2-mg ampoules, which is inconvenient for parents to use.

Vitamin K-enriched formulas (containing mainly 50 microg/L) provides good protection against late VKDB, since the disease is seen almost exclusively in breastfed infants (2, 4). Very few prophylactic regimens have tended to imitate formula feeding by giving continuous

prophylaxis. In The Netherlands during a regimen with 25 microgram, oral daily supplementation, three cases among 493 000 infants were found; in all three cases prophylaxis had been incomplete (6).

Weekly oral prophylaxis of late VKDB has only been studied in two small populations, both without any occurrences of late VKDB (10, 11). In one study (12) the vitamin K status was examined in 42 healthy neonates given 1 mg vitamin K orally weekly and also examined at 4, 8 and 12 wk of age. None had detectable PIVKA II (decarboxylated prothrombin, PIVKA = proteins induced by absence of vitamin K) in plasma, and vitamin K concentrations were within or above normal adult range without accumulation in any individual (12).

The Danish results of weekly prophylaxis were published after three years' experience (5). Our study confirms the good initial results: no cases of VKDB (0–0.9:100 000, 95% CI) were found in a cohort of 396 000, indicating almost complete protection, comparable with intra-muscular prophylaxis at birth. In the present study, VKDB cases retrieved from the consultants at the paediatric departments by the surveillance group were validated by checking the National Patient Register.

The present good result is not biased by a general low frequency of late VLDB in Denmark. During single at birth oral prophylaxis, late VKDB incidence in Denmark was 4.5:100 000 (5), which is comparable with other Western countries (2, 3, 5). The results were not due to formula feeding, as breastfeeding is prevalent in Denmark. Our data suggest that 71% of babies are still exclusively breastfed 3 mo after birth. Extending the use of i.m. prophylaxis to an "at risk" proportion does not improve the results, since recent studies do not show an increased risk of VKDB as a result of prematurity or instrument delivery.

Although the efficacy of any prophylactic vitamin K regimen depends largely on compliance, few compliance studies have been performed. The compliance was poor in a three-dose study (13), where the second dose was mainly administered by midwives and the third by general practitioners. Studies where the parents administered vitamin K after the first dose have shown good compliance, with more than 90% completion of prophylaxis (9, 14).

Our data suggest a good parental compliance of 94% to the once a week regimen. Selection bias was low: 1) the geographical distribution of the participating practitioners was the same as that for the whole group of practitioners in the two counties, 2) the compliance to vaccination at 3 mo of age in Denmark is 98%, 3) 97% of the invited parents participated in the survey and 4) the rather small fraction (36%) of participating general practitioners is not considered a bias factor since they were not involved in the Danish vitamin K prophylactic regimen. However, information bias was considerable, as 9.6% of the parents did not complete the questionnaire correctly. So, in the worst case the compliance was 86%. On the other hand, the compliance of 94% might be an underestimation, since the "do not remember" replies were considered to mean that the prophylaxis was not given.

The risk of cancer after i.m. vitamin K has been a matter of dispute. The review by Ross and Davies (15) concludes that no relation has been proven. Increased risk of solid tumours is excluded. Even without confirmation in population-based studies, the increased risk of lymphatic leukaemia in more locally based case-control studies is still worrying.

Intra-muscular injections to the neonates have some disadvantages. The newborn is sensitive to pain (16). There is a small risk of infection, haematoma and neuronal damage. Inadvertent injection of ergometrin intended for the mother causes a serious illness in the newborn and might be under-reported (17). Furthermore, i.m. injection of vitamin K is unphysiologic, and provides a transient plasma vitamin K level 1000 times greater than the normal adult values.

Preparations for continuous oral prophylaxis convenient for parental administration are licensed in The Netherlands (Vitamin K® drops 250 μg/g) for daily use, and recently (Orakay® 1-mg capsules) in the UK for weekly administration.

Conclusion

The data from our study indicate that continuous weekly oral prophylaxis was effective in the prevention of VKDB and that parental compliance was good.

Intra-muscular prophylaxis should be reserved for newborns with gastrointestinal function disorders, infants of mothers receiving antiepileptic drugs and very preterm infants.

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