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Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K

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Abstract There is consensus that late vitamin K deficiency bleeding (VKDB) should be prevented by vitamin K prophylaxis. One single dose of 1 mg vitamin K_1 is effective if given i.m. or s.c., but not if given orally. Repeated oral doses might be as effective as the parenteral dose but the optimal dose regimen remains to be established. Different oral dose schedules are presently used in different countries. In Australia, Germany, The Netherlands and Switzerland active surveillance data on late VKDB were collected in a similar manner and failure rates compared. Identical case definitions were used. There were three basic strategies for oral and one for parenteral vitamin K prophylaxis for healthy newborns in the four countries: (1) daily supplementation of low dose vitamin K (25 μg) for breast-fed infants (The Netherlands); (2) 3 × 1 mg orally [Australia (January 1993 – March 1994) and Germany (December 1992 – December 1994)]; (3) 1 mg vitamin K i.m. (Australia since March 1994); and (4) 2 × 2 mg vitamin K (new mixed micellar preparation) (Switzerland). The respective failure rates per 100,000 live births (including cases given all recommended doses and those given incomplete prophylaxis) were for strategy: (1) 0.2 (0–1.3) in The Netherlands; (2) 2.3 (95% CI 1.6–3.4) in Germany and 2.5 (1.1–4.8) in Australia (oral prophylaxis); (3) Australia (i.m. prophylaxis) 0 (0–0.9); and (4) 3.6 (0.7–10.6) in Switzerland. The failure rates for complete prophylaxis only were: strategy (1) 0 (0–0.7) in The Netherlands; (2) 1.8 (1.1–2.8) in Germany and 1.5 (0.5–3.6) in Australia; (3) Australia (i.m.) 0 (0–0.9); and (4) 1.2 (0–6.5) in Switzerland.

Conclusions The Australian data confirm that three oral doses of 1 mg vitamin K are less effective than i.m. vitamin K prophylaxis. A daily low oral dose of 25 μg vitamin K_1 following an initial oral dose of 1 mg after birth for exclusively breast-fed infants may be as effective as parenteral vitamin K prophylaxis. The effectiveness of the "mixed-micellar" preparation of vitamin K_1 needs further study.

Key words Vitamin K · Infancy · Prophylaxis · Late vitamin K deficiency · Bleeding

Abbreviations *CI* confidence interval · *HIV* human immunodeficiency virus · *VKBD* vitamin K deficiency bleeding

Introduction

Vitamin K prophylaxis is required for the prevention of late vitamin K deficiency bleeding (VKDB), which may be fatal or cause serious morbidity. Without prophylaxis incidences of 5–7 per 100,000 live births have been reported in Europe [10]. Administration of 1 mg vitamin K_1 i.m. is safe and effective in preventing late VKDB, and has been common practice in the U.S.A. since 1961, whereas a single oral dose of vitamin K_1 at birth is less effective [10].

In 1992, an unexpected association between i.m. vitamin K prophylaxis in the neonatal period and later childhood cancer was reported [7]. Although unconfirmed, the report caused considerable concern worldwide and prompted changes in national prophylaxis policies in several countries [5, 6]. In most of these countries the use of repeated oral vitamin K was re-

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commended for healthy neonates, reserving i.m. administration for ill newborns, in whom oral administration is impractical. Different countries, however, adopted different regimens. In Germany and Australia three oral doses of 1 mg vitamin K_1 were recommended in 1992 [5]. In the Netherlands a small daily dose of 25 μg is prescribed for breast-fed infants in addition to a 1 mg vitamin K dose at birth either orally for healthy neonates or i.m. in those unwell [22]. In Switzerland two oral doses of a new mixed-micellar vitamin K_1 preparation have been recommended since 1995 [19].

Is repeated oral prophylaxis as effective as i.m. administration for the prevention of late onset VKDB? Are there differences between oral regimens regarding their efficacy? Here we report the results of an active surveillance trial for late onset VKDB which was carried out in four different countries with three different oral prophylaxis schedules.

Methods

In The Netherlands, Germany, Australia and Switzerland active surveillance programmes for VKDB are in operation, using methods developed by the British Paediatric Association Surveillance Unit [8]. Surveillance is based on monthly report cards sent to paediatricians responsible for inpatient care in paediatric hospitals by the national paediatric organisation. A "nothing to report" option was included. A response rate of 85–99% was achieved in all countries.

The participating countries have agreed on uniform case definitions [21] to allow for meaningful international comparison. The definition for the first step (a postcard mailed to all paediatricians) is deliberately open, encouraging the reporting of all infants in whom bleeding may have resulted from VKDB. All notifications are verified by questionnaire, asking for information about the infant, vitamin K administration, clinical presentation and laboratory data.

Case definition of late onset VKDB: any infant between 8 days and the end of week 12, with spontaneous bruising/bleeding or intracranial haemorrhage associated with prolonged prothrombin assay, not due to an inherited coagulopathy or disseminated intravascular coagulation.

Confirmed VKDB was diagnosed, when the prothrombin assay results were grossly abnormal compared with standards for age (Quick values ≤ 15%; international normalised ratio ≥ 4; prothrombin time ≥ 4 × control value) and at least one of the following was present:

1. Platelet count normal or raised and normal fibrinogen and absent fibrin degradation products.
2. Prothrombin time returned to normal after vitamin K administration.
3. Concentration of PIVKA proteins exceeded normal controls.

Probable VKDB was assumed when the prothrombin and partial thromboplastin assay results were abnormal for age, but not as grossly as in "confirmed" cases and if at least one of the above mentioned items was documented.

Cases were also classified according to the cause of VKDB:

1. Idiopathic cases were defined as cases in whom no factor predisposing to vitamin K deficiency was identified.
2. Secondary cases were those in whom a predisposing cause, illness or diagnosis was discovered after presentation with bleeding.

In both idiopathic and secondary cases, vitamin K prophylaxis can be said to have failed either through inadequacy or omission. In other cases already known to have a disease predisposing to vitamin K deficiency, vitamin K administration was part of the normal disease management. Bleeding in those cases was not a failure of prophylaxis, but a failure of management. These are reported separately.

Oral vitamin K prophylaxis was considered complete if all nationally recommended doses had been given at the time of bleeding. Oral vitamin K prophylaxis was considered incomplete, if at least one oral dose had been given but not all recommended doses for age or if an inadequate dose or preparation had been administered. The number of oral vitamin K doses given was documented in the respective questionnaires. There were no means to estimate the proportions of healthy neonates given complete or incomplete oral vitamin K prophylaxis at different ages.

Results

The relevant vitamin K recommendations for different time periods and countries together with the periods of which active surveillance are shown in Table 1. The surveillance data allowed comparisons between the Dutch recommendations (25 μg vitamin K/day for breast-fed infants + 1 mg vitamin K at birth), three oral doses of 1 mg (Australia and Germany) and two oral doses of 2 mg vitamin K (mixed micellar preparation), as recommended in Switzerland.

The surveillance data are shown in Table 2. In The Netherlands, five confirmed cases of late VKDB were reported from October 1992 until December 1994: three cases had known predisposing liver disease not properly dealt with, and two were idiopathic cases. In the first idiopathic case vitamin K prophylaxis was omitted altogether, and in the second case the postnatal dose was not given. Both babies had been entirely breast-fed. There were no cases in infants who received the complete recommended prophylaxis. One of the idiopathic cases had fatal intracranial bleeding.

In Germany 32 infants met the case definition (28 confirmed and 4 probable cases) in the study period from April 1993 to September 1994. One had a predisposing disease requiring specific prophylaxis, not adequately dealt with. Seventeen cases had intracranial bleeding. The reported incidence of VKDB despite complete prophylaxis according to national recommendations was relatively high, 1.8 (1.1–2.8) per 100,000 live births.

In Australia, a similar prophylaxis protocol to that in Germany was used from January 1993 to March 1994. During this period intramuscular vitamin K_1, 1.0 mg, was much less commonly used than the oral doses used in healthy neonates (Peter Loughnan, personal communication). There were eight cases (seven confirmed/one probable), over this time [15]. Five of these had received prophylaxis according to national recommendations. Three cases had intracranial bleeding, one died. The failure rates were almost identical to those observed in Germany. In March 1994 the national policy was reversed to the previously recommended 1 mg i.m. at birth. Until May 1995, no cases of VKDB were observed with this regimen.

Table 1 Recommendations for vitamin K prophylaxis and surveillance periods for late VKDB in different countries

Country	Recommended prophylaxis		Time period	Surveillance data available for
The Netherlands*	*"well babies"*:	1 mg vitamin K p.o. & 25µg daily from week 1 to week 13 (breast-fed)	since 1990	October 1992 until December 1994
	"unwell babies":	1 mg vitamin K i.m. & 25µg daily (breast-fed)		
Germany*	*"well babies"*:	1 mg vitamin K p.o. day 1, 4–10, 28–42	December 1992 – December 1994	April 1993 until September 1994
	"unwell babies":	0,1–0,2 mg vitamin K i.m. or s.c. day 1 & 1 mg vitamin K p.o. day 4–10, 28–42		
Australia*	*"well babies"*:	1 mg vitamin K p.o. day 1, 3–5, 21–28	January 1993 – March 1994	January 1993 – March 1994
	"unwell babies":	0,1 mg vitamin K i.m. day 1 & day 3–5, 21–28 0,1 mg i.m. vitamin K (or 1 mg p.o.)		
	all babies:	1 mg vitamin K i.m. day 1	since March '94	March 1994 – May 1995
Switzerland	*"well babies"*:	2 mg mixed-micellar preparation p.o. day 1, 4	since 1995	January 1995 – December 1995
	"unwell babies":	0,5 mg mixed-micellar preparation i.v. or i.m., 2 mg MM-preparation p.o. week 4–6		

* Unless otherwise started the cremopher preparation Konakion was used for single oral or i.m. doses

In Switzerland a new mixed-micellar preparation of vitamin K_1 has been used from January 1995. All healthy neonates should receive 2 mg of vitamin K_1 (Konakion MM) orally on the 1st and 4th day of life. From January 1995 to December 1995 four cases of late VKDB were reported (three confirmed and one probable case); two of the confirmed cases were idiopathic and one of them had hepatobiliary disease. One of these three infants had received no prophylaxis, and two had been given the 'old' fat soluble drops (Konakion preparation). The probable case had very low vitamin K dependent clotting factors, which returned to normal after vitamin K administration. However, vitamin K deficiency may not have been the cause of the intracranial bleeding because the baby additionally had a low platelet count of 14,000/µl, and angiomatosis of the choroid plexus. Because of the limited number of children studied in Switzerland to date, 95% confidence limits of the failure rate are broad: 1.2 (0–6.5).

Discussion

There is good evidence that parenteral vitamin K prophylaxis (1 mg i.m. at birth) can prevent almost all cases

Table 2 Late VKDB in countries with different recommendations for vitamin K prophylaxis

	Netherlands	Germany	Australia		Switzerland
Birth population	439,000	1,200,000	325,000 (vitamin K p.o.)	325,000 (vitamin K i.m.)	83,000
Number of cases	5	32	8	0	4
a. idiopathic cases	2	13	3	0	3
b. secondary cases	0	18	5	0	1
c. predisposing illness	3	1	0	0	0
Total incidence a+b+c[1] (95% CI)[2]	1.1 (0.4–2.7)	2.7 (1.8–3.8)	2.5 (1.1–4.8)	0 (0–0.9)	4.7 (1.3–11.9)
True incidence a+b[1](95% CI)[2]	0.5 (0.1–1.6)	2.6 (1.8–3.7)	2.5 (1.1–4.8)	0 (0–0.9)	4.7 (1.3–11.9)
Prophylaxis					
I. omitted	1	2	0	0	1
II. incomplete	1	6	3	0	2 [3]
III. complete	0	22	5	0	1
IV. not documented	0	1	0	0	0
Prophylaxis failures [1] (95% CI)[2]					
– complete prophylaxis	0 (0–0.7)	1.8 (1.1–2.8)	1.5 (0.5–3.6)	0 (0–0.9)	1.2 (0–6.5)
– complete or incomplete prophylaxis	0.2 (0–1.3)	2.3 (1.6–3.4)	2.5 (1.1–4.8)	0 (0–0.9)	3.6 (0.7–10.6)

[1]per 100,000 live births
[2]assuming a Poisson distribution
[3]An older preparation, Konakion oral drops was given instead of "mixed-micellar"

of late VKDB [10]. Data from switch-over studies in one country [4], and from the simultaneous use of different prophylaxis strategies in three other countries [9, 16, 20] show that vitamin K prophylaxis with one oral dose (1–3 mg) is less effective than parenteral vitamin K. Repeated oral dose schedules have therefore been recommended. However, a recent publication from Germany suggests that even repeated oral vitamin K prophylaxis may not be as effective as the 1 mg dose administered i.m. at birth [12].

The Dutch recommendation for daily supplementation of vitamin K in exclusively breast-fed infants mimics formula-feeding, which prevents late VKDB almost completely [11], by providing a daily intake of about 50 μg vitamin K_1. Daily supplementation already exists for vitamin D. A diluted vitamin K preparation was marketed as a food supplement in The Netherlands, therefore bypassing time-consuming drug licensing procedures. Gynaecologists, midwives and general practitioners instruct the parents. The incidence of late VKDB despite oral prophylaxis (failure incidence) was 0 (95% CI 0–0.7) per 100,000 live births. Before vitamin K prophylaxis was introduced in 1990, the estimated incidence was 7 per 100,000 (1984–1986) [24]. A recommendation for daily low oral doses therefore appears sound.

In Germany and Australia three oral doses of 1 mg vitamin K_1 had been recommended in 1992. The "Cremophor" solution (Konakion) was used for oral vitamin K prophylaxis in both countries. The failure rates were almost identical in both countries and were much higher than with parenteral vitamin K prophylaxis [9]. Failures resulted not only from "non compliance" (forgotten repeat doses) but were also observed in children given the recommended vitamin K dose. These observations prompted a reversal to i.m. vitamin K in Australia, and a dose increase to 3 × 2 mg oral vitamin K in Germany. The data following the switch over in Australia confirm previous observations, that i.m. prophylaxis with 1 mg vitamin K can prevent almost all cases of late VKDB [4, 9, 10, 16, 19].

The new mixed-micellar preparation is well absorbed [18], even in children with cholestasis [2]. In Switzerland, two of the three reported failures of oral vitamin K prophylaxis occurred in children given the Konakion preparation. In 1993/94 when two oral doses of 2 mg of the old Konakion were recommended in Switzerland, the incidence of late VKDB had been about 4.2 per 100,000 [17]. Under the assumption that most children received the mixed-micellar preparation during 1995 in Switzerland it appears possible that the number of failures will be lower with the use of the new mixed-micellar preparation (Konakion MM) although the evidence is not conclusive.

Several potential sources of bias must be considered for between country comparisons of prophylaxis failure rates for the assessment of the relative efficacy of different regimes for oral vitamin K prophylaxis.

1. Constant and identical baseline incidences (without vitamin K prophylaxis) in the respective countries are mandatory. These baseline incidences are influenced by e.g. the breastfeeding habits and the prevalence of cholestatic liver disease in the respective countries. Although the baseline incidence was similar in reports from The Netherlands [24] and Germany [9, 10] corresponding data from Switzerland and Australia are lacking.
2. Completeness of ascertainment is an issue in all forms of surveillance systems. Even with active surveillance, complete ascertainment is unlikely, as shown by attempts to measure the incidence of childhood diabetes [3, 23], vertical HIV infections [1], multiple births [14] and systemic Haemophilus influenzae infections [13]. The under ascertainment, however, appears to be in a similar range for most conditions within one national surveillance system [1, 14, 23] and even between similar active surveillance systems [3, 23]. Major differences in the ascertainment between different active surveillance programmes therefore appear unlikely and meaningful between country comparison seems possible.
3. All failure rates had to be calculated with all live births in the denominator because the exact numbers of children eligible for oral vitamin K prophylaxis in each country is unknown. The proportions of eligible children, however, are likely to be similar, due to the similarities of the eligibility criteria.
4. The proportions of children, who received all recommended doses for oral vitamin K prophylaxis are unknown. It is likely, however, that less than 100% of the eligible cases received the recommended prophylaxis in all countries. All failure rates therefore are likely to be underestimated due to a greater denominator than the true numbers exposed. If the same proportions of children failed to receive the recommended prophylaxis in each country this would not account for bias in the international comparison. Bias could be introduced, however, if the proportions of children given the recommended doses was different between the countries compared.

The contribution of these potential sources of bias for the comparison of different oral vitamin K prophylaxis schedules is difficult to measure. In terms of proper epidemiology these results therefore can only be used to generate hypotheses to be tested in randomized controlled trials. Such trials would require about 700,000 children on standard oral vitamin K prophylaxis (e.g. 3 × 1 mg: 2 expected cases of VKDB/100,000 live births) versus about 700,000 children on an optimal regime (e.g. 3 × 2 mg mixed micellar preparation or daily doses of 25 μg in breast-fed babies plus 1 mg oral vitamin K at birth: 0.01 expected cases of late VKDB per 100,000 livebirths). It is evident that such a trial is logistically extremely difficult and expensive. The size of the clinical problem (about 7 relevant bleedings due to VKDB per 100,000 livebirths without any vitamin prophylaxis in

western countries) will hardly convince grant donating bodies even in extremely affluent societies to support such a study.

Poor evidence from international comparisons – as presented in this paper – will therefore remain the only basis for decision making on the optimal form of vitamin K prophylaxis.

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