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G. Schubiger · C. Stocker · O. Bänziger · B. Laubscher · H. Zimmermann

Oral vitamin K_1 prophylaxis for newborns with a new mixed-micellar preparation of phylloquinone: 3 years experience in Switzerland

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Abstract In 1995, a new water-soluble mixed-micellar analogue of vitamin K_1 (Konakion MM paediatric) was introduced in Switzerland to replace the formerly used fat-soluble Konakion drops for the prevention of vitamin K_1-deficiency-bleeding (VKDB) in infants. According to the new guidelines, an oral dose of 2 mg is given after birth and again on the 4th day of life. We examined the compliance with these guidelines and the impact on the incidence of VKDB. To assess compliance, questionnaires were sent to all hospitals with delivery services 6 months after the introduction of the new guidelines. Using the database of the Swiss Paediatric Surveillance Unit (SPSU) which records rare paediatric diseases, we assessed the incidence of VKDB in Switzerland between July 1995 and June 1998. In addition, we determined the precise circumstances under which the episodes of VKDB occurred. More than 99% of infants received vitamin K_1 prophylaxis. Since July 1995, 93% of newborns have received prophylaxis according to the new guidelines; the remaining infants were given fat-soluble Konakion drops or parenteral vitamin K_1. Within 3 years, one case of classical and 12 cases of late-onset VKDB (11 confirmed, 1 probable) were reported to the SPSU. Of the 11 confirmed late-onset cases, 7 received the recommended prophylaxis, whereas 3 had not and 1 had been given fat-soluble Konakion drops. All confirmed cases of late-onset VKDB occurred in fully breast-fed infants and 8 of 11 had hepatobiliary disease.

Conclusion With the introduction of two oral doses of a mixed-micellar vitamin K_1 preparation administered in the 1st week of life, the incidence of late vitamin K_1-deficiency-bleeding has decreased from 7.2:100 000 between 1986–1987 to 2.8:100 000 between 1995 and 1998. This regimen may be suitable for prophylaxis of vitamin K_1-deficiency-bleeding, however, it does not fully protect infants with cholestatic disease from late-onset bleeding. If oral prophylaxis is considered for these infants, vitamin K_1 has to be administered repeatedly to all infants during the breast feeding period.

Key words Vitamin K · Prophylaxis · Newborn · Vitamin K_1-deficiency-bleeding · Mixed-micelles

Abbreviation *VKDB* vitamin K_1-deficiency-bleeding

C. Stocker · O. Bänziger
Department of Paediatrics, Intensive Care Unit,
University Children's Hospital, Zurich, Switzerland

B. Laubscher
Department of Paediatrics, Hôpital Pourtalès,
Neuchâtel, Switzerland

H. Zimmermann
Swiss Federal Office of Public Health, Division of Epidemiology
and Infectious Disease, Berne, Switzerland

G. Schubiger (✉)
Department of Paediatrics, Kinderspital,
CH-6000 Luzern 16, Switzerland
e-mail: kispiluzern@bluewin.ch,
Tel.: +41-205-31 51,
Fax: +41-205-32 42

Introduction

The need for vitamin K_1 administration to newborns to prevent vitamin K_1-deficiency-bleeding (VKDB) is undisputed [17]. Both parenteral and oral administration of vitamin K_1 protect against the classical form of VKDB (2nd to 7th day of life). The optimal strategy to prevent late-onset VKDB (2nd to 12th week of life), which can occasionally be fatal, is currently under discussion. In Europe, different countries have made different recommendations [4, 8, 9]. In three European countries, the incidence of late-onset VKDB is recorded prospectively by national surveillance units, allowing cross-comparison [5]. In 1995, Switzerland introduced new guidelines for the prevention of VKDB based on a newly approved water-soluble mixed-micellar preparation of phylloquinone (Konakion MM) [15] (Table 1).

The aim of our study was to evaluate how the new guidelines have been accepted by the Swiss maternity hospitals and to study their impact on the incidence of VKDB.

Methods

By January 1, 1995, the new guidelines outlined in Table 1 had been approved by the Swiss Neonatal Society, the Nutrition Committee of the Swiss Paediatric Society and the Swiss Society of Obstetrics and Gynaecology. The guidelines were published in the official bulletin of the Swiss Medical Society and distributed to all 186 maternity units in Switzerland [15]. Six months later, a questionnaire was sent to all maternity units to evaluate the acceptance of the new guidelines. The following questions were asked:

- Since when have you been using Konakion MM exclusively for VKDB prophylaxis?
- Do you strictly adhere to the new guidelines?
- In which situations do you administer vitamin K_1 prophylaxis parenterally?

Since 1 January 1995, information regarding the incidence of VKDB has been prospectively collected on a monthly basis from all 39 paediatric hospitals with the help of the Swiss Paediatric Surveillance Unit [22]. This instrument is comparable to surveillance units in England, Germany (ESPED), the Netherlands and Australia. All these countries use the same case definition of VKDB which was proposed at a consensus conference in 1994 [21]. The following criteria are used to define late-onset VKDB:

- Occurrence between the 2nd and the completed 12th week of life
- Quick values ≤15%, INR (International Normalized Ratio) ≥4, prothrombin time ≥4× control value and at least one of the following: normal or increased platelet count, normal fibrinogen and absence of fibrin degradation products, return of prothrombin time to normal after vitamin K_1 administration, elevated concentration of protein induced in vitamin K absence.

Data were collected over a 3-year period from 1 July 1995 until 30 June 1998.

Results

Of the 186 questionnaires sent to the maternity services, 176 (95%) were completed and returned. Their analysis shows that more than 99% of all newborns in Switzerland receive some form of vitamin K_1 prophylaxis. Since July 1995, 93% of all newborns have received their prophylaxis according to the new guidelines with Konakion MM. The formerly used fat-soluble Konakion drops were only given occasionally, mainly to use up stocked supplies. Routine intramuscular administration of vitamin K_1 is no longer practised by any of the hospitals, but 20 maternity units use the intramuscular route more liberally than suggested by the guidelines. Overall, less than 1% of all term infants in maternity units receive their vitamin K_1 prophylaxis parenterally. On the other hand, approximately 8% of all newborns are admitted to newborn services where vitamin K_1 prophylaxis is frequently administered parenterally.

Over the 3-year period, no case of early (i.e. first 24 h of life) VKDB and one case of classical VKDB were reported (247 000 deliveries). The latter occurred in a newborn that had received one oral dose of vitamin K_1 MM and presented with bloody stools and a Quick value of 10% on the 2nd day of life. No maternal risk factors were identified.

Details of the 12 cases of late-onset VKDB that were reported to the Swiss Paediatric Surveillance Unit are shown in Table 2. All were exclusively breast-fed. Three infants had received no prophylaxis. One infant had been given fat-soluble Konakion drops. One case must be classified as "probable": the patient presented at 10 weeks of age with severe intracranial haemorrhage and very low vitamin K_1-dependent clotting factors. However, vitamin K_1 deficiency may not have been the cause of the intracranial bleeding because the infant also had a low platelet count and angiomatosis of the choroid plexus [2]. Of the 11 confirmed cases, 9 were later found to have predisposing hepatobiliary disease. Of the remaining two confirmed cases, one infant had not received vitamin K_1 prophylaxis and one infant suffered intracranial haemorrhage in spite of correct prophylaxis.

In 7 of the 12 infants, haematomas were observed as a typical warning symptom several days before the diagnosis of VKDB was made [19]. There were five cases of intracranial haemorrhage, two of which were fatal.

Table 1 Recommendations for vitamin K_1 prophylaxis in Switzerland since 1.1.1995 [15]

Term or preterm infants in regular nurseries:	
– Day 1:	2 mg mixed-micellar preparation of phylloquinone* p.o.
– Day 4:	2 mg mixed-micellar preparation of phylloquinone* p.o.
Term or preterm infants in neonatal units with i.v. lines:	
– Day 1:	0.5 mg mixed-micellar preparation of phylloquinone* i.v. (or i.m.)
– Week 4:	2 mg mixed-micellar preparation of phylloquinone* p.o.

* Konakion MM paediatric 0.2 ml = 2 mg

Table 2 Cases of late-onset VKDB over 3 years. (*CMV* cytomegalovirus, *MM* mixed-micellar preparation)

Case	1	2	3	4	5	6	7	8	9	10	11	12
Date of birth	04.08.95	28.08.95	22.11.95	31.12.95	07.10.96	18.07.96	24.11.96	25.11.96	07.02.97	11.03.98	18.03.98	05.04.98
Classification of VKDB	Probable	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed
Number of doses given (2 mg vitamin K p.o.)	2 MM	2 Fat-soluble	2 MM	2 MM	None	2 MM	2 MM	None	2 MM	2 MM	2 MM	None
Age at bleeding (weeks)	10	6	6	5	4	7	6	3	10	11	6	4
Localisation of bleeding	Intracranial	Intracranial	Intracranial	Pleura	Skin	Skin	Skin	Umbilicus	Skin	Skin	Intracranial	Intracranial
Outcome of bleeding	Minimal sequelae	Lethal	No sequelae	No sequelae	No sequelae	No sequelae	No sequelae	No sequelae	No sequelae	No sequelae	Survived sequelae?	Lethal
Breast feeding	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Hepatobiliary disease	No	Biliary atresia	Biliary atresia	Biliary atresia	Cystic fibrosis	Biliary atresia	Biliary atresia	No	CMV-hepatitis	CMV-hepatitis	No	Biliary atresia
Other disease	Vascular*	–	–	–	–	–	–	–	–	–	–	–

* Angiomatosis of choroid plexus

Three infants (including the "probable" case) survived their intracranial haemorrhage. Two of them were neurologically normal at follow up (2 years and 6 months, respectively). At 18 months the "probable" case showed slight asymmetry in muscle tone.

Discussion

Different countries use different regimens of vitamin K_1 prophylaxis with regard to galenic formulation, mode of application, dosage and dosing interval. There are a number of likely reasons for this.

Intramuscular administration of 1 mg of vitamin K_1 after delivery offers great protection from VKDB [6]. However, because of the invasiveness and associated risks, the acceptance of this form of prophylaxis has decreased in many places [3, 12, 13].

Repetitive oral doses of vitamin K_1 offer better protection than a single oral dose after delivery [5, 7, 9]. A rational approach to prophylaxis of VKDB is the daily administration of small amounts of vitamin K_1 (25 μg) in fully breast-fed infants as currently used in the Netherlands [4]. In many countries, the required low-dose preparation of vitamin K_1 is not available. In addition, repetitive administration of vitamins in fully breast-fed infants is not generally accepted, and complicated recommendations may negatively affect compliance [8].

Until very recently, lipophilic vitamin K_1 was only available as an oily solution. In 1995, a new galenic preparation of vitamin K_1 in the form of a mixed-micellar solution (Konakion MM paediatric, 0.2 ml = 2 mg) was introduced. Phylloquinone molecules are embedded in mixed micelles of bile acid and lecithin forming a water-soluble preparation [18]. This new galenic formulation has resulted in three distinct advantages and one significant drawback. Enteral bioavailability of Konakion MM is improved compared to the oily vitamin K_1 solutions [16] and theoretically should be unaffected by endogenous bile acids as suggested by one study [1]. Anaphylactic reactions after intravenous injection of fat-soluble vitamin K_1 preparations which have been linked to the solvent Cremaphor can be avoided when Konakion MM is used. Finally, the addition of preservatives such as benzoic acid is unnecessary. Because mixed-micellar solutions do not form regular droplets, the solution has to be drawn up from a light-protected glass vial into a dispenser which then allows oral administration of Konakion MM. This process is more labour-intensive, causes slightly higher costs (currently, a single dose of Konakion MM costs SFr. 1.80) and produces more waste.

Switzerland was the first country to obtain approval by its National Drug Administration (Interkantonale Kontrollstelle für Heilmittel Schweiz) to use Konakion MM for prophylaxis of VKDB in newborns. The formerly used dosing recommendations (2 mg of vitamin K_1 orally soon after birth and then again on the 4th day

of life) remained unchanged. In 1995, there were no established well baby care programmes that would have guaranteed that all infants could be contacted at the age of 4 weeks, and therefore additional vitamin K_1 doses after the 1st week of life were not recommended as in Germany [9].

The incidence of late-onset VKDB has decreased from 7.2:100 000 (95% CI 3.1–14.2) between 1986 and 1987 when 41% of the infants received 1 mg Konakion i.m. and 59% a single dose of 2 mg Konakion drops per os [20] to 2.8:100 000 (95% CI 1.1–5.8) between 1995 and 1998 with prophylaxis according to the new recommandations. Since the introduction of Konakion MM only one cases of late-onset VKDB has been reported in infants without undelying cholestatic disease. Unfortunately, despite its better bioavailability the mixed-micellar vitamin K_1 preparation does not protect all infants with underlying cholestatic disease. Our observations raise questions regarding the reported pharmacokinetics of Konakion MM [1, 11, 14, 16]. It appears that absorption of this drug in infants with cholestasis is not as good as had been expected. This issue is the topic of a current investigation in infants with known cholestatic disease.

Although, on day 4 of life, similar plasma concentrations are observed after oral and intramuscular administration of vitamin K_1 preparations, the parenteral route yields better protection from late-onset VKDB. Plasma vitamin K_1 concentrations after enteral and parenteral administration have only been determined in a small number of patients [14]. Perhaps, as Loughnan and McDougall have suggested [10], intramuscular administration is associated with a depot effect.

The Swiss experience to date shows that a regimen consisting of two oral doses of Konakion MM given during the 1st week of life offers almost complete protection against late-onset VKDB to healthy infants. However, it does not protect all infants with cholestatic disease. Oral prophylaxis in fully breast-fed infants would have to include repetitive doses if protection from general prophylaxis is expected to include infants with hepatobiliary disease.

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References

1. Amédée-Manesme O, Lambert WE, Alagille D, Leenheer AP (1992) Pharmacokinetics and safety of a new solution of vitamin $K_{1(20)}$ in children with cholestasis. J Pediatr Gastroenterol Nutr 14:160–165
2. Baenziger O, Braegger CP, Fanconi S (1996) Oral vitamin K prophylaxis for newborn infants: safe enough? Lancet 348:1456
3. Baum CR, Hilpert PL, Bhutani VK (1996) Accidental administration of an Ergot Alkaloid to a neonate. Pediatrics 98:457–458
4. Cornelissen EAM, Kollée LAA, Lith TGPJ van, et al (1993) Evaluation of a daily dose of 25 μg vitamin K_1 to prevent vitamin K deficiency in breast-fed infants. J Pediatr Gastroenterol Nutr 16:301–305
5. Cornelissen EAM, Kries R von, Loughnan P, Schubiger G (1997) Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. Eur J Pediatr 156:126–130
6. Eklund H (1991) Late haemorrhagic disease in Sweden 1987–89. Acta Paediatr Scand 80:966–968
7. Hansen KN, Ebbesen F (1996) Neonatal vitamin K prophylaxis in Denmark: three years' experience with oral administration during the first three months of life compared with one oral administration at birth. Acta Paediatr 85:1137–1139
8. Jonville-Bera AP, Autret E (1997) Study of the use of vitamin K in neonates in France. Eur J Clin Pharmacol 52:333–337
9. Kries R von, Hachmeister A, Göbel U (1995) Repeated oral vitamin K prophylaxis in West Germany: acceptance and efficacy. B M J 310:1097–1098
10. Loughnan P, McDougall P (1994) The duration of vitamin K_1 efficacy: is intramuscular vitamin K_1 acting as a depot preparation? In: Sutor AH, Hathaway WE (eds) Vitamin K in infancy. Schattauer, Stuttgart, pp 225–234
11. Maurage C, Dalloul C, Moussa F, Cara B, Dudragne D, Lion N, Amédée-Manesme O (1995) Efficacité de l'administration orale d'une solution micellaire de vitamine K en période néonatale. Arch Pédiatr 2:328–332
12. Mitchell AM, Lacouture PG, Crone RK (1983) Accidental administration of ergonovine to a newborn. JAMA 250:730–731
13. Pandey SK, Haines CI (1982) Accidental administration of ergometrine to newborn infant. B M J 285:693
14. Schubiger G, Tönz O, Grüter J, Shearer MJ (1993) Vitamin K_1 concentration in breast-fed neonates after oral or intramuscular administration of a single dose of a new mixed-micellar preparation of phylloquinone. J Pediatr Gastroenterol Nutr 16:435–439
15. Schubiger G, Roulet M, Laubscher B (1994) Vitamin K_1-Prophylaxe bei Neugeborenen: neue Empfehlungen. Schweiz Ärzte 75:2036
16. Schubiger G, Grüter J, Shearer MJ (1997) Plasma vitamin K_1 and PIVKA-II after oral administration of mixed-micellar or Cremophor EL-solubilized preparations of vitamin K_1 to normal breast-fed newborns. J Pediatr Gastroenterol Nutr 24:280–284
17. Shearer MJ (1995) Vitamin K. Lancet 345:229–234
18. Steffen H, Schmid D, Ferro A (1994) Principles of different vitamin K_1 formulations In: Sutor AH, Hathaway WE (eds) Vitamin K in infancy. Schattauer, Stuttgart, pp 331–336
19. Sutor AH, Dagres N, Niederhoff H (1995) Late form of vitamin K deficiency Bleeding in Germany. Klin Pädiatr 207:89–97
20. Tönz O, Schubiger G (1988) Neonatale Vitamin K-Prophylaxe und Vitamin K-Mangelblutungen in der Schweiz. Schweiz Med Wochenschr 118:1747–1752
21. Tripp J, Cornelissen M, Loughnan, McNinch A, Schubiger G, Von Kries R (1994) Suggested protocol for the reporting of prospective studies of vitamin K deficiency bleeding. In: Sutor AH, Hathaway WE (eds) Vitamin K in infancy. Schattauer, Stuttgart, pp 395–401
22. Zimmermann H, Desgrandchamps D, Schubiger G (1995) The Swiss Paediatric Surveillance Unit (SPSU). Soz Präventivmed 40:392–395