Joint statement and recommendations on vitamin K administration to newborn infants to prevent vitamin K deficiency bleeding in infancy

October 2010

National Health and Medical Research Council
Paediatric Division of the Royal Australasian College of Physicians
Royal Australian and New Zealand College of Obstetrics and Gynaecology
Royal Australian College of General Practitioners
Australian College of Midwives

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ISBN Online: 1864965053

NHMRC (National Health and Medical Research Council) (2010). Joint statement and recommendations on Vitamin K administration to newborn infants to prevent vitamin K deficiency bleeding in infancy – October 2010 (the Joint Statement).

Contact:

National Health and Medical Research Council
Level 1
16 Marcus Clarke Street
Canberra ACT 2601
GPO Box 1421
Canberra ACT 2601

Ph: 61 2 6217 9000
Fax: 61 2 6217 9100
Email: nhmrc@nhmrc.gov.au

NHMRC publication reference: CH54

This publication was endorsed at the 137th Session of Council, 13 October 2000 and re-issued at the 160th Session of Council, 8 March 2006.

NHMRC Council advised the CEO of NHMRC to re-issue this publication at the 183rd Session of Council, 8 October 2010.

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Recommendations

1. All newborn infants should receive vitamin K prophylaxis.[8,17]
2. Healthy newborn infants should receive vitamin K either:
   - by intramuscular injection of 1 mg (0.1 mL) of Konakion® MM[1] at birth. This is the preferred route for reliability of administration and level of compliance.

     or
   - as three 2 mg (0.2 mL) oral doses of Konakion® MM, given at birth, at the time of newborn screening (usually at three to five days of age) and in the fourth week. The last dose is not required in infants predominantly formula fed. It is imperative that the third dose is given no later than four weeks after birth as the effect of earlier doses decreases after this time. Undertaking this form of prophylaxis requires that the parent accepts responsibility and that clinicians support and advise them in the administration of the third dose. If the infant vomits or regurgitates the formulation within one hour of administration, the oral dose should be repeated.[1] If at the time any oral dose is to be given the infant is sick, vomiting or unable to take it by mouth, then medical advice should be sought as to whether the intramuscular preparation should be given.
3. Newborns who are too unwell and are unable to take oral vitamin K (or whose mothers have taken medications that interfere with vitamin K metabolism) should be given 1 mg of Konakion® MM by intramuscular injection at birth. A smaller intramuscular dose of 0.5 mg (0.05 mL) should be given to infants with a birth weight of less than 1.5 kg.
4. Parents should receive written information during the antenatal period about the importance of vitamin K prophylaxis, and the options and relevance of oral or intramuscular prophylaxis. Health practitioners and institutions should ensure that appropriate informed consent procedures are in place and are followed.
5. A mechanism should be in place to ensure that the decision made antenatally about the method of prophylaxis is still valid and is communicated to staff caring for the mother during childbirth and postnatally.

1 The Konakion® MM Paediatric Product Information reflects the Joint Statement and Recommendations.

6. Hospitals should have written protocols for medical and nursing staff to administer prophylactic vitamin K to infants. These should include that it be routine practice to record the date, dose and method of administration in the infant's personal health record.
7. Child health workers and parents should be aware that unexplained bleeding or bruising in infants is uncommon and should be promptly investigated and treated. Information on unexplained bleeding should be included in the general information given to parents antenatally.
8. Further research should be undertaken into the implementation strategies for oral Konakion® MM and for the efficacy of Konakion® MM by any route. The possibility of prophylaxis via maternal supplementation to enhance levels of vitamin K in breast milk should also be investigated. However it is generally believed that a baby cannot receive treatment via breast milk.
9. The Australian Paediatric Surveillance Unit should be supported to continue monitoring the incidence of Vitamin K Deficiency Bleeding.

Introduction

In December 1999 the Australian Drug Evaluation Committee approved the application by Roche Australia to register Konakion® MM Paediatric, which is the current formulation of vitamin K1 (phytomenadione) containing 2 mg in 0.2 mL, for intramuscular (IM) and oral use. In this mixed micelles formulation naturally occurring substances sodium glycocholate (bile acid) and lecithin generate a stable colloidal micellar system capable of solubilising the fat-soluble vitamin K1 in an aqueous medium.

The active ingredient, phytomenadione (vitamin K1) has been marketed in Australia since the 1950s as a cremophor formulation for IM injection, Konakion® 1 mg/ 0.5 mL, also containing propylene glycol, phenol and polyethylated castor oil. These latter components have been associated with anaphylaxis following IV use and local irritation when given IM. In 1992 Golding reported an association between intramuscular (but not oral) use of the cremophor formulation and childhood cancer. Subsequent studies of better methodological quality have not confirmed this[13], although a consistent small but non-significant trend towards an increased incidence of acute lymphoblastic leukaemia remained[15] (reviewed by Von Kries 1998, Wariyar *et al* 2000). Although not licensed for oral use, the cremophor formulation has been used when parents do not wish their infant to receive an intramuscular injection. Gastrointestinal irritation has been a problem with oral use. The production of the cremophor formulation has ceased.

In 2000, the National Health and Medical Research Council (NHMRC)[2] developed the *Joint statement and recommendations on Vitamin K administration to newborn infants to prevent vitamin K deficiency bleeding in infancy*, in collaboration with the Royal Australasian College of Physicians, the Royal Australian and New Zealand College of Obstetrics and Gynaecology, the Royal Australian College of General Practitioners and the Australian College of Midwives. This was reviewed and reissued in March 2006.

Further to the review of the Joint Statement undertaken in 2006, in January and February 2010 a literature review on vitamin K prophylaxis to newborns was undertaken by NHMRC staff. The literature review was sent to the collaborators of the original Joint Statement as well as Australian State and Territory health departments for advice and comments. Comments were received and an overall consensus was that there has not been any substantial new literature on vitamin

2 Information on NHMRC can be found at http://www.nhmrc.gov.au/

K prophylaxis to newborns, as well as on the new Konakion® MM Paediatric formulation, and as such the recommendations in the Joint Statement remain current.

This revised Joint Statement has been widely consulted, including receiving advice from clinicians, government health departments, professional colleges and the Council of NHMRC in 2010.

Background

The term 'haemorrhagic disease of the newborn' was first used in 1894 (Townsend 1894) to describe bleeding in the newborn, which was not due to traumatic birth or to haemophilia. Later many cases were found to be associated with vitamin K deficiency. The term 'vitamin K deficiency bleeding' (VKDB) has now been adopted (Sutor *et al* 1999). This is preferred since not all bleeding in the newborn is due to vitamin K deficiency and bleeding due to this cause is not confined to the newborn.

Vitamin K occurs in two forms, vitamin K1 whose source is dietary intake and vitamins K2 (menaquinones) that are produced by gut bacteria. All newborn infants have a relative vitamin K deficiency at birth (Shearer 1992). Vitamin K1 crosses the placenta poorly resulting in low fetal plasma concentrations of the vitamin, with a 30:1 maternal-infant gradient. After birth vitamin K status is related to dietary intake, being determined by the volume of milk ingested and the amount of vitamin K1 in the milk. Symptomatic VKDB can be precipitated in the first week of life by delayed or inadequate early feeding, or can occur later in the first six months as a result of inadequate oral absorption of vitamin K1. Human breast milk contains relatively low concentrations of vitamin K1 (1 to 2 mg/L), whereas infant formula milks are by law supplemented with additional vitamin K1 to a minimum concentration of 30 mg/L). Therefore exclusively breast-fed infants are at increased risk of developing VKDB, unless supplemental vitamin K is administered.

Cholestatic liver disease also impairs absorption of vitamin K1 and increases the risk of VKDB. Hepatic menaquinones (vitamins K2) protect adults and older infants from developing VKDB even in the presence of vitamin K1 deficiency. Vitamins K2 cannot be detected in the livers of newborn infants but gradually accumulate in the first few months of life. The source of vitamins K2 in young infants is from synthesis by gut flora. Until adequate stores of hepatic menaquinones have accumulated young infants remain susceptible to the occurrence of VKDB.

Diagnosis

VKDB includes spontaneous or excessive induced bleeding (eg venipuncture or surgery) at any site associated with decreased activity of the vitamin K dependent coagulation factors (II, VII, IX and X) with normal activity of vitamin K independent factors fibrinogen levels and platelet count (Sutor *et al* 1999). Confirmation of the diagnosis requires that the coagulation disorder is rapidly reversed following vitamin K administration and that other causes of coagulopathy are excluded.

Classification

VKDB is classified into early, classical and late, based on the age of presentation (Sutor *et al* 1999, Von Kries 1999).

- **Early VKDB**, occurring on the first day of life, is rare and confined to infants born to mothers who have received medications that interfere with vitamin K metabolism. These include the anticonvulsants phenytoin, barbiturates or carbamazepine, the antitubercular drug rifampicin, and the vitamin K antagonists warfarin and phenindione. The reported incidence in infants of mothers who have received such medications without vitamin K supplementation is between 6 and 12 per cent (reviewed by Sutor *et al* 1999).
- **Classical VKDB** occurs from one to seven days after birth and is more common in infants who are unwell at birth or who have delayed onset of feeding. Bleeding is usually from the umbilicus, gastrointestinal tract, skin punctures, surgical sites and uncommonly in the brain. The incidence reported in the literature is variable, with rates of 0.25 to 1.5 per cent in early reports of both sick and well infants to 0 to 0.44 per cent in recent reviews predominantly of well infants. There is considerable uncertainty about the true rates of classical VKDB since full diagnostic criteria outlined above were seldom met.
- **Late VKDB** occurs from eight days to six months after birth, with most presenting at one to three months. It is almost completely confined to fully breast-fed infants. About half of the infants have underlying liver disease or occasionally other malabsorptive states. Serious intracranial haemorrhage occurs in about 30 to 50 per cent. Other sites of bleeding include skin, gastrointestinal tract, umbilicus or surgical sites. About 30 per cent have minor bruising or other signs of coagulopathy (warning bleeds), preceding the serious haemorrhage. Infants at risk may have signs of predisposing cholestatic liver disease such as prolonged jaundice, pale stools, and hepatosplenomegaly. The rate of VKDB in infants without prophylaxis has been reported as between five and 20 per 100,000 births. The mortality is about 30 per cent (Loughnan and McDougall 1993).

Prophylaxis

In Australia prophylaxis with a single IM injection of 1 mg Konakion® (cremophor) was introduced in the early 1970s. This was initially given to 'sick' infants such as those born preterm or following perinatal asphyxia, and later became routine for all infants.

In 2000 over 95 per cent of approximately 260,000 newborn infants born in Australia each year received IM vitamin K® (cremophor) prophylaxis at birth, most of the remainder receive either oral prophylaxis with repeated doses of the same formulation and a small number receive no prophylaxis (Australian Paediatric Surveillance Unit – unpublished). In 1994 the NHMRC recommended that all infants should receive prophylaxis and that the IM route was preferred for reliability of administration. Prophylaxis has been recently reviewed (Brousson *et al* 1996, Cornelissen *et al* 1997, Sutor *et al* 1999, Von Kries 1999) and these studies underpin the statements below.

Cremophor formulation is no longer in use. When the Joint Statement was first released in 2000 Konakion® MM Paediatric had just been introduced. Konakion® MM Paediatric is now the current formulation of vitamin K prophylaxis.

Except perhaps for the early onset variant, VKDB is a disease of exclusively (or almost exclusively) breast fed infants. Hence the main target group for extended monitoring and for prophylaxis is the breast fed infant who has had no or only oral vitamin K prophylaxis.

Effectiveness of prophylaxis

There are no randomised-controlled trials that adequately address the effectiveness of prophylaxis in preventing VKDB. The results of surveillance systems in different countries, including Australia, have been used to infer effectiveness by recording the type of prophylaxis used in reported cases of VKDB (Cornelissen *et al* 1997).

Early VKDB can appear at birth and so it has been recommended that women who are taking medication known to interfere with vitamin K metabolism should receive 20 mg of vitamin K daily for at least two weeks before birth. Further, newborn infants born to such mothers should have intramuscular vitamin K immediately after birth (Fetus and Newborn Committee 1988).

Classical VKDB is virtually eliminated by the administration of a single dose of vitamin K given by any route on the day of birth.

Late VKDB in the first six months of life is the main concern because, although rare, bleeding can be serious and life threatening and the incidence varies with different regimens of prophylaxis. Cornelissen *et al* (1997) and Von Kries (1999) summarised the results from different countries using various methods of administration. A single IM injection of 1 mg of Konakion® (cremophor) had been the most reliable and effective form of prophylaxis[17] with rates of less than 0.3 per 100,000 births reported. Regular oral dosing such as 25 mg daily (Netherlands) or 1 mg weekly (Denmark) requires parental diligence but is as effective as a single IM (cremophor) dose at birth. Formula feeding also supplies a regular dose and late VKDB is very rare in such infants.

Where the intended regimen is three oral doses of Konakion® (cremophor) (usually on day one, later in the first week and at four to six weeks, the reported rates per 100,000 births have been 2.6 (Germany) and 2.5 (Australia). The rate for infants actually receiving the full course is lower at 1.8 and 1.5 respectively. In Germany an increased dose of Konakion® (cremophor) to 2 mg at the three times was associated with a lower rate of 0.9 per 100,000 births (Von Kries 1999). A single oral dose of 1 to 2 mg of Konakion® (cremophor) at birth is less effective, although the onset appears to be delayed (Loughnan and McDougall 1993) with reported rates per 100,000 births varying from 1.5 in the UK and Germany to 4.5 in Denmark and 6.5 in Switzerland.

Effectiveness of Konakion® MM Paediatric (mixed micelles) preparation

Intramuscular injection of 1 mg of Konakion® MM in adults results in a slow rise in blood vitamin K levels suggesting a depot effect. In newborns a similar depot effect has been observed although this has only been studied in the first eight hours after injection. Tween vitamin K1 formulation is used in a single IM dose in the USA and has a similar initial pharmacokinetic profile to that of Konakion® MM following IM injection in adults. After a single IM dose of a Tween preparation of vitamin K1, adequate vitamin K1 levels at 56 days are found in about 70 per cent of infants (Greer *et al* 1998). The relationship between blood levels and risk of bleeding are unclear. The effectiveness of IM Konakion® MM or the Tween formulation in preventing late VKDB is not known.

Konakion® MM is well absorbed orally. With three single doses (administered at days one, seven and 30) blood levels of vitamin K1 are adequate in 89 per cent at 56 days (Greer *et al* 1998). Proteins that accumulate in the blood when there is a deficiency of vitamin K (PIVKAs) were not detected in the 79 infants who received oral prophylaxis with Konakion® MM.

The only data on effectiveness of oral Konakion® MM comes from Switzerland where since 1995, 93 per cent of infants have received it by this route. The intended regimen was two oral doses of 2 mg, the first on day one and the second on day four. Three years of surveillance data reported by Schubiger *et al* 1999 found one case of classical VKDB and 11 definite cases of late VKDB in 247,000 cases. Nine of these 11 were found to have underlying liver disease. Of the remaining two, one had no prophylaxis and the other had the recommended two oral doses.

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Appendix: History of the development of the Joint Statement

In 2000, the National Health and Medical Research Council (NHMRC) was requested to:

- review research published since 1994 on the efficacy, safety and bioavailablity of the new vitamin K formulation, Konakion® MM Paediatric when given orally or intramuscularly
- consider the different needs of formula and breast fed infants for the administration of vitamin K
- consider if a requirement for booster doses of vitamin K will have implications for the NHMRC Australian Standard Vaccination Schedule,
- prepare advice for health care workers and parents on the need and schedule for vitamin K administration
- recommend areas for further research.

A multidisciplinary Working Party was formed to address these issues.

Methods

The Working Party had two face to face meetings and two teleconferences. The detailed submission to ADEC by Roche Australia for the licensing of Konakion® MM Paediatric was made available. In addition a systematic literature search was undertaken of MEDLINE (1994-2000) and the Cochrane Library for reports on the incidence of vitamin K deficiency bleeding and effectiveness of different forms of prophylaxis. This was supplemented by a search for unpublished, ongoing orplanned studies through contact with Roche Australia and international experts in the field. The experts included Drs Shearer, Tripp, McNinch and Hey in the UK, Sutor and Von Kries in Germany and Greer in the USA.

A five week phase of full public consultation was undertaken following NHMRC endorsement of the draft Joint Statement and Recommendations.

The final product was endorsed by Council in October 2000. In 2006, NHMRC Council recommended the Joint Statement be reissued unchanged.