VITAMIN K_1 (Commentary)

Current policy in the UK

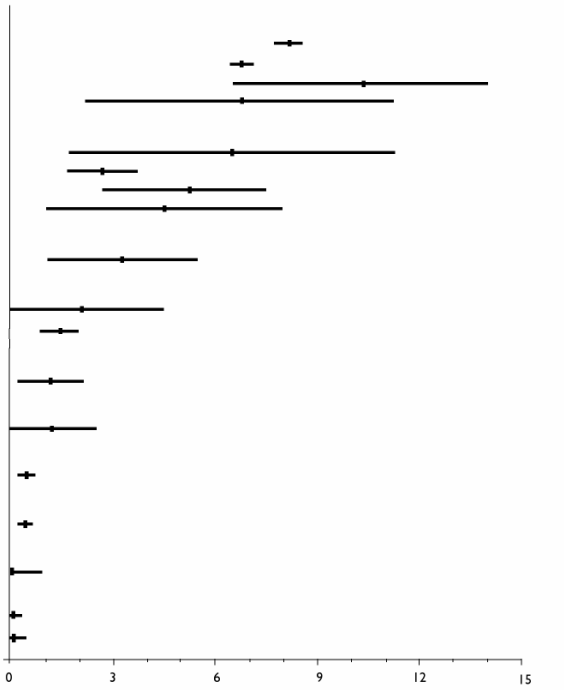
Public health policy over the prevention of vitamin K deficiency bleeding (VKDB) has been in serious disarray in the UK for the last ten years. Hospital practice is now extremely variable, and midwives are understandably confused (Ansell, 2001). Community staff have also had to contend with conflicting policies (McNinch, 1997). Most countries have clear national guidelines (as with vaccine policy). The UK Government "recommends that all new-born babies are given vitamin K in the new-born period" (DoH, 1998). They also say that "Available regimes (oral or intramuscular) can be effective – but only if fully completed." However, in asserting that both oral and IM policies ***can*** be effective, they have not given any guidance as to which policies actually ***are*** effective. Failure of staff to offer prophylaxis, or of parents to accept it, is now a significant cause of severe vitamin deficiency bleeding in the UK.

Neonatal prophylaxis

A range of prophylactic strategies are currently in use across the world. A single 1 mg IM injection is still the preferred option almost everywhere in North America, but a range of oral policies have been adopted in many parts of Europe, even though most are not currently as good at preventing potentially lethal late vitamin K deficiency bleeding. Practice is even more confused and varied within the UK at the present time. All strategies effectively abolish all risk of ***early*** vitamin K deficiency bleeding in the first week of life. The extent to which oral prophylaxis reduces the risk ***late*** bleeding correlates with the nature of the policy for giving further post-discharge booster doses (see graph).

INCIDENCE OF LATE VITAMIN K DEFICIENCY BLEEDING (VKDB)*

NO PROPHYLAXIS			
	Japan	1978-80	424 / 4,930,000
	Japan	1981-85	484 / 6,740,000
	U.K.	1988-90 & 93-4	30 / 290,000
	Germany	1988	10 / 138,750
1 or 2mg BY MOUTH at birth			
	Switzerland	1986-87	7 / 109,000
	U.K.	1988-90 & 93-4	23 / 850,000
	Sweden	1987-89	17 / 332,686
	Denmark	1990-92	6 / 134,500
2mg OF THE MICELLAR PRODUCT BY MOUTH* at 1 & 4 days			
	Switzerland	1995-98	8 / 247,000
1mg BY MOUTH at birth and at 1 and 4-6 weeks			
	Australia	1993-98	2 / 101,700
	Germany	1993-94	18 /1,400,000
1mg at birth & 25μg BY MOUTH daily for 3 months			
	Netherlands	1993-94	5 / 439,000
1mg BY MOUTH at birth and at 2, 4 and 6 weeks			
	North of England	1993-00	3 / 254,000
2mg BY MOUTH at birth and at 1, and 4-6 weeks			
	Germany	1995-98	14 / 3,200,000
2mg OF THE MICELLAR PRODUCT three times as above			
	Germany	1997-00	8 / 1,817,000
1mg BY MOUTH weekly for 3 months			
	Denmark	1993-00	0 / 396,000
1mg INTRAMUSCULARLY at birth			
	UK	1988-90 & 93-4	1 / 1,570,000
	Australia	1993-98	1 / 779,477



*when treatment was given as intended
Data from Wariyar (2000) updated

Cases of late VKDB per 100,000 births and 95% confidence intervals

Care must be exercised in interpreting this illustration, since late bleeding is almost only seen in breast fed babies, and the proportion so fed varied from study to study. Two studies in Japan before the introduction of routine prophylaxis suggested that, among babies who continue to be breast fed, ***late*** bleeding might be seen in 1 in every 6,000 births. The precise risk of ***early*** bleeding is even harder to quantify, but it was three times as common as late bleeding in one recent Malaysian study where no prophylaxis was available (Choo, 1994).

IM prophylaxis: The argument in favour of IM prophylaxis is that a single injection is easy to give, unlikely to be overlooked, and provides almost complete protection from both early and late vitamin K deficiency bleeding. There is, furthermore, no proof that such a strategy increases the risk of later childhood cancer (see below). While a single 1 mg IM dose of the *original* Roche product (Konakion) has been shown to provide sustained protection, it remains to be established whether the new colloidal preparation (Konakion Paediatric MM) is equally effective when given IM. A study in Australia is currently looking into this. Whether a smaller IM weight-related dose at birth provides comparable long term protection for the breast fed baby is also not yet clear. Neither can it be assumed that those given the new mixed micellar preparation by mouth are free from the supposed cancer risk associated with IM prophylaxis, given that blood levels 24 hours later are similar to those seen after an IM injection.

Oral prophylaxis: The argument in favour of oral prophylaxis is that if a policy could be found that protected breast fed babies as reliably as 'formula' feeding does, lingering doubt over the safety of IM prophylaxis would become irrelevant. Unfortunately no commercial low dose preparation is yet available for daily use (except in the Netherlands), and it can not be assumed that large oral doses are totally free from the carcinogenic concern that currently surrounds IM treatment. However, since a single oral dose offers virtually complete protection from early bleeding, and bottle fed babies almost never develop late vitamin K deficiency, it is very difficult to justify routine IM prophylaxis for these babies on any ground other than administrative convenience. Oral prophylaxis was used in all the early studies - IM prophylaxis only came in because no commercial company marketed an oral product (except in Japan). Products currently available seem to be of equivalent oral efficacy (von Kries, 2003).

IV prophylaxis: A 1 mg dose given IV provides rapid protection, but there are grounds for thinking that it does not provide the same sustained 2–3 month protection as a 1 mg dose IM (Loughnan, 1996).

Choice of strategy: A 'risk assessment' approach has long been common in the UK (much influenced by an editorial that appeared in the *Lancet* in 1978). It was initially used to identify which babies merited *any* prophylaxis, but is now widely used in the UK to select which families should be advised to let their child have IM rather than oral prophylaxis.

Those who first introduced prophylaxis 60 years ago (Lehmann, 1944) realised that babies were more likely to bleed into their head or abdomen if subjected to a traumatic assisted or unassisted delivery. However this has now metamorphosed (as a time when traumatic delivery has become very rare) into a misguided policy of classifying every baby born with instrumental help, or by section, as at increased risk. There is also a widespread belief that preterm babies are at increased risk, but studies in countries where babies do not normally get prophylaxis (Lulseged, 1993; Choo 1994) provide little support for such a belief. What *is* true is that babies who are not fed at birth are at substantially increased risk, since all have low vitamin K stores at birth and milk provides their only vitamin source. Maternal treatment with some drugs also increases the risk of bleeding, but this can occur at any time in the first 2–3 days of life (Hey, 1999). The idea that there is something different about cases presenting in the first day of life is ingrained (Lane, 1985), but gains no support from the studies just cited.

Evidence to support a 'risk based' approach is ***totally*** lacking, and its adoption seems to account for much of the confusion that Ansell recently documented in the UK. It is little used elsewhere. Parents should be told that babies who are not well enough to feed soon after birth, and babies likely to be more hypoprothrombinaemic than most because of maternal medication (as specified in the main monograph), merit IM prophylaxis. However, it is an oversimplification to classify *all* anti-epileptic drugs as making the baby more vulnerable to vitamin K deficiency bleeding (see below). Oral or IM prophylaxis can be equally effective at preventing vitamin deficiency bleeding in other babies as long as an appropriate dose is used (and its timing is appropriate).

Maternal prophylaxis

Pre delivery: Women on anti-epileptic drugs are often advised to take vitamin K before delivery (Delgado-Escueta, 1992; American Academy of Neurology, 1998). In fact, only those taking carbamazepine, phenobarbital and phenytoin seem to be at risk of delivering a baby with severe hypoprothrombinaemia. Furthermore, in the 40 years since this condition was first described, the world literature has only documented two babies as ever having developed early symptomatic vitamin K deficiency bleeding despite prompt IM vitamin K prophylaxis at birth. Both had sustained trauma to the liver (Bleyer, 1976; Srinivasan, 1982). There is, therefore, no good evidence that pre delivery treatment is necessary as long as post delivery treatment is prompt (Kaaja, 2002). Women interested in this option need to take 10 mg of vitamin K by mouth daily throughout the last month of pregnancy (Mandelbrot, 1988; Cornelissen, 1993). A Cochrane review found no evidence that the risk of intraventricular bleeding in the preterm baby was decreased by pre-delivery treatment.

Post delivery: An alternative strategy for boosting the vitamin K intake of breast fed babies is for the mother to take a daily supplement herself after birth. A 2·5 mg oral dose twice a day (one hundred times the amount that would otherwise need to be given to the baby each day) was enough to raise the vitamin content of the milk to acceptable levels in the small study conducted by Bolisetty (1998). 15 mg of vitamin K_2 by mouth once a day was used in the larger study reported by Nishiguchi (1996).

Prophylaxis and the risk of leukaemia

The publication of the papers from Bristol (Golding, 1990, 1992) reporting an excess of later childhood cancer among children given intramuscular vitamin K at birth stimulated further epidemiological studies. Of these the most informative were the six studies that compared such children with others, matched for date and either place or hospital of birth, who never developed cancer. A pooled analysis of these data, commissioned by the Department of Health in 1998, has now appeared: 2,431 children developing cancer before 15 were matched afresh with 6,338 controls for sex and year (but not place) of birth. The resultant analysis (Roman, 2002) confirms that solid tumours are certainly no commoner in children who had IM vitamin K. The situation with regard to childhood leukaemia is less clear and, since almost every baby now

gets prophylaxis in some form or other, is unlikely to be clarified by the collection of further data. The increased risk, if real, is small (unadjusted odds ratio 1·25; 95% CI 1·06 to 1·46), and could be due to the fact that those selected for prophylaxis (because of prematurity, operative delivery or the like) were already more at risk of later cancer for some unknown reason. Only a controlled trial could resolve the residual uncertainty, and this would have to be unrealistically large.

In many cases it was not possible to be certain whether prophylaxis was given or not. Only the units at Bristol and around Newcastle had records that required an entry both when vitamin K was given and when it was not. If it is assumed that prophylaxis was never given where no paper record of this could be found 5–20 years later, even though it should have been had unit policy been followed, then the odds ratio is smaller and (given the size of the data set) not significant (odds ratio 1·13; 95% CI 0·97 to 1·32). Clinicians will hold differing views as to whether it is safe to make any such assumption. An audit of case notes in the north of England for 1980–1990 found no record of vitamin K being given to 15–20% of children in several units with a policy of universal prophylaxis. Faced with this evidence staff were insistent that treatment would not have been overlooked as often as this, even if documentation was deficient. Treatment in some units could be recorded in one or more different places, including the feed chart or cot label, neither of which were retained permanently with the case notes. Documentation by doctors seemed more incomplete than that undertaken by midwives in at least three units.

Lack of evidence of treatment may not, therefore, be evidence of lack of treatment, although Ansell (2001) and Roman (2002) would dispute this. They have argued that the lack of any record of administration probably means that midwives treated unit policy documents as guidelines, and interpreted them flexibly, while always writing down every drug they actually gave. Against this view others have pointed out that, in units with a policy of selective prophylaxis, it was a junior paediatrician who would have 'stood by' for the delivery of nearly every baby qualifying for vitamin K prophylaxis, and they would have been firmly discouraged from treating unit policy 'flexibly'.

The conclusion of the unnamed Expert Working Group convened by the UK Committee on Safety of Medicines in 1998 was that "an increase in the risk of leukaemia ….cannot be excluded." However, no plausible carcinogenic mechanism had been established and "the observed results were compatible with the play of chance." Nevertheless, since childhood leukaemia is quite common (1:2000) while late vitamin K deficiency bleeding is rare, there are those who will agree with Passmore (1998) that there must remain some residual risk that *universal* IM prophylaxis could be doing more harm than good. The development of an effective regimen of oral prophylaxis during the last ten years does at least mean that families now have a genuine choice in this matter. The 'precautionary principle' carries great resonance, but the balance in the end is between a known risk of vitamin K deficiency bleeding without treatment and a possible increase in the risk of leukaemia with IM treatment that the existing evidence can neither confirm nor refute.

It is now thought that many children who develop leukaemia in the early years of life may have been born with this propensity as the result of a translocation of chromosomal material during early fetal life. However some second factor seems to be necessary to trigger overt leukaemic change. Epidemiological evidence suggests that environmental factors, including radiation, exposure to certain chemicals (such as benzene), viruses (such as the Epstein-Barr virus) and bacteria (such as Helicobacter pylori) could, possibly, account for a few cases. If vitamin K (or one of the excipients in the IM preparation) is truly implicated in childhood leukaemia it presumably operates by triggering further genetic change. One hypothesis currently being studied suggests that delayed exposure to infection may cause an aberrant immune response (Greaves, 2002).

Advising parents

The above considerations can be summarised for parents as follows -

"Babies have no reserves of vitamin K at birth, and get what they need after birth from milk. Lack of this vitamin can cause a potentially dangerous bleeding tendency. Healthy babies not given a boost at birth, either by mouth, or by injection, have perhaps a 1:2000 chance of developing some such problem in the first week of life, and the risk is very much higher in those not well enough to be fed. Luckily early bleeding is seldom serious, and such a tendency is easy to recognise. Babies who are entirely breast fed are at greater risk, and remain at some small risk for three months, rather than just the first week of life, because human milk contains less vitamin K than artificial milks. Only about one breast fed baby in six thousand develops such a problem, but when late bleeding does occur it sometimes occurs without much warning, and it can occur into the head. Any unexplained bleeding or bruising in a young baby should never be ignored therefore.

A single 1 mg intramuscular injection of the vitamin provides complete protection for the full three months, probably by forming an artificial 'depot' of vitamin in the muscle at the injection site. However a study in 1992 suggested that such treatment might be associated with an increase in the risk of leukaemia. Five more studies have been done since then to look into this possibility, and we now know that any such a risk is certainly not nearly as great as was originally though. It is, however, very difficult to prove that no risk exists. Luckily, in babies who are *unwell* at birth, any risk is certainly less

than the risk of bleeding from lack of vitamin K. In babies who are *well*, there is also the option of giving the extra vitamin K by mouth instead of by injection - a choice that most hospitals in the UK now leave for parents to make. It is, nevertheless, important to stress that fully breast fed babies can only be completely protected from a small risk of later bleeding if given further oral doses at intervals after discharge (as already happens to bottle fed babies because the manufacturers add extra vitamin K to all artificial milk)."

Parenteral products currently available

European products: Roche is the only international company currently manufacturing Vitamin K_1 for IM use in Europe. They have two products. (Konakion®) comes in 0·5 ml (1 mg) ampoules containing 20mg of propylene glycol, phenol and polyoxyl 35 castor oil. In a little advertised move, Roche varied the SPC for this product in the UK in November 2000 to render its use in babies of less than 36 weeks gestation "off label", citing advice from a paediatric advisory group. The reason for the change remains unknown, and the membership of the advisory group unknown. The company has, however, made it clear that they plan to complete their withdrawal of this product from the UK market in the relatively near future. It has already been withdrawn from sale nearly everywhere else in the world. Unfortunately, it is still almost certainly the more appropriate product to use for IM prophylaxis in small babies, because the newer product (Konakion Paediatric MM®) is formulated in too concentrated a suspension for accurate administration to a very preterm baby. The latter product, which is five times as concentrated, and six times as expensive, has the virtue of being licensed for IV use, but there are strong grounds for believing that IV administration does not produce the same long term protection as a comparable IM dose.

Other products: Merk and Abbott both market 0·5 ml ampoules (containing 4·5 mg of benzyl alcohol and polysorbate-80) in North America, but these have not been approved for use in the UK, and would be expensive to import. Roche also have their original Konakion product on sale in America in a formulation that contains polysorbate-80 rather than polyoxyl 35 castor oil. While they are only licensed for IM use, some units in America have given these products by mouth. Sabex in Canada make a generic product in 1 ml ampoules that contain 10 mg of vitamin K_1. These ampoules cost $0·55 each (bulk purchase). The product mostly used in Japan is menaquinone-4 (Kaytwo®), otherwise known as MK-4, a form of vitamin K_2 manufactured by Eisai Co Ltd, Tokyo.

Parenteral nutrition: Vitamin supplementation currently results in many preterm babies on Intralipid® developing vitamin K levels that are unphysiologically high (Kumar, 2001). Plasma levels twenty times higher than normal have been reported.

Oral products currently available

The IM preparations available in North America are often given my mouth, although they have never been licensed for administration by this route. The cheap oral multi-dose formulation of Konakion that was marketed by Roche in Europe was withdrawn without much warning three years after the new mixed micellar preparation [Konakion Paediatric MM], licensed for oral, IM or IV use, came onto the market in 1996. The problem with this new, more expensive, preparation is that it was formulated in a manner that presupposed that all doses would be given by a health professional. An alternative oral preparation (Orakay®), made up in coconut oil and dispensed in 1 mg capsules, is currently in the process of being licensed in the UK. Parents are instructed to snip open the tip of the capsule and drop the liquid into the baby's mouth. There has been one report (Bhandari, 2002) suggesting that this product could be aspirated into the lung, but this is a problem common to all fat-soluble vitamin drops. All the oral formulations seem to be of comparable efficacy (von Kries, 2003). An important study from Denmark (Hansen, 2003) has also now established that 1 mg of vitamin K once a week by mouth during the first three months of life eliminates all risk of late vitamin K deficiency bleeding just as effectively as a 1mg IM 'depot' injection at birth. Absorption is poor in babies with serious obstructive jaundice, even when the mixed micellar product is used (Periera, 2003). The outcome of all the studies reported to date is summarised in the illustration at the start of this commentary.

The above analysis indicates that the most physiological approach to preventing the risk of symptomatic VKDB in the breast fed baby would be to give a small *daily* supplement (Tripp, 1998). Such a strategy had long been recommended for preventing vitamin D deficiency rickets – a much less potentially lethal problem. It is also the policy that has been used with apparent success in the Netherlands since 1990. Unfortunately no commercial company has yet thought fit to market such a preparation.

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