Vitamin K—what, why, and when

E Hey

Arch. Dis. Child. Fetal Neonatal Ed. 2003;88;80-83
doi:10.1136/fn.88.2.F80

REVIEW

Vitamin K—what, why, and when

E Hey

Arch Dis Child Fetal Neonatal Ed 2003;**88**:F80–F83

Policies for giving babies vitamin K prophylactically at birth have been dictated, over the last 60 years, more by what manufacturers decided on commercial grounds to put on the market, than by any informed understanding of what babies actually need, or how it can most easily be given. By a pure fluke a 1 mg IM dose, designed to prevent early vitamin deficiency bleeding ("haemorrhagic disease of the newborn") has been found to protect against late deficiency bleeding—a condition unrecognised at the time this policy took hold. Alternative strategies for oral prophylaxis are now opening up (see pp 109 and 113), but these are also, at the moment, dictated more by what the manufacturers choose to provide than by what would make for ease of delivery either in poor countries, or in the developed world.

Vitamin K is a fat soluble vitamin, and the development of a suitable commercial formulation for clinical use has long presented something of a challenge. Indeed, when it was first shown in 1939 that treatment with vitamin K could abolish symptomatic prothrombin deficiency in the first week of life,[1–3] babies were generally given menadione, a water soluble analogue. A paper in the *Lancet* in 1944 generated widespread interest.[4] It showed a five fold reduction in death from haemorrhage 2–8 days after birth once all babies were given 1 mg of oral menadione at delivery in Göteborg, Sweden, in 1940. A similar policy was soon widely adopted elsewhere even though many were unable to replicate these findings.[5 6] The argument, as Ethel Dunham put it in 1948, was that "since the vitamin does no harm and may do good, it is probably best to give it to all premature infants immediately after birth".[7]

When this did not stop some babies from developing a bleeding tendency, or dying with an intraventricular haemorrhage, physicians started using larger and larger doses. Prothrombin levels are always relatively low at birth by adult standards, and remain so for some time, and it was (wrongly) thought that the low level seen at birth, and not just the further postdelivery drop, must be due to relative fetal vitamin K deficiency. By 1953 came a first report that high dose use could cause haemolytic anaemia,[8] and by 1956 it had been established that this could, in turn, cause severe jaundice and even death from kernicterus after unbound bilirubin entered the brain.[9 10] The dose administered was cut back after that but, within five years, the water soluble product (Synkavit®) was starting to be replaced by the natural, fat soluble, plant form of vitamin K (phylloquinone; vitamin K_1). This product did not seem to cause haemolysis,[11] and it is this product that has dominated the market in Europe and North America ever since, although menaquinone-4 (a member of the K_2 series) remains the main product still used in Japan.

Routine prophylaxis soon became the norm for every baby (not just every preterm baby) in some countries.[12] Intramuscular prophylaxis also became the route universally adopted, mainly because manufacturers never got round to licensing a product for oral use. It also became routine to give a 1 mg injection, even though this was a thousand times more than the dose of menadione needed each day,[13] and 10 times the dose used in the only controlled trial of clinical efficacy ever conducted.[14] Reluctance to advocate universal use persisted however, especially in the UK where most of the cases of kernicterus due to excessive dosage had been reported.[10] There was also growing uncertainty as to just how common the condition really was. As a result it became increasingly common to only treat babies considered "at risk"—mostly preterm babies and babies having an operative delivery (a policy that gained increased credence and spread even more widely as a result of an influential editorial in the *Lancet* in 1978).[15]

Spontaneous bleeding, in the absence of trauma, was seldom seen during the next decade, either in units that opted for universal or for selective prophylaxis, and those cases that did occur were quickly spotted and controlled. Most presented with dark melaena stools, bloody vomit, nose bleed, blood stained urine, or bleeding from the umbilical stump, two to six days after birth. Circumcision before seven days brought many cases to light in cultures where this ritual remained common.[14] Presentation was much the same in countries where prophylaxis is not generally available,[16 17] although here the babies risked death from blood loss.[16] Then another paper appeared in the *Lancet* describing a resurgence of the condition in the UK not just in the first week of life but also in older babies.[18] These were healthy children with a generalised bleeding tendency that responded promptly to treatment with vitamin K but where, typically, no abnormality had been suspected until there was a catastrophic intracerebral bleed two to 10 weeks after birth. It soon became clear that such problems were only being seen in breast fed babies who had never had even a few "complementary" feeds of bottle milk, and who had never received intramuscular vitamin K. Quite rapidly the previous policy of selective prophylaxis gave way to a policy of universal prophylaxis—the same policy as that long advocated in north America—although a growing number of units

Correspondence to:
Edmund Hey, Retired Paediatrician, Newcastle upon Tyne, NE3 1UD;
shey@easynet.co.uk

Accepted
16 December 2002

opted for oral rather than intramuscular prophylaxis for those babies who were well enough to be fed at birth.[19] A survey showed that policy in the UK varied widely from unit to unit,[20] and a more recent retrospective survey has suggested that midwifery staff were often quite uncertain as to what unit policy actually was.[21]

Then, just as people were beginning to accept that universal prophylaxis was justified, not so much to manage the occasional case of early bleeding, but to prevent late bleeding in the breast fed baby, a paper was published from Bristol suggesting that babies given intramuscular vitamin K might be more likely to develop cancer (and particularly leukaemia) later in childhood.[22] What made life even more difficult was the fact that the news broke in the *Daily Mail* almost two months before the definitive paper appeared in the *BMJ* in August 1992.

Different countries responded to the news in different ways. Several countries in Europe moved increasingly towards a uniform policy of oral prophylaxis.[23] The American Academy of Pediatrics reiterated its confidence in universal intramuscular prophylaxis,[24] and a small case control study from that country soon appeared suggesting that the risk, if real, was certainly not as big as the Bristol study had originally suggested.[25 26] Australia and New Zealand changed to universal oral prophylaxis and then reverted to intramuscular prophylaxis when cases of late vitamin K deficiency bleeding started to reappear.[27] The UK just got itself into a muddle. The Department of Health drew back from issuing any specific guidance,[28] although it had not shown any such reluctance some years earlier.[29] Indeed decades earlier it taken a much firmer line and made its own low cost multivitamin product available when presented with evidence that many young children were developing vitamin D deficiency rickets.[30] Fat soluble vitamin K could have been added to this product, but it was not. Their one pivotal pronouncement, after six years, was that parents should be allowed a choice between the oral and intramuscular options.[31] The British Paediatric Association (the predecessor of the present College) recommended regular low dose oral prophylaxis[32] but, since no licensed oral product existed in the UK, this advice was not widely followed. The Health Visitors Association, on legal advice, advised its members to avoid the issue altogether.[33] Midwives, who could give licensed products on their own authority,[34] were given the job of counselling parents, but not told what to say. Policy varied widely from unit to unit,[20] and cases of late bleeding continued to be reported quite regularly.[35] Other countries were able to assess the impact of policy on late bleeding,[23] but even this was difficult in the UK because policy varied so widely. Attempts to persuade Roche to apply for a UK licence for the oral product they already had a license to sell in the rest of Europe came to nothing. One small pharmaceutical company did start making something similar on request (Orakay®) that the parents of breast fed babies could give their child at regular intervals after discharge,[36] but is has taken 10 years to assemble enough evidence of efficacy for the Medicines Commission to recommend the granting of a product licence.

Slowly, however, the situation started to become clearer, especially when the old term "haemorrhagic disease of the newborn" was replaced by "vitamin K deficiency bleeding" (or VKDB)—both because much bleeding in the newborn was not caused by vitamin K deficiency, and also because deficiency bleeding is not only seen in the first week of life.[37] Recent studies, using a standardised definition,[38] seem to show that the condition is not now very common, even in communities where prophylaxis is not yet available. It is certainly not nearly as common as some authoritative reports claim.[24] Two studies in Japan before the introduction of routine prophylaxis had suggested that one in every 6000 breast fed babies might sustain a late bleed when more than two weeks old.[39] The true risk of bleeding in the first week of life (the "classic" presentation) remains less clearly defined. It was nearly twice as common as late bleeding in breast fed babies offered no prophylaxis in the UK in 1988–89,[35] and three times as common in a recent Malaysian study.[17] It has also become clear that oral prophylaxis can be as reliable as intramuscular prophylaxis (for further evidence relating to this statement see the web site: www.bmjpg.co.uk/books/neonatalformulary/chapters/vitk2comment.htm). What matters here is not so much the total dose given as the need for the dose regime to allow for the fact that natural body stores are low and turnover is rapid (a realisation that reinforces the suggestion that the solitary large intramuscular dose traditionally given at birth functions as a slow release "depot" store).[40] Even in adult life body stores are limited (~1 μg/kg), and the turnover time is only 1–2 days.[41] Low dose daily "drops" would be the most physiological option,[42] but no commercial company has yet shown an interest in such a product.

Recent studies have certainly not provided any support for the belief that vitamin deficiency bleeding is commoner in preterm babies. Although prothrombin levels are lower than in term babies at birth, giving vitamin K does not cause a rise. Neither is bleeding commoner in babies undergoing operative delivery. However babies who are not fed at birth are certainly at increased risk, since all have low vitamin K stores at delivery, and milk provides their only source of vitamin K until bacterial activity in the gut starts to provide a secondary source. Bottle fed babies are at almost no risk because almost all these milks are artificially fortified. The babies of mothers on some anticonvulsants are also at risk, but such bleeding can occur at any time in the first 2–3 days of life.[43 44] The idea that cases presenting in the first day of life form a clearly distinct subgroup is ingrained,[37] but it gains no support from recent reports.[16 17]

Further studies have also been done into the suggestion that intramuscular prophylaxis could be associated with a higher incidence of cancer in later childhood. The most informative of these were six studies that compared such children with others, matched both for date and either place or hospital of birth, who never developed cancer. A pooled analysis of these data, commissioned by the UK Department of Health in 1998, finally appeared last year: 2431 children developing cancer before 15 were compared afresh with 6338 controls matched for sex and year (but not place) of birth.[45] The resultant analysis confirms that solid tumours are certainly no commoner in children given intramuscular vitamin K at birth. 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. Interpretation also depends on whether you believe that staff followed unit policy with regard to prophylaxis, as they claim, even where there is no proof of this in those records that do still exist (for further evidence relating to this statement see above website commentary). It has certainly proved difficult to prove that no risk exists. Only a controlled trial could ever resolve the residual uncertainty, and this would have to be quite unrealistically large.

For nearly 40 years now clinicians have been using a fat soluble form of vitamin K (phytomenadione) dispersed in a polyethoxylated oil or in polysorbate 80 with either propylene glycol (Konakion®) or benzyl alcohol (AquaMEPHYTON®), and giving this product uneventfully at birth to prevent vitamin K deficiency bleeding. However intravenous use in adults has occasionally been associated with severe anaphylaxis, possibly due to the polyethoxylated castor oil triggering histamine release.[46] As a result Roche finally brought out a new colloidal product, solubilised with lecithin and a bile salt (glycocholic acid), in 1996, and started to phase out their former

product. Little was known about the new mixed micellar product (Konakion MM®) when it first became available, but it did seem to be better absorbed when given by mouth.[47] Roche therefore sought and obtained a licence, from the outset, for oral as well as intravenous and intramuscular use. This was something they never did with their earlier product in the UK, or in North America, even though it had been awarded a licence for oral use in Europe. However, it only has a license for the prevention of "haemorrhagic disease of the newborn." Roche have not, as yet, claimed to have evidence that it prevents late vitamin K deficiency bleeding, so the administration of further doses after one week is, in some senses, currently an "off label" use.

A change in the formulation of a well established product might hardly seem to be a big issue. The new product has generated relatively little study since the early work required by the licensing authorities first appeared seven years ago, but two important papers in this issue of *Fetal and Neonatal* (see pp 109 and 113) have now established, with some precision, the effectiveness of oral administration.[48 49] It seems that, although the new product may be safer than the old product when given intravenously, its efficacy when given by mouth is no greater than that of other products. Neither do we yet know whether a single intramuscular injection provides the same long term protection as the product it has replaced, although this is currently under evaluation in Australia.[27]

CONCLUSION

So what have we learnt in the last 64 years? That babies have very limited reserves of vitamin K at birth, and that some will soon bleed if a continuing intake is not guaranteed. We also know that a few "supplements" of cows milk[50] or formula milk[14] can suffice to restock those reserves, and that there is really no case for giving the healthy, artificially fed, baby further supplementation, either by injection or by mouth, other than administrative convenience. Babies who are not fed, and a very small number of fully breast fed babies, will develop symptomatic deficiency. Without prophylaxis the risk of early (easily recognised) bleeding in a healthy non-traumatised term baby in the first two weeks of life is probably only 1–2 in a thousand. The risk of a later (potentially more dangerous) bleed is perhaps a third of that. Both these risks can be virtually eliminated by given a single 1 mg intramuscular "depot" injection of phytomenadione, or by giving the baby 1 mg by mouth once a week for the first three months of life. Indeed the only babies not protected by four 1 mg (or three 2 mg) oral doses, if well spaced out, are those with some as yet unrecognised liver disease.[36 48]

Manufacturers have been resisting calls for an oral product for more than 40 years.[12 19 24 26 32 42] Childrens' needs carry little clout with the pharmaceutical industry. One product licensed for oral use (Konakion MM) did finally reach Europe (but not north America) in 1996. Two papers in this issue of *Fetal and Neonatal* now tell us that it does not perform any better than the earlier European product it replaced, even though it costs eight times as much, and has not been presented in a way that allows parents to administer the drops for themselves. Children in the third world still await the arrival of a simple generic product that they can afford. Much the same is true for vitamin D and folic acid. Available commercial products cost a hundred times more than the basic cost of their one active ingredient. Those whose original research (unfunded by any commercial organisation) gave us a scientific understanding of how these vitamins work, would be shocked to discover that they still remain, after half a century, beyond the financial reach of most of the world's women and children.

REFERENCES

1 **Dam H**, Tage-Hansen E, Plum P. Vitamin-K lack in normal and sick infants. *Lancet* 1939;**ii**:1157–61.
2 **Nygaard KK**. Profylactic and curative effect of vitamin K in hemorrhagic disease of the newborn (hypothrombnemia hemorrhagica neonatorum). *Acta Obstet Gynaecol Scand* 1939;**19**:361–70.
3 **Waddell WW**, Guerry D. The role of vitamin K in the etiology, prevention, and treatment of hemorrhage in the newborn infant. *J Pediatr* 1939;**15**:802–11.
4 **Lehmann J**. Vitamin K as a prophylactic in 13,000 babies. *Lancet* 1944;**i**:493–4 (see also **i**:506–8 and **ii**:737–8).
5 **Sanford HN**, Shmigelsky L, Chapin JM. Is administration of vitamin K to the newborn of clinical value? *JAMA* 1942;**118**:697–702.
6 **Gröntoft O**. Intracranial haemorrhage and blood-brain barrier problems in the new-born: a pathologico-anatomical and experimental investigation. *Acta Pathol Microbiol Scand* 1954;**Suppl 100**.
7 **Dunham EC**. *Premature infants: a manual for physicians.* Washington: Federal Security Agency. Children's Bureau Publication 325, 1948.
8 **Gasser C**. Die hämolytische Frügeburtenamie mit spontaner Innerkörperbildung: Ein neues Syndrom, beobachten an 14 Fällen. *Helvet Paediatr Acta* 1953;**8**:491–528.
9 **Allison AC**. Danger of vitamin K to newborn. [Letter] *Lancet* 1955;**i**:669 (see also 819).
10 **Mayer TC**, Angus J. The effect of large doses of 'Synkavit' in the newborn. *Arch Dis Child* 1956;**31**:212–5.
11 **Asteriadou-Samartzis E**, Leiken S. The relation of vitamin K to hyperbilirubinemia. *Pediatrics* 1958;**21**:397–402.
12 **American Academy of Pediatrics**. Committee on Nutrition. Vitamin K compounds and the water soluble analogues. *Pediatrics* 1961;**28**:501–7.
13 **Sells RL**, Walker SA, Owen CA. Vitamin K requirements of the newborn infant. *Proc Soc Exper Biol Med* 1941;**47**:441–5.
14 **Sutherland JM**, Glueck HI, Gleser G. Hemorrhagic disease of the newborn. Breast feeding as a necessary factor in the pathogenesis. *Am J Dis Child* 1967;**113**:524–33.
15 **Anon**. Vitamin K and the newborn. [Editorial] *Lancet* 1978;**i**:755–7.
16 **Lulseged S**. Haemorrhagic disease of the newborn: a review of 127 cases. *Ann Trop Paediatr* 1993;**13**:331–6.
17 **Choo KE**, Tan KK, Chuah SP, *et al*. Haemorrhagic disease in newborn and older infants: a study of hospitalised children in Kelantan, Malasia. *Ann Trop Paediatr* 1994;**14**:231–7.
18 **McNinch AW**, L'Orme R, Tripp JH. Haemorrhagic disease of the newborn returns. *Lancet* 1983;**i**:1089–90.
19 **Dunn PM**. Vitamin K for all newborn babies. *Lancet* 1982;**i**:770.
20 **Barton JS**, Tripp JH, McNinch AW. Neonatal vitamin K prophylaxis in the British Isles: current practise and trends. *BMJ* 1995;**310**:632–3.
21 **Ansell P**, Roman E, Flear NT, *et al*. Vitamin K policies and midwifery practice: questionnaire survey. *BMJ* 2001;**322**:1148–52.
22 **Golding J**, Greenwood R, Birmingham K, *et al*. Childhood cancer, intramuscular vitamin K and pethidine given during labour. *BMJ* 1992;**305**:341–6 (see also 326–9 and 709–11).
23 **Cornelissen M**, von Kries R, Loughnan P, *et al*. Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. *Eur J Pediatr* 1997;**156**:126–30.
24 **American Academy of Pediatrics**. Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993;**91**:1001–3.
25 **Klebanoff MA**, Read JS, Mills JL, *et al*. The risk of childhood cancer after neonatal exposure to vitamin K. *N Engl J Med* 1993;**329**:905–8.
26 **Hilgartner MW**. Vitamin K and the newborn. *N Engl J Med* 1993;**329**:958–9.
27 **Loughnan P**, Chant KM Elliott E, *et al*. The frequency of late onset haemorrhagic disease in Australia with different methods of prophylaxis, 1993–1997. An update. [Abstract] *J Paediatr Child Health* 1999;**35**:A8.
28 **Chief Medical Officer**. *Prophylaxis against vitamin K deficiency bleeding in infants.* London: Department of Health, 1992;(PL/CMO/92/20).
29 **Department of Health and Social Security**. *Report on health and social subjects. No 18. Artificial feeds for the young infant.* London: Her Majesty's Stationery Office, 1980:38.
30 **Department of Health**. *Report on health and social subjects. No 51. Scientific review of the welfare food scheme.* London: The Stationery Office, 2002:4–6.
31 **Chief Medical Officer**. *Vitamin K for newborn babies.* London: Department of Health, 1988; (PL/CMO/98/3).
32 **British Paediatric Association**. *Vitamin K prophylaxis in infancy. Report of an expert committee.* London: British Paediatric Association, 1992.
33 **Health Visitors' Association**. *Administration of vitamin K.* London: Health Visitors' Association (Centre Circular CS/93/21), 1992.
34 **Prescription Only Medicines (Human Use) Order**, 1997; Statutory Instrument 1830.
35 **McNinch AW**, Barton J, Tripp JH. Vitamin K deficiency bleeding in the British Isles and the changing pattern of vitamin K prophylaxis. In: Sutor AH, Hathaway WE, eds. *Vitamin K in infancy.* Stuttgart: Schattauer Verlag, 1995:165–72.
36 **Wariyar U**, Hilton S, Pagan J, *et al*. Six years' experience of prophylactic oral vitamin K. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F64–8.
37 **Sutor AH**, von Kries R, Cornelissen EAM, *et al*. Vitamin K deficiency bleeding (VKDB) in infancy. *Throm Haemost* 1999;**81**:456–61.
38 **Tripp JH**, Cornelissen M, Loughnan P, *et al*. Suggested protocol for the reporting of prospective studies of vitamin K deficiency bleeding (previously called hemorrhagic disease of the newborn). In: Sutor AH, Hathaway WE, eds. *Vitamin K in infancy*. Stuttgart: Schattauer Verlag,1995:395–401.

39 **Hanawa Y**, Maki M, Murata B, *et al*. The second nation-wide survey in Japan of vitamin K deficiency in infancy. *Eur J Pediatr* 1988;**147**:472–7.
40 **Loughnan PM**, McDougall PN. Does intramuscular K_1 act as an unintended depot preparation? *J Paediatr Child Health* 1996;**32**:251–4.
41 **Olson RE**, Chao J, Graham D, *et al*. Total body phylloquinone and its turnover in human subjects at two levels of vitamin K intake. *Br J Nutr* 2002;**87**:543–53.
42 **Tripp JH**, McNinch AW. The vitamin K debacle: cut the Gordian knot but first do no harm. *Arch Dis Child* 1998;**79**:295–7.
43 **Hey E**. Effect of maternal anticonvulsant treatment on neonatal blood coagulation. *Arch Dis Child Fetal Neonatal Ed* 1999;**81**:F208–10.
44 **Kaaja E**, Kaaja R, Matila R, *et al*. Enzyme-inducing antiepileptic drugs and the risk of bleeding in the neonate. *Neurology* 2002;**58**:549–53.
45 **Roman E**, Flear NT, Ansell P, *et al*. Vitamin K and childhood cancer: analysis of individual patient data from six different case-control studies. *Br J Cancer* 2002;**86**:63–9.
46 **Hopkins CS**. Adverse reactions to a cremophor-containing preparation of intravenous vitamin K. *Intensive Therapy Clin Monit* 1988;**9**:254–5.
47 **Schubiger G**, Grüter J, Shearer MJ. Plasma vitamin K_1 and PIVKA-II after oral administration of mixed micellar or cremophor EL-solubilized preparations of vitamin K_1 in normal breast-fed newborns. *J Pediatr Gastroenterol Nutr* 1997;**24**:280–4.
48 **von Kries R**, Hachmeister MJ, Göbel U. Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F109–12.
49 **Pereira SP**, Shearer MJ, Williams R, *et al*. Intestinal absorption of mixed micellar phylloquinone (vitamin K_1) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F113–18.
50 **Salomonsen L**. On the prevention of hemorrhagic disease of new-born by administration of cow's milk during the first two days of life. *Acta Paediatr Scand* 1940; **28**:1–7.