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CURRENT TOPIC

Vitamin K prophylaxis in the newborn – again

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Current situation in the UK

Paediatricians have all pondered why the newborn should have marginal stores of vitamin K, and why breast milk contains very little. Even before reading Professor Golding's studies[1 2] and the attendant press publicity, most had reviewed their vitamin K policy at intervals in order to try to spare newborn babies intramuscular injections. Some were already using oral vitamin K despite the lack of a suitable licensed preparation.[3] A single oral dose regimen is now known not to be fully protective against late haemorrhagic disease of the newborn (HDN).[4 5] The high profile which the debate then enjoyed, and the recommendations of the British Paediatric Association (BPA) published in November 1992, caused many more units to change their policy and to reduce the prescribed dose both of oral and intramuscular vitamin K. Review of 50 protocols received in response to a request for information in the BPA newsletter of spring 1993 reveals that current UK practice is now more varied than during the last survey.[6] Parental consent is much more widely sought, although not all practitioners are willing to take responsibility for oral administration of vitamin K so that some infants are discharged unprotected if parents refuse the parenteral route. Doses prescribed include 500, 250, 200, and 100 μg intramuscularly with or without subsequent oral doses, and some use 1 mg or 500 μg of vitamin K as a single oral dose. Many have adopted the regimen of 500 μg divided into two doses on the first day of life with two subsequent doses of 250 μg at intervals in breast fed babies. Some are giving as many as five repeat oral doses and most specify that intramuscular doses should continue to be given to 'high risk' babies, although the definition of this group is not uniform. In particular not all include maternal anticonvulsant treatment, none mention maternal antituberculous treatment, and some add a family history of bleeding disorder or bruising in the baby.

The publication of two studies,[1 2] which in the words of the Department of Health[7] 'fell far short of providing conclusive evidence' have resulted in many British babies now receiving an initial dose of vitamin K one tenth that shown to be effective in previous studies.[4] A smaller initial dose requires that further doses be prescribed for breast fed infants, and these are also needed for those treated with an oral dose at birth in order to improve the demonstrably weaker protection offered by this mode of therapy. This course of action as yet lacks definitive published evidence in its favour, and the problem of correctly identifying all those who should receive intramuscular treatment initially will inevitably result in some babies missing out: the maternal drug history may not be accurate, and some will have liver disease which is not apparent in the maternity hospital. Many hours of consultant time have been spent drafting policies and parent information leaflets, talking to the local press, and devising ploys to bypass the problems created by the presentation of Konakion (phytomenadione, Roche) in glass vials and the fact that it is anyway unlicensed for oral use. The need to prescribe oral vitamin K on a named patient basis and for individual parent counselling has not helped the drive to reduce the workload of paediatric juniors either. Adverse press publicity has resulted in some frightened parents refusing vitamin K for their infants altogether. Advice from antenatal clinics and parent group newsletters is sometimes biased and inadequate, and there is a need for a non-discriminatory approach to breast feeding mothers. Even in the climate of litigation created by current American medical practice the Academy of Pediatrics has continued to advise that 1 mg of intramuscular vitamin K be given to all newborns, citing as evidence the failure to observe an increase in childhood leukaemia since its introduction 30 years ago.[8] More recently, publication of two large studies from Sweden and the United States have failed to confirm the link suggested by Golding *et al.*[9 10] Other than providing a welcome helmet from the pavilion for those who remained allegiant to the beleaguered standard of intramuscular treatment in the battle of the summer of 1992 what does this latest work mean and, more importantly, where should we go from here?

Studies on neonatal vitamin K prophylaxis for HDN and later childhood cancer

The first study that described an association between drugs given in the first week of life and later childhood cancer was published in 1990.[1] Thirty three cases of cancer developing by the age of 10 were identified in a cohort of infants enrolled because they were all born during the same week of April 1970. Information regarding pregnancy, labour, and delivery had been

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collected by midwives over the first seven days of life. Three controls were generated for each case. Compared with the controls, mothers of cases were more likely to have smoked or had radiographs taken during pregnancy, received pethidine during labour, and more of the babies had been given drugs of any kind in the first week (of which vitamin K was the most common). These workers followed up the unexpected vitamin K association with a second study in which the neonatal records of 195 cases of childhood cancer diagnosed in Bristol in the decade 1971–81 were compared with 558 unmatched controls.[2] The route of administration of vitamin K was not always recorded in the notes and notes were inevitably incomplete or missing, and this major weakness has been highlighted in editorial discussion elsewhere.[11] An association between intramuscular vitamin K administration, but not oral, was shown with an odds ratio of 1·97:1 for the development of childhood cancer when compared to no or oral vitamin K. The authors cite in support of their hypothesis a small rise in cases of childhood leukaemia between 1962 and 1974, and an increase in sister chromatid exchanges with high ambient vitamin K concentrations.[12] They point out that Konakion contains cremophor EL, phenol, and propylene glycol which have been suggested to be possible carcinogens. Cremophor EL can certainly be active in vitro, reversing drug resistance in doxorubicin resistant human breast cancer cell lines.[13] Based on the incidence figures for early and late haemorrhagic disease of about four cases per 100 000 deliveries for each type,[4] Golding *et al* suggest that the trade off for cancer risk comparing oral and intramuscular vitamin K might be between 10 cases of late HDN and no 'extra' cases of cancer (oral) versus 980 extra cases of cancer and one case of late HDN using an intramuscular regimen. The suggestion that childhood cancer might be doubled by neonatal intramuscular vitamin K administration has not been supported by data from the United States, where the drug was introduced in 1961 and there has been no increase in the annual incidence of childhood leukaemia.[8] There has been no trend in Australia either.[14] The figures Golding *et al* cite for the UK were contested by Draper and Stiller using data from the Oxford childhood cancer registry.[15] The American task force continue to recommend 1 mg of intramuscular vitamin K for all infants, and consider that if an oral form were to be developed the dose should be 2 mg at birth, 1 week, and 4 weeks.

Two new studies have now examined the hypothesis raised by Golding *et al*. Ekelund *et al* linked two computerised registers for the whole of Sweden: the birth register and the Swedish cancer registry.[9] Over one million babies had been given intramuscular vitamin K (as Konakion) and just over a quarter of a million had received the drug orally. There was no difference in the risk of developing childhood cancer, or leukaemia alone, between the two groups. Klebanoff *et al* used information from the Collaborative Perinatal Project in the United States to study the problem.[10] The cohort was born between 1959 and 1966, as vitamin K was becoming more widely used in the United States, and information on 48 cases of cancer was compared with 226 controls. Altogether 68% of the cases and 71% of the controls had been given intramuscular vitamin K. There were few missing data in this study as the subjects had been enrolled prospectively, using a questionnaire which asked specifically about drug dosage, preparation, and route. Several brands of vitamin K were in use during this time, including Aquamephyton (Merck Sharpe and Dohme) and Konakion. In the United States the vehicle for Konakion is different from the preparation used in Europe (table).

Brands of vitamin K and vehicle used in different countries

	Konakion		
	UK/ Sweden	*United States*	*Aquamephyton (United States)*
Phenol	+	+	
Cremophor EL	+		
Polysorbate-80		+	+
Propylene glycol	+	+	
Benzyl alcohol			+

The latest studies argue against the hypothesis that the vehicle may be carcinogenic,[9 10] and also the biologically more plausible hypothesis of increased sister chromatid exchanges related to high plasma concentrations of vitamin K or a protective effect induced by vitamin K deficiency at a critical stage of development. Formula fed infants receive about 1 mg of vitamin K per month and there has only once been a suggestion that they are at higher risk of developing childhood cancer.[16]

Work regarding the efficacy, dose, and route of administration of vitamin K

CLASSICAL HDN (1–7 DAYS)

Vitamin K prophylaxis was introduced to protect against this type of HDN, which is characterised by rectal, umbilical, oral, or circumcision bleeding and in which there is only occasional central nervous system bleeding. Either parenteral or oral treatment is effective. Certain plasma proteins, precursors of prothrombin, are induced by vitamin K absence (acarboxy prothrombin: PIVKA-II), and can be measured. PIVKA-II is usually undetectable, expressed as an amount of <20 arbitrary units/l (AU/l). Normal adult concentrations of vitamin K are usually above 2 ng/l. A single intramuscular dose of 1 mg of vitamin K resulted in a peak serum vitamin K concentration of 350–900 ng/l at 12 hours while an oral dose of 1 mg gave rise to 20–330 ng/l at four hours.[17] One mg of oral vitamin K given with the first feed reduced the PIVKA detection rate to zero compared to 50% in babies not given prophylaxis.[18] The minimum amount of vitamin K_2 which was needed to prevent PIVKA-II concentration above 15 AU/l was estimated at 15 μg over the first three days of life in a group of Japanese breast fed

infants,[19] but these authors reinforced the recommendation for 1–2 mg orally at birth to take into account those with potential malabsorption problems.

VERY EARLY (<24 HOURS) HDN

Ideally mothers taking anticonvulsants or having antituberculous treatment should be prescribed oral supplements of vitamin K during late pregnancy, but parenteral treatment probably represents the best protection for this small but high risk group of infants.

LATE HDN

No specific prospective studies have been carried out to identify the best method of prophylaxis against this condition, which carries a higher morbidity and mortality (20%) than that of classical HDN. Small warning bleeds are common but may not be recognised for what they are, and the condition is associated with a risk of intracerebral haemorrhage of 50%. The disease is fortunately rare and virtually confined to breast fed infants, particularly those with malabsorption or liver disease. Von Kries could find only four cases among 65 described in the world literature who had been given parenteral vitamin K.[5] Neither the British, Swiss, or Swedish studies found any cases of late HDN in those receiving parenteral vitamin K.[4 20 21] In a German study a single oral dose was more likely than intramuscular vitamin K to be followed by late HDN, although the differences between the groups did not reach statistical significance: in the UK study the difference was statistically significant.[4 22] Certain countries of the world (Japan, Thailand) have used 2 mg of vitamin K_2 orally as a single dose prophylaxis but reported a consistently higher incidence of late HDN than in the UK. By 4 weeks of age, more Thai infants who had been randomised to receive 2 or 5 mg orally (compared to 1 mg intramuscularly) at birth had vitamin K concentrations below adult norms.[23] Even with two oral doses of 2 and 4 mg vitamin K at birth and 5 days the PIVKA-II detection rate at 1 month was high.[24] Three of 135 Dutch infants given 1 mg vitamin K orally at birth compared with 1/127 given the intramuscular form had PIVKA detectable at 1 month, although there was no difference between the groups at 3 months.[25] By the age of 3 months a high percentage of children who had received either oral or intramuscular vitamin K had PIVKA detectable, suggesting that neither regimen offered complete haematological correction,[26] although demonstration of a difference in the incidence of late HDN would be far more important.

Konakion Mixed Micelles (MM)

A new preparation of Konakion has been under development and the preparation is now licensed for use in adults. The solubilising agent used in the standard Konakion, cremophor EL, is replaced by natural components. These are the bile acid glycocholic acid and the phospholipid is lecithin. This has been developed to avoid the possibility of anaphylaxis after intravenous injection, not a problem in neonatal practice, and has the advantage that it is better absorbed after enteral administration even in babies with liver disease. Concentrations in infants given an oral dose of 3 mg of this preparation were similar to those given 1·5 mg intramuscularly.[27] Concentrations at 24 days had fallen significantly lower in the group who initially received an oral dose in this study, but were still within the adult reference range. At this stage, the holy grail of effective single dose oral prophylaxis remains elusive. As pointed out by Professor Hull,[28] if high concentrations carry a risk of later childhood cancer then achieving the same high concentrations with better oral preparations will not prevent the risk.

Conclusion

'While we await confirmation or otherwise of the association between [intramuscular] vitamin K and childhood cancer it seems reasonable to develop a programme of oral administration for all infants at birth ...'.[28] This recommendation followed the report of an association between intramuscular vitamin K and later childhood cancer.[2] Two large studies, one with good quality prospectively collected information, have now challenged this association. Assuming that a suitable licensed oral preparation will soon appear, should we still go down the road of developing a multiple dose regimen for oral prophylaxis? Vitamin K prophylaxis is clearly essential, and it is now obvious that repeated oral dosing will be required in breast fed infants. The best oral regimen required to prevent late HDN has yet to be defined. Multiple oral dosing will always be less reliable than the intramuscular route due to non-compliance and malabsorption. However, it has philosophical advantages and will prove more acceptable to parents. A unified approach is required in the UK as any individual cannot hope to establish the risks of the preferred regimen in his or her own practising lifetime. Using the information from the last British Paediatric Surveillance Unit (BPSU) survey, if all 'normal risk' UK infants were given one dose of oral vitamin K there would be about 20 cases of late HDN per annum in the whole country. The best way of reducing this to zero and reliably confirming the reduction needs to be carefully thought through; the logistics of a trial involving half a million deliveries would make such a study virtually impossible and a common protocol adhered to for several years is the only practical approach. When Konakion MM becomes available a four dose oral regimen should be universally adopted and monitored by the BPSU. Until this time the only certain and licensed regimen remains 1 mg intramuscular vitamin K. The infrastructure exists for routine administration at birth and the system has worked well for many years. Routine intramuscular administration has the benefit of simplicity, and avoids the necessity of identifying

breast feeding mothers and those on anticonvulsant therapy and the uncertainty of predicting liver disease. For those who are not prepared to return to the intramuscular route while awaiting Konakion MM an initial oral dose of 500 μg in two divided doses giving the existing form should be prescribed. At least two further doses must be arranged for breast fed babies and will also be required if the intramuscular dose used for those considered to be at high risk is 100 μg. Death from late HDN after a single intramuscular dose of this size has already been reported from Australia.[27]

A bitter lesson has again been learned from the release of important new research results to the national press before most of the profession have been able to read the original paper and before a response from a suitably qualified expert group has been drafted and discussed. As a consequence of this latest scare, some babies have been put at increased risk of developing HDN by being denied prophylaxis by their parents or doctors, and mothers may be less likely to breast feed as they perceive that bottle feeding provides adequate sources of vitamin K. Paediatricians should do all they can to redress the balance in this debate by presenting a balanced view.

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1 Golding J, Paterson M, Kinlen LJ, Factors associated with childhood cancer in a national cohort study. *Br J Cancer* 1990; **62:** 304–8.
2 Golding J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992; **305:** 341–6.
3 Dunn PM. Vitamin K_1 for all newborn babies. *Lancet* 1982; ii: 770.
4 McNinch AW, Tripp JH. Haemorrhagic disease of the newborn in the British Isles: two year prospective study. *BMJ* 1991; **303:** 1105–9.
5 Von Kries R, Shearer MJ, Göbel U. Vitamin K in infancy. *Eur J Pediatr* 1988; **147:** 106–12.
6 Handel J, Tripp JG. Vitamin K prophylaxis against haemorrhagic disease of the newborn in the United Kingdom. *BMJ* 1993; **303:** 1109.
7 Calman KC, Moores T. Prophylaxis against vitamin K deficiency bleeding in infants. (Numbers FL/CMO/(92)20 and FL CNO (92) 14.) London: Department of Health, 1992.
8 Merenstein GB, Hathaway WE, Miller RW, Paulson JA, Rowley DL. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993; **91:** 1001–2.
9 Ekelund H, Finnström O, Gunnarskog J, Källén B, Larsson Y. Administration of vitamin K to newborn infants and childhood cancer. *BMJ* 1993; **307:** 89–91.
10 Klebanoff MA, Read JS, Mills JL, Shiono PH. The risk of childhood cancer after neonatal exposure to vitamin K. *N Engl J Med* 1993; **329:** 905–8.
11 Hilgartner MW. Vitamin K and the newborn. *N Engl J Med* 1993; **329:** 957–8.
12 Israels LG, Freisen E, Jansen AH, Israels ED. Vitamin K_1 increases sister chromatid exchange in vitro in human leukocytes and in vivo in fetal sheep cells: a possible role for 'vitamin K deficiency' in the fetus. *Pediatr Res* 1987; **22:** 405–8.
13 Fjallskog M-L, Frii L, Bergh J. Is cremophor EL, solvent for paclitaxel, carcinogenic? *Lancet* 1993; **342:** 873.
14 Frommer M, Murphy E, Churches T, Henderson-Smart D. Vitamin K prophylaxis in newborn infants. *New South Wales Public Health Bulletin* 1993; **4:** 13–7.
15 Draper GJ, Stiller CA. Intramuscular vitamin K and childhood cancer. *BMJ* 1992; **305:** 709.
16 Davis MK, Savitz DA, Graubard BI. Infant feeding and childhood cancer. *Lancet* 1988; ii: 365–8.
17 McNinch AW, Upton C, Samuels M, *et al.* Plasma concentrations after oral or intramuscular vitamin K_1 in neonates. *Arch Dis Child* 1985; **60:** 814–8.
18 Von Kries R, Kreppel St, Becker A, Gobel U. PIVKA-II levels after prophylactic vitamin K. *Arch Dis Child* 1987; **62:** 938–40.
19 Motohara K, Matsukane I, Endo F, Kiyota Y, Matsuda I. Relationship of milk intake and vitamin K supplementation to vitamin K status in newborns. *Pediatrics* 1989; **84:** 90–3.
20 Tonz O, Shubiger G. Neonatale vitamin K prophylaxe und vitamin-k-Mangelblutungen in der Schweiz 1986–1988. *Schweiz Med Wochenschr* 1988; **118:** 1747–52.
21 Ekelund H. Late haemorrhagic disease in Sweden 1987–1989. *Acta Paediatr Scand* 1991; **80:** 966–8.
22 Von Kries R, Göbel U. Vitamin K prophylaxis and vitamin K deficiency bleeding in early infancy. *Acta Paediatr Scand* 1992; **81:** 655–7.
23 Hathaway WE, Isarangukura PB, Mahasandana C, *et al.* Comparison of oral and parenteral vitamin K prophylaxis for prevention of late hemorrhagic disease of the newborn. *J Pediatr* 1991; **119:** 461–4.
24 Motohara K, Endo F, Matsuda I. Screening for late neonatal vitamin K deficiency by acarboxy prothrombin in dried blood spots. *Arch Dis Child* 1987; **62:** 370–5.
25 Verbruggen B, Monnens LAH. Effects of oral and intramuscular vitamin K prophylaxis on vitamin K_1, PIVKA-II, and clotting factors in breast fed infants. *Arch Dis Child* 1992; **67:** 1250–4.
26 Cornelissen EAM, Kolee LAA, De Abreu RA, *et al.* Effects of oral and intramuscular vitamin K prophylaxis in vitamin K1, PIVKA-II, and clotting factors in breast fed infants. *Arch Dis Child* 1992; **67:** 1250–4.
27 Schubiger G, Tonz O, Gruter J, Shearer MJ. Vitamin K concentration in breast fed neonates after oral or intramuscular administration of a single dose of a new mixed micellar preparation. *J Pediatr Gastroenterol Nutr* 1993; **16:** 435–9.
28 Hull D. Vitamin K and childhood cancer. *BMJ* 1992; **305:** 326–7.
29 Loughnan PM, McDougall PN, Williams M, Bowden D, Smith AL. Epidemiology of late onset haemorrhagic disease: a pooled data analysis. *Med J Aust* 1993; **29:** 177–81.