

ORIGINAL ARTICLE

Intestinal absorption of mixed micellar phylloquinone (vitamin K₁) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding

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Objective: To compare the pharmacokinetics and efficacy of oral versus intravenous mixed micellar vitamin K prophylaxis in infants with cholestatic liver disease, a known risk factor for vitamin K deficiency bleeding.

Design: Prospective randomised controlled study.

Setting: Paediatric Liver Unit.

Patients: Forty four infants less than 6 months of age with conjugated hyperbilirubinaemia.

Main outcome measures: Serum concentrations of vitamin K₁ and undercarboxylated prothrombin (PIVKA-II; a sensitive functional indicator of vitamin K status) before and for up to four days after a single dose of mixed micellar K₁ 1 mg intravenously or 2 mg orally. Comparison of K₁ levels 24 hours after oral K₁ with those from 14 healthy newborns given the same dose.

Results: At admission, 18 infants (41%) had elevated levels of serum PIVKA-II and eight (18%) had low K₁ concentrations, indicative of subclinical vitamin K deficiency. Median serum K₁ concentrations were similar in the oral and intravenous groups at baseline (0.92 v 1.15 ng/ml), rising to 139 ng/ml six hours after intravenous K₁ but to only 1.4 ng/ml after oral administration. In the latter group, the low median value (0.95 ng/ml) and wide range (< 0.15–111 ng/ml) of serum K₁ compared unfavourably with the much higher levels (median 77, range 11–263 ng/ml) observed in healthy infants given the same oral dose, and suggested impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 4/24 (17%) achieved an incremental rise in serum K₁ > 10 ng/ml.

Conclusions: The intestinal absorption of mixed micellar K₁ is unreliable in infants with conjugated hyperbilirubinaemia. Given the strong association between cholestasis and late vitamin K deficiency bleeding, these data provide an explanation for the failure of some oral vitamin K₁ prophylaxis regimens in infants with latent cholestasis.

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Vitamin K deficiency bleeding (VKDB) in infancy (previously known as haemorrhagic disease of the newborn) comprises early (0–24 hours), classical (1–7 days), and late (2–12 weeks) syndromes according to the time of presentation.^{1–3} Late VKDB was first described in Thailand in 1963,⁴ and in the 1980s became recognised world wide as a significant cause of infant morbidity and mortality.⁵ Of major concern is its sudden and unpredictable onset and the high (50–82%) frequency of intracranial haemorrhage as the presenting feature.^{6–8} Known risk factors include breast feeding and the failure to give vitamin K prophylaxis at birth. An association between late VKDB and undiagnosed abnormalities of liver function has also been reported in surveillance programmes from several countries, including Japan,⁶ the United Kingdom,^{9–10} Sweden,¹¹ Denmark,¹² Switzerland,¹³ and Germany,^{3–14} as well as in individual case reports.^{15–18} Evidence for liver dysfunction in some cases has rested on transient, mildly abnormal biochemical indices,^{6–15} but several surveys have indicated that certain cholestatic liver diseases such as biliary atresia and α_1 antitrypsin deficiency may be responsible for the great majority of cases of late VKDB.^{9–11–13–19}

In Europe, the most widely used vitamin K preparation is Konakion (F Hoffmann-La Roche Ltd, Basle, Switzerland).²⁰ Since 1994, the original Konakion, which contained the non-ionic detergent Cremophor EL as solubiliser, has been superseded by a mixed micellar formulation (Konakion MM) in which phylloquinone (vitamin K₁ (K₁)) is solubilised in gly-

cocholic acid and phosphatidylcholine. A paediatric Konakion MM formulation is now in wide use for oral vitamin K prophylaxis of VKDB, and in healthy babies has been shown to give higher serum levels than the earlier preparation, suggesting a superior bioavailability.²¹ It has also been claimed that Konakion MM is well absorbed in infants with severe cholestasis, although vitamin K absorption kinetics have been studied in only three infants with biliary atresia given a 20 mg dose.²² The need for a more thorough evaluation of the influence of cholestasis on the bioavailability of orally administered vitamin K is highlighted by reports of failures of some oral regimens, especially in infants with latent cholestasis.^{12–13–23–24}

In 1993, the American Academy of Pediatrics Vitamin K Ad Hoc Task Force recommended further research on the efficacy, safety, and bioavailability of oral formulations of vitamin K.²⁵

To study this, we compared the pharmacokinetics of mixed micellar K₁ (Konakion MM) in infants with conjugated hyperbilirubinaemia randomised to a single dose of either 1 mg intravenously—the standard treatment in infants with liver disease and an associated coagulopathy²⁶—or 2 mg orally.

Abbreviations: INR, international normalised (prothrombin) ratio; PIVKA, proteins induced by vitamin K absence or antagonism; VKDB, vitamin K deficiency bleeding

In addition, we measured serum undercarboxylated prothrombin (PIVKA-II), which is a sensitive functional indicator of vitamin K status, allowing the detection of subclinical deficiency states which would not be detected by conventional coagulation assays.^{2 27 28}

METHODS

Patients

Over an 18 month period, 44 infants (27 boys, 17 girls), aged 1–26 weeks (median 6.5) with conjugated hyperbilirubinaemia were referred to the Paediatric Liver Service of King's College Hospital and enrolled in the study. The most common cause of their liver dysfunction was idiopathic neonatal hepatitis ($n = 17$; 39%), followed by biliary atresia in 13 (30%) and total parenteral nutrition cholestasis in three (7%). There were two cases each of Alagille's syndrome, α_1 antitrypsin deficiency, and inspissated bile syndrome, and five miscellaneous diagnoses (fructosaemia, galactosaemia, choledochal cyst, necrotising enterocolitis, cytomegalovirus hepatitis). Inclusion criteria were a serum bilirubin concentration above the normal range, without haematological evidence of haemolysis or bleeding. Infants with an international normalised ratio (INR) of ≥ 2.0 , who were considered to be at high risk of bleeding, were excluded. Those who had been given K_1 prophylaxis before admission were not excluded, apart from one patient who had received intravenous K_1 just before transfer and had a very high serum K_1 (331 ng/ml) at admission. Breast feeding was encouraged during the study, but all infants also underwent dietetic assessment and received supplemental formula feeding with either Caprilon (Cow & Gate, Trowbridge, Wiltshire, UK) or Pregestimil (Bristol-Myers, Hounslow, Middlesex, UK), which contain 50 and 110 $\mu\text{g/l}$ K_1 respectively.

After written informed consent had been obtained from the parents, the infants were randomised, in an open labelled fashion, to either (a) an intravenous injection of 1 mg mixed micellar K_1 (given over one minute) or (b) 2 mg by mouth (dispensed on to the back of the infant's tongue just before bottle feeding). The study medications were administered as a single dose in the morning. Blood samples were taken immediately before and at six hours after treatment, and for up to four consecutive mornings thereafter. Samples were protected from light (K_1 assays) and refrigerated immediately. After centrifugation, serum aliquots were stored at -70°C .

To compare the intestinal absorption of mixed micellar K_1 in cholestatic and healthy infants, we used the results from a previous study²¹ in which 14 healthy newborns (mean birth weight 3740 g) who were to be fully breast fed were given the same oral dose of 2 mg within one hour of birth, and serum K_1 was measured 24 hours later using methods identical with those of the present study.

Serum vitamin K_1 assay

Serum K_1 was measured by high performance liquid chromatography with electrochemical detection in the redox mode, as described previously.²⁹ Volumes of 0.05 ml serum were first analysed by a protocol designed to measure K_1 concentrations > 5 ng/ml.²⁹ If < 10 ng/ml by this protocol, volumes of 0.2–0.5 ml serum were subjected to a protocol for endogenous concentrations.²⁹ Menaquinone 6 was used as the internal standard. For 0.5 ml serum extracted, the lower limit of detection was 0.05 ng/ml. The normal adult reference range by the same assay was 0.17–0.68 ng/ml (median 0.37) in the fasting state, and 0.15–1.55 ng/ml (median 0.53) in non-fasting subjects.³⁰

Functional assessment of vitamin K status by PIVKA-II assay

PIVKA-II was assayed using a conformation specific monoclonal antibody (which does not cross react with fully

carboxylated native prothrombin) in a modification of an enzyme linked immunosorbent assay based assay.³¹ Serum PIVKA-II by immunoassay is conventionally expressed as arbitrary units per ml (AU/ml) because, in states of vitamin K deficiency, circulating PIVKA-II may comprise multiple forms of partially carboxylated prothrombin, and neither their relative abundance in plasma nor their relative affinity for the antibody is known. Calibration is therefore made against PIVKA-II species purified from patients treated with oral anticoagulants. With electrophoretic techniques, 1 AU is equivalent to 1 μg purified PIVKA-II.³¹ The minimum limit of detection for our assay was 0.15 AU/ml. PIVKA-II circulates at high levels in overt vitamin K deficiency; the mean value in our laboratory in 43 adult patients receiving warfarin treatment (INR > 1.5) was 40.0 AU/ml (range 6.9–99.5 AU/ml), and in an infant with fatal late VKDB it was 67.9 AU/ml.³² As previously reported,²⁸ there was good agreement between the specificity of this assay and a commercial kit (Eitest mono-II; Eisai Co Ltd, Tokyo, Japan) which has been widely used in infant studies.^{21 33 34}

Statistical analysis

Statistical analysis between the two groups was carried out using a two tailed Student's t test (for serum K_1) and non-parametric tests (for serum PIVKA-II prevalence), as appropriate. Differences in proportions were compared using the χ^2 or Fisher's exact test.

The study was approved by the research ethics committee of King's College Hospital.

RESULTS

The two groups of cholestatic infants were well matched for sex, age, and cause and severity of liver dysfunction, with median serum bilirubin levels of 136 and 153 $\mu\text{mol/l}$ in the oral and intravenous groups respectively (table 1). Infants in the oral group had a higher median gestational age and birth weight than those in the intravenous group, but body weights at the time of the study were similar (3.8 v 3.2 kg; $p = 0.08$). Undernutrition was common in both groups; 50% of the 44 babies were below the 3rd centile for weight, and a further 23% were between the 3rd and 10th centile.

At baseline, serum K_1 concentrations in the oral and intravenous groups were similar (median 0.92 v 1.15 ng/ml; $p = 0.1$) and were below the lower limit of the adult normal range (< 0.15 ng/ml) in 5/24 (21%) infants in the oral group and 3/20 (15%) in the intravenous group. Seventeen infants (39%) had baseline serum K_1 levels that were above the upper limit for healthy adults (1.5 ng/ml), indicating recent K_1 administration and/or the use of supplemented formula feeds before transfer; the latter often produce higher serum K_1 levels than those found in healthy adults.³⁵

Figure 1 shows the time course of serum K_1 concentrations after the administration of mixed micellar K_1 (2 mg) orally or intravenously (1 mg). Although serum levels in the oral group at 6 and 24 hours varied widely (from non-detectable to 454 ng/ml), the very low median values of 1.40 and 0.95 ng/ml respectively indicated a poor overall absorption in cholestatic infants. In all five infants in the oral group who had low or undetectable serum K_1 at baseline (< 0.15 ng/ml), the highest serum level achieved was 1.4 ng/ml, and at 48 hours the levels had again fallen to or below the lower limit of normal.

In contrast with the levels in the oral group, 90% of the infants given intravenous K_1 had a high serum K_1 (median 139 ng/ml) at six hours, reflecting the rapid bioavailability by this route. Thereafter, the median serum K_1 level remained higher than that after oral administration at all time points (fig 1), although this difference was only significant over the first 24 hours, reflecting the well known rapid serum clearance of K_1 after intravenous injection.³⁶ Two of the infants in the intravenous group had serum K_1 levels of < 1 ng/ml at six

Table 1 Clinical data and laboratory values at admission in the two groups

	Oral group	Intravenous group
No of babies	24	20
Sex (% male)	54.2	70.0
Gestational age (weeks)	39 (35–42)	37 (28–41)*
Birth weight (g)	3000 (900–4200)	2500 (900–3400)**
Age at time of study (weeks)	6.0 (1–26)	6.5 (1–12)
Weight at time of study (kg)	3.8 (1.8–5.7)	3.2 (1.7–5.0)
No. less than 10th centile for weight	15 (56%)	16 (80%)
Serum bilirubin (normal, 3–20 µmol/l)	136 (46–438)	153 (36–288)
Aspartate aminotransferase (10–50 IU/l)	140 (32–1768)	168 (23–558)
Alkaline phosphatase (30–150 IU/l)	484 (213–893)	602 (214–1853)
γ Glutamyl transferase (5–55 IU/l)	175 (30–1073)	298 (15–1830)
International normalised ratio (0.7–1.2)	0.90 (0.76–1.17)	0.90 (0.74–1.08)

Results are expressed as median (range).

*p=0.038, **p=0.034 compared with oral group. There were no significant differences between the two groups with respect to the other variables.

hours, which then rose to 1.8–2.8 ng/ml at 24 hours. This slow rise after six hours rather than the expected decrease was suggestive of inadvertent extravascular injection, and was supported by the finding in one infant (no samples were available beyond 24 hours in the other) of a peak serum K₁ level of 13.1 ng/ml at 48 hours.

In those infants with a peak incremental serum K₁ level of > 10 ng/ml, the median terminal serum half life of disappearance of K₁ between 24 and 96 hours was 21 hours (range 17–39 hours) compared with a terminal K₁ half life of 14 hours (range 8–22 hours) in healthy adults after intravenous injection,³⁷ and of 76 hours (range 26–193 hours) in healthy newborns after oral dosing.³⁸ There were no significant correlations between serum K₁ terminal half life and creatinine or bilirubin concentrations.

Figure 2 shows the serum K₁ levels at 24 hours in infants in the oral group compared with those from a previous study in healthy newborn infants using the same dose, preparation, and vitamin K assay.²¹ There was a highly significant difference in median serum K₁ levels (p < 0.001) between cholestatic infants (0.95 ng/ml, range < 0.15–111.3) and healthy newborns (77.2 ng/ml, range 10.8–262.8). Compared with the healthy newborn group, the cholestatic infants were on average 6.5 weeks older, but their mean body weights were similar (3.8 kg for newborns v 3.6 kg for cholestatic infants).

Figure 3 shows the results of serum PIVKA-II determinations. Despite baseline INRs within the normal range, (median 0.90, range 0.74–1.17) 7/24 infants (29%) in the oral group and 11/20 (55%; NS) in the intravenous group had a detectable PIVKA-II (> 0.15 AU/ml), indicative of subclinical vitamin K deficiency. The concentrations of detectable PIVKA-II at baseline ranged from 0.16 to 27.6 AU/ml (median 1.84; mean

3.95). Three of the seven infants with a raised PIVKA-II in the oral group, and four of the 11 in the intravenous group, had baseline serum K₁ levels below the normal range. An examination of the feeding records before hospital transfer showed a trend between prior breast feeding and a raised PIVKA-II. Thus, partly or wholly breast fed infants comprised 51% (21/41) of those for whom feeding records were available, but 78% (14/18) of those with a raised PIVKA-II at baseline ($\chi^2 = 2.6$, p = 0.1).

In the 18 infants with a raised PIVKA-II at baseline, 16 (89%) had lower levels as early as six hours after vitamin K, and in 15 the values declined further up to 72 hours. The median half life of PIVKA-II disappearance was 20 hours (range 10–45 hours), comparable to the known serum PIVKA-II half life in newborn infants of about 45 hours.³⁴ In two infants in the oral group, there was a paradoxical rise in serum PIVKA-II after vitamin K. In one of these infants, PIVKA-II had initially declined (from 1.50 to 0.54 AU/ml) at 24 hours, before rising progressively to 1.6 AU/ml at 96 hours; in both infants serum K₁ did not rise above 1 ng/ml. In another infant from the intravenous group, PIVKA-II increased from 0.2 AU/ml at baseline to 0.58 and 0.86 AU/ml at six and 24 hours respectively; this was the same infant in whom the peak serum K₁ occurred at 48 hours, suggestive of extravascular administration.

One infant in each group had baseline PIVKA-II levels within the range usually found during warfarin anticoagulation (9.9 and 27.6 AU/ml respectively), although both had a normal INR. After vitamin K administration, there was a logarithmic decline in PIVKA-II over 48 hours, with half lives of disappearance of 20 and 35 hours respectively.

During the study, there were no adverse events attributable to vitamin K administration, and no clinical bleeding episodes.

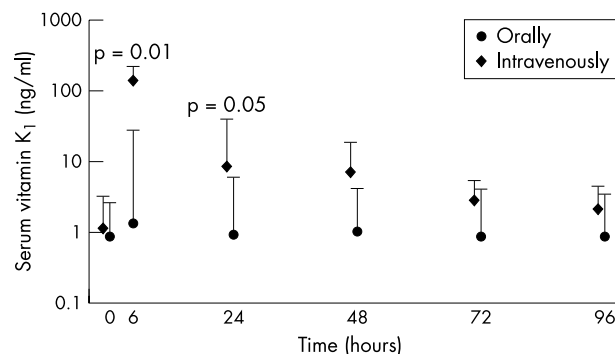


Figure 1 Median (SE) serum vitamin K₁ concentrations in 44 infants with conjugated hyperbilirubinaemia before and after the administration of mixed micellar K₁, 2 mg orally or 1 mg intravenously.

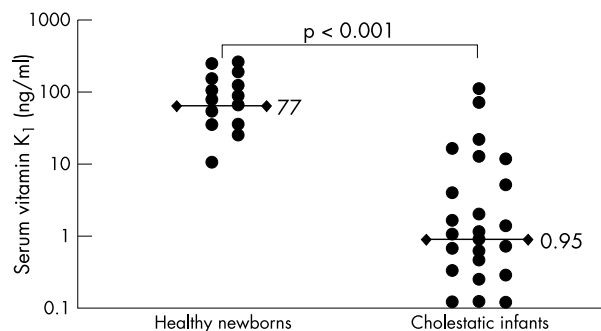


Figure 2 Individual serum vitamin K₁ levels in healthy newborns and cholestatic infants 24 hours after the oral administration of a 2 mg dose of mixed micellar K₁. The horizontal bars represent the median values.

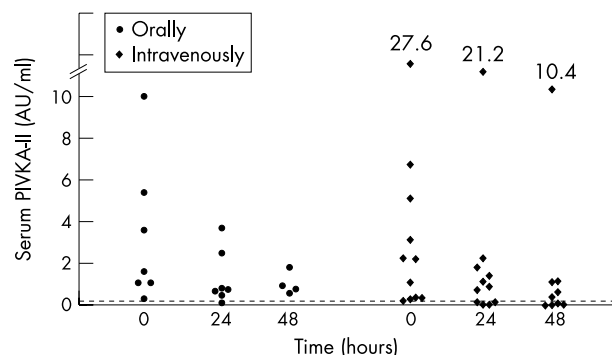


Figure 3 PIVKA-II profile in the cholestatic infants with initially raised serum PIVKA-II before treatment, and at 24 and 48 hours after mixed micellar vitamin K₁ 2 mg orally or 1 mg intravenously. The dashed horizontal line at 0.15 AU/ml represents the limit of sensitivity of the assay and the upper limit of normal in healthy adults.

All 13 infants with biliary atresia later underwent a Kasai procedure; 10 are currently well with a normal serum bilirubin, one has mild residual jaundice, one underwent liver transplantation, and one died while on the waiting list. Of the remaining 31, one infant with Alagille's syndrome underwent liver transplantation, one died of multiple cardiac anomalies, and 29 made a full recovery.

DISCUSSION

To our knowledge, this is the first randomised controlled study of vitamin K status and metabolism in infants with conjugated hyperbilirubinaemia. All had severe liver dysfunction, with idiopathic neonatal hepatitis and biliary atresia predominating. Overt vitamin K deficiency was absent at admission, as evidenced by INR values within the age related normal range. However, 41% (18/44) of the infants had a raised serum PIVKA-II at presentation, consistent with subclinical vitamin K deficiency, and 18% had low serum K₁ concentrations indicative of reduced tissue stores, and in 16% both abnormalities were present. The lack of an association between a raised baseline PIVKA-II and low serum K₁ (and vice versa) has been reported previously,^{22, 34} and may relate to interindividual differences between circulating vitamin K and liver stores (which include bacterial menaquinones; K₂ vitamins) and to delayed clearance of PIVKA-II after correction of deficiency.

PIVKA-II is a sensitive functional marker of vitamin K status.² In those infants who presented with an elevated (> 0.15 AU/ml) PIVKA-II, the median value of 1.84 AU/ml was about sixfold higher than that found in a recent study of healthy 2–5 month old infants in the United Kingdom.³⁹ Two infants had PIVKA-II levels within the range usually found in adults undergoing warfarin treatment, indicating a severity of vitamin K deficiency that, without intervention, would have progressed to overt coagulopathy. As previously reported in healthy infants,^{39, 40} PIVKA-II tended to be found more commonly in the partly or wholly breast fed cholestatic infants, whose K₁ intake would have been less than that in the exclusively formula fed infants.⁴¹

The importance of an elevated PIVKA-II as a specific functional marker of vitamin K deficiency in early life has been questioned because of the possibility that raised levels may result from delayed maturation of the liver enzyme γ glutamyl carboxylase.³⁴ Another caveat is that PIVKA-II may simply reflect liver dysfunction, because raised levels in the absence of demonstrable vitamin K deficiency are occasionally found in adults with chronic liver disease.^{42–45} Our results argue strongly against either possibility because in 15/18 infants, the initially raised PIVKA-II declined after the administration of vitamin

K at rates consistent with previous estimates of the plasma disappearance of PIVKA-II.^{34, 46}

The wide range of but low median serum K₁ concentrations after oral administration of Konakion MM is clear evidence of a variable and often low efficiency of intestinal absorption in infants with cholestasis. Time course studies in adults have shown that serum/plasma concentrations of K₁ generally peak two to four hours after an oral dose and then decline to endogenous concentrations by 24 hours.^{47, 48} Ethical considerations limit longitudinal blood sampling in healthy neonates, but a cross sectional study in 42 babies given a 1 mg dose of K₁ (Konakion, old formulation) orally at birth showed that the time course over the first 12 hours was similar to that in adults, with the peak plasma K₁ level occurring at the four hour time point.⁴⁹ Although this cross sectional study also showed a high interindividual variability in plasma K₁, the median values at four and eight hours were 75 and 30 ng/ml respectively, and in only one neonate was the concentration < 10 ng/ml.⁴⁹ These results contrast strongly with those of the present study of cholestatic infants, in whom the median concentration at six hours after double the dose of Konakion MM was only 1.4 ng/ml, and 20/24 infants (83%) failed to attain an incremental serum rise above 10 ng/ml. The extremely poor response (maximum serum K₁ of 1.4 ng/ml) in the five infants who had undetectable serum K₁ (< 0.15 ng/ml) at baseline also suggests, as may be expected, that a very low serum K₁ is predictive of a low absorption efficiency for vitamin K. The comparative data for the 24 hour concentrations (fig 2) confirm the high degree of malabsorption of K₁ in infants with cholestasis, at a sampling time that is representative of the postabsorptive phase when serum K₁ concentrations are less variable than during the first eight hours after oral administration.⁴⁹ In infants, serum K₁ concentrations at 24 hours remain higher than in adults because the terminal half life of disappearance of K₁ is longer.³⁸ We consider that the comparative data at 24 hours are especially valid because they reflect serum concentrations after the same dose (2 mg) of Konakion MM, and serum concentrations of K₁ were measured in the laboratory of one of us (MJS) by the same analytical method.

One explanation for the severely impaired intestinal absorption of K₁ in cholestasis is a deficiency of bile salts that are essential for the micellar solubilisation of this fat soluble vitamin. Studies with tritium labelled K₁ in adult patients with extrahepatic cholestasis have shown that, in the absence of endogenous bile acids, there is little or no absorption of K₁, as assessed by the recovery of tritium label in thoracic duct lymph,⁵⁰ plasma, and faeces.⁴⁷ The intestinal absorption of K₁ from the ionic, mixed micelles of Konakion MM, with natural bile salt/phospholipid components, may be expected to be superior to that from the non-ionic, artificial Cremophor vehicle of the original Konakion. Indeed, comparative pharmacokinetic studies have shown increased peak plasma levels after oral Konakion MM in healthy infants given a 2 mg dose²¹ and also in infants with biliary atresia given a 20 mg dose.²² However, the latter study²² was limited to three patients per group, and the large dose (20 mg) administered is unrepresentative of current community prophylaxis policies.

Our finding of unreliable and often severely impaired intestinal absorption of mixed micellar K₁ in cholestatic infants has important implications for oral prophylactic policies for the prevention of late VKDB. Since a reported,³¹ but unconfirmed,^{8, 52} association between childhood leukaemia and intramuscular vitamin K prophylaxis, there has been an increasing trend towards oral administration.^{53, 54} Ideally, oral prophylactic regimens need to be as effective as a single intramuscular dose (1 mg) of K₁, which prevents almost all cases of late VKDB.^{8, 55} In many countries, current recommendations for oral prophylaxis are to administer two or three doses of 1 or 2 mg K₁ over the first 4–6 weeks of life. However, recent surveillance data from Australia, Germany, and Switzerland suggest that this strategy is less effective than intramuscular

prophylaxis in preventing late VKDB,^{13 14 53} and the potential improved efficacy of the mixed micellar preparation compared with the old formulation given orally also remains unproven.¹⁴ Population surveys carried out in the last decade indicate that underlying cholestatic liver disease, usually asymptomatic, is a major causative factor for late VKDB.^{12 13 54} Although it has been presumed that this association is due to an impaired absorption of vitamin K,⁵⁴ our study is the first to document the potential severity of malabsorption in individual infants with cholestasis. The existence of a reservoir of infants with cholestasis who remain unprotected, even by three doses of Konakion MM, is highlighted by a new surveillance study by von Kries *et al.*⁵⁶

Before the introduction of vitamin K prophylaxis, estimates of the incidence of late VKDB in Europe and Japan ranged from four to 11 cases per 100 000 births.⁵⁵ A single oral dose of vitamin K given at birth may reduce this incidence by 50–80%.^{8 55 57 58} The Swiss and German experiences suggest that giving a second dose of 2 mg K₁ in the first week of life,¹³ or 2 mg instead of 1 mg in a three dose regimen,¹⁴ may further reduce (but not eliminate) the incidence of late VKDB. Data from Denmark,¹² The Netherlands,⁵³ and the United Kingdom⁵⁷ indicate that additional benefits accrue with higher dose frequencies. Our findings and the known physiology of vitamin K suggest why even three oral doses may not provide sufficient protection in infants with underlying cholestasis. K₁ differs from other fat soluble vitamins in that it has limited tissue reserves and is rapidly catabolised, with 60–70% of a single dose being excreted via the urine and bile in about three days.^{47 59} The rate of catabolism does not seem to be dose related; in adults the same 60–70% losses accrue for doses ranging from 45 µg to 1 mg.^{47 59} Unless there are additional unknown factors that limit excretion under conditions of deficiency, it may therefore be predicted that the length of protection afforded by a given dose is proportional to the fraction absorbed. Thus, although oral K₁ administration may improve vitamin K status in infants with latent cholestasis in the short term, the absorbed dose will be insufficient to afford a buffer of reserves for longer term protection. In contrast, it has been suggested that the effectiveness of a single intramuscular dose of K₁ is due to a depot effect and consequent delayed release of the highly lipophilic vitamin from muscle tissue.⁶⁰ This is supported by studies in adults showing very different pharmacokinetics and lipoprotein distribution when K₁ is given intramuscularly compared with the oral route.⁶¹

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Intestinal absorption of mixed micellar phylloquinone (vitamin K₁) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding

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