

Plasma concentrations after oral or intramuscular vitamin K₁ in neonates

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SUMMARY One hundred and seven healthy, breast fed infants received 1 mg vitamin K₁ either at birth (orally or intramuscularly) or with the first feed (orally). Venous blood samples collected in the next 24 hours were assayed for plasma vitamin K₁. In babies given the vitamin orally at birth, the peak median concentration (73 ng/ml) occurred at four hours. By 24 hours median plasma concentrations had fallen to 23 ng/ml and 35 ng/ml in the groups fed vitamin K₁ at birth or with the first feed, respectively; this difference was not, however, significant. Plasma concentrations after intramuscular injection exceeded those in the oral groups at all comparable times, with a peak median concentration of 1781 ng/ml at 12 hours falling to 444 ng/ml at 24 hours. Since median plasma vitamin K₁ concentrations 24 hours after oral administration were some 100 times and 1000 times greater than previously estimated adult and newborn values respectively, this study supports giving vitamin K₁ orally at birth to well, mature babies to protect against early haemorrhagic disease of the newborn. Further studies are needed to determine the optimum dose for protection over subsequent weeks.

In 1980, fewer than half the maternity units in this country gave vitamin K routinely to every neonate and the Exeter unit was among those that practiced a selective policy of giving prophylaxis only to babies considered most at risk of developing haemorrhagic disease of the newborn. In the years 1972–80 only two patients with haemorrhagic disease of the newborn were seen in Exeter, giving an incidence of no more than 1 in 20 000 live births. Over a 17 month period beginning November 1980, however, six cases occurred, an incidence of at least 1 in 1200 live births. All the affected babies were mature, breast fed infants who had not received vitamin K: three of them died.¹ Faced with the need to reintroduce prophylaxis for all babies we were reluctant to use the usual intramuscular injection routinely and considered the alternative of oral administration. This method has been used by a few maternity units for many years with seeming success,² but we have been unable to find any published data on intestinal absorption of vitamin K₁ in neonates to support the practice. To make a comparison between the two methods of prophylaxis we studied plasma concentrations of vitamin K₁

in the first 24 hours after administration of a 1 mg dose by mouth or by intramuscular injection.

Patients and methods

All infants were well and fed only breast milk or dextrose. Their birthweights and gestational ages are summarised in Table 1. Each was given 1 mg of vitamin K₁ (Konakion, 1 mg/0.5 ml ampoule, Roche Products), measured by 1 ml syringe. Blood samples (1 to 3 ml) were collected by venepuncture from the dorsum of the hand into glass tubes containing EDTA anticoagulant, and were thereafter protected from the light. Plasma was separated by centrifugation and stored at –20°C until assayed. Vitamin K₁ was measured in 0.1 to 0.7 ml plasma by high performance liquid chromatography with photometric detection, using methods previously described.^{3 4} The limit of detection of the assay was 1 ng vitamin K₁. The precision for the assay of vitamin K₁ in plasma pools containing 232, 72, and 13 ng/ml was 3.0 (n=8), 4.0 (n=8), and 7.4% (n=7) respectively.

Phase 1. Three groups, each of 15 infants, received

vitamin K₁ either intramuscularly at birth (group IM), orally at birth (group OB), or orally with the first feed (group OF). Each baby had a single blood sample taken 24 hours after the dose.

Phase 2. Two groups of infants received vitamin K₁ at birth, either intramuscularly (group IM, n=20)

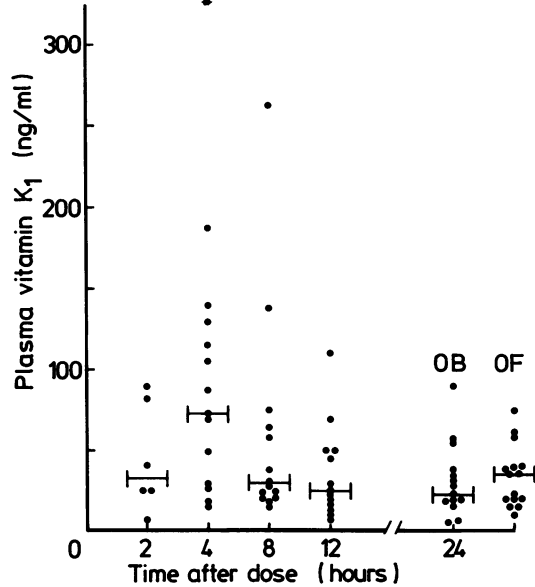


Fig. 1 Individual plasma vitamin K₁ concentrations and median values (horizontal bars) after oral administration of 1 mg vitamin K₁.

The results are shown for 72 babies studied over 24 hours and include the sequential data given in Table 2. Vitamin K₁ was undetectable in two babies. Vitamin K₁ was given with the first feed to 15 babies studied at 24 hours (group OF), at birth to the remainder (group OB).

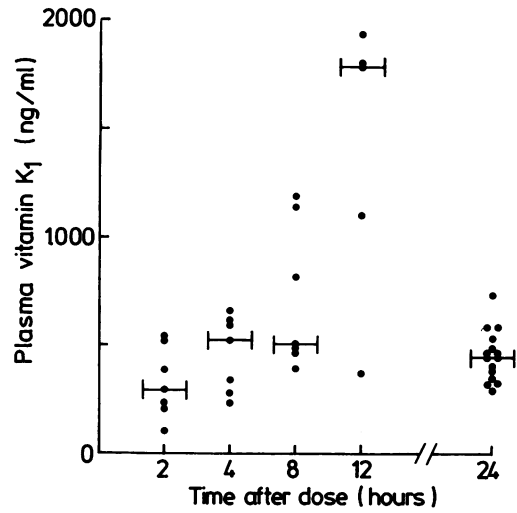


Fig. 2 Individual plasma vitamin K₁ concentrations and median values (horizontal bars) after intramuscular injection of 1 mg vitamin K₁.

The results are shown for 35 babies studied over 24 hours and include the sequential data given in Table 2.

or orally (group OB, n=42) (Table 1). Babies of less than 35 weeks' gestation (n=3) were deliberately allocated to group IM. For ethical reasons most babies had only one blood sample collected at either two, four, eight, 12, or 24 hours after the dose; however, serial observations were possible in 10 babies who required repeated blood tests for measurement of blood sugar or bilirubin. Four of these babies were in group OB (median birthweight 2255 g, range 2080 to 2780 g; median gestation 37 weeks, range 35 to 40 weeks) and six were in group

Table 1 Number, gestational age, and birthweight of babies studied 2, 4, 8, 12 or 24 hours after receiving vitamin K₁ orally at birth (group OB) orally with the first feed (group OF) or intramuscularly at birth (group IM)

	Hours after receiving vitamin K ₁				
	2	4	8	12	24
Group OB					
No	6	15	14	13	15
Gestation (wks), median (range)	39 (38-40)	40 (35-42)	40 (35-43)	40 (35-42)	39 (35-43)
Birthweight (kg) median (range)	2.8 (2.7-3.9)	2.8 (2.2-4.2)	3.4 (2.2-4.4)	3.2 (2.1-4.5)	3.4 (2.5-4.3)
Group OF					
No	—	—	—	—	15
Gestation (wks), median (range)	—	—	—	—	40 (35-43)
Birthweight (kg), median (range)	—	—	—	—	3.1 (2.8-3.8)
Group IM					
No	7	7	7	5	15
Gestation (wks), median (range)	40 (34-41)	38 (33-41)	37 (33-41)	40 (36-40)	40 (36-43)
Birthweight (kg) median (range)	3.2 (2.0-3.9)	2.2 (1.6-3.8)	2.2 (1.5-3.3)	2.2 (2.0-3.4)	3.4 (2.7-3.9)

Table 2 *Serial plasma concentrations of vitamin K₁ (ng/ml) in babies given 1 mg vitamin K₁ orally at birth (group OB, n=4) or by intramuscular injection at birth (group IM, n=6)*

Group	Birthweight (g)	Time after vitamin K ₁ (hours)				
		1.5-2.0	3.5-6	7-8	11-12	14-15
OB	2340	—	49	30	25	—
	2080	82	42	—	50	—
	2170	—	115	138	—	110
	2780	—	105	262	—	—
IM	2150	—	655	1187	1781	1463
	2220	—	811	1137	1791	—
	2015	292	—	—	1929	—
	1960	—	278	390	—	—
	1510	—	225	488	—	—
	3310	106	—	505	—	—

IM (median birthweight 2085 g, range 1510 to 3310 g; median gestation 38 weeks, range 33 to 41 weeks).

The difference between groups was tested by the Mann Whitney U test.

Results

Figure 1 shows plasma concentrations of vitamin K₁ at two, four, eight, 12, and 24 hours for babies who were given vitamin K₁ orally at birth (group OB) and at 24 hours for those who were given the vitamin orally with their first feed (group OF). For group OB the peak median concentration (73 ng/ml) occurred at four hours; concentrations at 12 and 24 hours were significantly lower ($P < 0.05$ and < 0.02 respectively). Median concentrations at 24 hours for group OB (23 ng/ml) and group OF (35 ng/ml) did not, however, differ significantly.

Figure 2 shows the corresponding plasma concentrations of vitamin K₁ in babies who were given vitamin K₁ intramuscularly at birth (group IM). The highest median concentration occurred at 12 hours (1781 ng/ml) and the values exceeded those in groups OB and OF at all time points ($P < 0.001$). The median plasma concentration 24 hours after intramuscular injection (444 ng/ml) was some 10 to 20 times higher than that in either of the groups given vitamin K₁ orally.

The results of the sequential studies, in which plasma concentrations were measured in 10 babies at two or more time points, are shown in Table 2.

In two babies, both from group OB, no vitamin K₁ was detected. The first weighed 3620 g and had a blood sample taken at four hours; the second weighed 3560 g and had a blood sample taken at 24 hours. The respective plasma concentrations of vitamin K₁ were recorded as less than 10 ng/ml and less than 4 ng/ml, according to the volume of plasma assayed.

Discussion

Vitamin K₁ does not cross the placenta easily. Its concentration in cord blood is probably less than 10% of the mean maternal values³ and the mean concentrations of vitamin K dependent clotting factors (prothrombin VII, IX, and X) are only 30 to 60% of the normal adult values.⁵ In some babies the coagulation defect at birth is already sufficient for them to be in danger of spontaneous haemorrhage.⁶ Unless vitamin K is given in sufficient quantity, either as a prophylactic dose or as cows' milk or formula feed, mean concentrations of these factors fall still further⁵ and in a small number of babies haemorrhage results.

Haemorrhagic disease of the newborn, whether presenting in the early days of life (as classically described) or in later weeks, is virtually confined to breast fed infants who have not received vitamin K prophylaxis at birth,^{7, 8} and published reports affirm that it is still an important cause of death and handicap.^{2, 9-11} Although it is often stated that the gut flora of the bottle fed baby are an important source of vitamin K, this is unproved.¹² The infant may, however, be protected in two other ways. Firstly, cows' milk and formula feeds have a higher concentration of vitamin K₁ than either human milk or colostrum.¹³ Secondly, the bottle fed infant receives a greater volume of milk in the first days of life, the critical period for early haemorrhagic disease. In the first three days a breast fed, term baby takes about 180 ml of colostrum and milk¹⁴ containing less than 1 µg vitamin K₁, while a bottle fed baby takes 500 ml or more, which contains 2 to 50 µg vitamin K₁ depending on the formula.¹³ When feeding is fully established the daily vitamin K₁ intakes will be approximately 0.5 to 3 µg for the breast fed and 1.5 to 45 µg for the bottle fed infant, assuming an intake of 150 ml/kg per day in a 3.5 kg

baby. Since the majority of breast fed infants do not develop haemorrhagic disease, the daily intake necessary for protection of those at risk must be extremely small—indeed it was reported more than 40 years ago that as little as 90 ml of cows' milk supplement (estimated vitamin K₁ content less than 2 µg) given over the first 48 hours of life to breast fed infants virtually eliminated this disorder in a unit that had previously seen an incidence of 0.8%.¹⁵ In the Exeter area the practice of giving formula milk supplements to breast fed infants has sharply declined in recent years (although no directives to this effect have been given) because of concern about cows' milk intolerance, and this may have contributed to the recently reported resurgence of haemorrhagic disease.¹

There is no information on intestinal absorption of vitamin K₁ in neonates but there is evidence that in adults 70 to 80% of an orally administered dose is absorbed and that plasma concentrations reach a peak at two to four hours and decline to 10 to 20% of the peak value by 24 hours.¹⁶ The vitamin is thought to be rapidly accumulated in the liver, while excretion occurs via the bile and, to a lesser extent, the urine.¹⁷ In the present study most newborn infants achieved high plasma values of vitamin K₁ after oral administration of 1 mg at birth. The peak median plasma concentration (73 ng/ml at four hours) is some 300 times the adult median and nearly 4000 times the estimated maximum cord plasma concentration.³ It represents approximately 8.5 µg of vitamin K₁ in the plasma, which is equivalent to the total vitamin K₁ content of the first 10 days breast milk,¹³ not all of which will be absorbed. After the same dose given intramuscularly the peak median plasma concentration (1781 ng/ml at 12 hours) is nearly 9000 times the adult value.

As vitamin K₁ is fat soluble, bile is necessary for its absorption from the gut, and it might be assumed that a bolus would be better absorbed when given with the first feed rather than at birth. This is not confirmed by the 24 hour plasma concentration in groups OB and OF and there is an advantage in the dose being given at birth when its administration can be the clear responsibility of the attending midwife.

The fact that the changes in plasma concentrations of vitamin K₁ with time shown in the sequential studies are relatively gradual (Table 2), suggests that the wide spread of values at each time point in the cross sectional studies (Figs. 1 and 2) represent differences between individuals. These differences could be caused by a number of factors. Only a proportion of the oral dose placed in the infant's mouth will actually be swallowed and available for absorption. The difference between individuals

could be considerable. The fact that we followed tradition and used a standard dose of 1 mg regardless of body weight might also be implicated, although there is no clear evidence from our data that it was the smaller infants that had the higher plasma values. It is also probable the rate of absorption of the vitamin by the intestinal mucosa or from the injection site could vary, as could the rate of plasma clearance.

Although two babies given vitamin K₁ orally at birth had plasma values that were not detected by our assay, the limits of detection (4 and 10 ng/ml respectively) were relatively high and allow the possibility that sufficient vitamin K₁ was absorbed to raise the plasma value well beyond endogenous concentrations. Neither baby developed haemorrhagic disease of the newborn.

Further research is necessary to determine what proportion of an oral dose of vitamin K₁ is absorbed and retained to give protection over subsequent weeks, and to find the optimal dose. Reported clinical experience² and the results of this study, however, give support to the practice of using oral prophylaxis in well, mature babies. Our present policy is to give vitamin K₁ intramuscularly at birth to preterm babies, to those admitted to the special care baby unit for any other reason, and to babies born by traumatic delivery or to mothers receiving oral anticonvulsants. All others are given 1 mg vitamin K₁ orally at birth by the midwife in attendance. For economy and simplicity we use a solution of 10 mg/ml stored in amber dropper bottles at 4°C. This solution is stable under these conditions, despite repeated opening of the bottle, for at least two weeks (unpublished data). Using a sterile dropper supplied in the cord-care packs for each infant, three drops (approximately 1 mg) of the solution are placed on the tongue when the cord care is completed.

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