Annotations

Haemorrhagic disease and vitamin K

By 1950, haemorrhagic disease of the newborn (HDN) seemed fairly well understood. It caused spontaneous bleeding in the early days of life, typically in breast fed infants, and was associated with a clotting defect that rapidly corrected with vitamin K. It was established that cow's milk was a richer source of vitamin K than mother's milk and that small supplements of cow's milk given to breast fed infants conferred protection against HDN.¹ While the role of vitamin K prophylaxis was not universally accepted, many maternity units adopted a policy of giving it routinely to all neonates and reported a dramatic decline in the incidence of HDN.²

In the mid-1950s, however, came reports of increased severity of jaundice and raised incidence of kernicterus after the introduction of routine vitamin K prophylaxis, and confidence in the practice was shaken.³ At that time the type of vitamin K commonly used was a water soluble, synthetic analogue, vitamin K₃ (Synkavit) often in doses exceeding 50 mg even in premature infants. It was subsequently established that high doses of vitamin K₃ in neonates caused haemolysis, while vitamin K₁ (phytomenadione, fat soluble and occurring naturally in green vegetables) was safe and gave protection against HDN in doses as small as 0.5–1 mg given intramuscularly.⁴ Nevertheless, the association of vitamin K with kernicterus had become firmly entrenched in people's minds, and in many maternity units (perhaps the majority in the United Kingdom) the practice of giving it routinely to all babies was either abandoned or never established. Instead, prophylaxis was usually reserved for babies considered especially at risk from HDN, and this selective method seemed a satisfactory compromise.⁵

Vitamin K research

Recent years have seen the development of sensitive assays for vitamin K in blood and milk, the discovery of PIVKAs ('Proteins Induced in Vitamin K Absence'—clotting factor precursors that require carboxylation to become functional), and further elucidation of the mechanisms of the vitamin's action.^{6,7} Information about liver storage is becoming available.⁸ Nevertheless, our understanding of

HDN remains far from complete. Among the questions awaiting answers are: What determines the extent of the baby's vitamin K stores at birth? How long do these stores last? Is malabsorption of vitamin K the major factor in causing HDN? Do gut flora make any contribution to the baby's vitamin K supply?

Vitamin K prophylaxis

While admitting the wide gaps in our knowledge of HDN, two facts are undisputed. Firstly, the condition is virtually confined to breast fed infants who are not given vitamin K prophylaxis. Secondly, it carries a high risk of morbidity or death. Now that it is again common for babies to be solely breast fed, even to the exclusion of supplementary formula feeds while breast feeding is becoming established (perhaps a significant source of vitamin K in the past), we strongly recommend that all infants should receive prophylaxis. The experience in our own unit, where six cases of HDN occurred in 17 months,⁹ emphasises that a selective policy of vitamin K prophylaxis is no longer adequate.

Given that all infants should receive vitamin K, how should it be given? From the experience of the 1950s and '60s it is well established that vitamin K₁ (1 mg given intramuscularly) protects against HDN, and reports to the contrary are exceedingly rare. The injection, however, does cause some discomfort to the baby, is viewed with suspicion by many parents as an 'unnatural' intervention in the birth process, and has occasionally led to disaster when the baby was inadvertently given the Syntometrine intended for the mother.¹⁰

Vitamin K can also be given orally—indeed, this was the method of choice in one of the earliest studies.¹¹ Prophylaxis by this route is potentially less certain as the dose may not be swallowed, absorbed, or metabolised, particularly if the infant has underlying disease yet undiagnosed—for example, cystic fibrosis, biliary atresia, α_1 antitrypsin deficiency, or abetalipoproteinaemia. In one well documented case a baby seemed to have temporary malabsorption of vitamin K alone.¹²

An oral dose of 1 mg vitamin K₁ gives peak plasma concentrations some 300 times the normal adult concentrations (which in turn exceed cord

blood concentrations by a factor of 10^{13}) but only 5% of those achieved after intramuscular injection of the same dose.¹⁴ If the intramuscular dose is not considered to be excessive it could be inferred that a larger dose should be used orally for equally effective prophylaxis. It is by no means certain, however, that peak plasma concentrations after prophylaxis relate to either the total amount of vitamin absorbed or retained and there is good evidence that a 1 mg oral dose gives protection.¹⁵ If considered necessary an increased oral load of vitamin K₁ could be achieved in several ways, including a larger single dose at birth, repeated oral doses for breast fed infants, or supplementation of breast feeding mothers to increase the vitamin K content of their milk. The latter methods, requiring repeated doses to either baby or mother, have the attraction that effective prophylaxis may be more reliably extended into the second and third months of life, when there is still risk of late onset HDN and stores from a single prophylactic dose at birth may be exhausted. Compliance with a regimen of repeated doses, however, may be poor and difficult to supervise and our own preference is to give a single prophylactic dose at birth.

For reasons of acceptability to parents, safety, convenience, and cost we currently use a 1 mg oral dose of vitamin K₁ for routine prophylaxis and continue to use intramuscular prophylaxis in infants at special risk from HDN—that is, those born prematurely or admitted to the special care baby unit for any other reason and those born by traumatic delivery or to mothers taking oral anti-convulsants. We have now used this policy in some 25 000 babies and have not seen any further cases of HDN.

References

- ¹ Salomonsen L. On the prevention of haemorrhagic disease of the newborn by the administration of cow's milk during the first two days of life. *Acta Paediatr Scand* 1940;**28**:1–7.
- ² Dam H, Dyggve H, Hjalmar L, Plum P. The relation of vitamin K deficiency to haemorrhagic disease of the newborn. *Adv Pediatr* 1952;**5**:129–53.
- ³ Meyer T, Angus J. The effect of large doses of "Synkavit" in the newborn. *Arch Dis Child* 1956;**31**:212–5.
- ⁴ Dyggve H. Bilirubin studies in premature infants who received menadione derivatives or vitamin K₁ at birth. *Acta Paediatr* 1960;**49**:230–42.
- ⁵ Anonymous. Vitamin K and the newborn [Editorial]. *Lancet* 1978;ii:755–7.
- ⁶ Savage D, Lindenbaum J. Clinical and experimental human vitamin K deficiency. In: Lindenbaum J, ed. *Contemporary issues in clinical nutrition*. New York: Churchill Livingstone, 1983:271–320.
- ⁷ Lane PA, Hathaway WE. Vitamin K in infancy. *J Pediatr* 1985;**106**:351–9.
- ⁸ McCarthy PT, Shearer MJ, Gau G. Vitamin K content of human liver at different ages. *Haemostasis* 1986;Suppl 5:84–5.
- ⁹ McNinch AW, L'E Orme R, Tripp JH. Haemorrhagic disease of the newborn returns. *Lancet* 1983;ii:1089–90.
- ¹⁰ Whitfield MF, Salfeld SAW. Accidental administration of Syntometrine in adult dosage to the newborn. *Arch Dis Child* 1980;**55**:68–70.
- ¹¹ Lehmann J. Vitamin K as a prophylactic in 13,000 infants. *Lancet* 1944;ii:493–4.
- ¹² Von Kries R, Reifenhauer A, Gobel U, McCarthy PT, Shearer MJ, Barkhan P. Late onset haemorrhagic disease of newborn with temporary malabsorption of vitamin K₁. *Lancet* 1985;ii:1035.
- ¹³ Shearer MJ, Rahim S, Barkhan P, Stimmler L. Plasma vitamin K₁ in mothers and their newborn babies. *Lancet* 1982;ii:460–3.
- ¹⁴ McNinch AW, Upton C, Samuels M, et al. Plasma concentrations after oral or intramuscular vitamin K₁ in neonates. *Arch Dis Child* 1985;**60**:814–8.
- ¹⁵ Dunn PM. Vitamin K₁ for all newborn babies. *Lancet* 1982;ii:770.

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