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VITAMIN K PROPHYLAXIS IN NEWBORN INFANTS

VITAMIN K AND HAEMORRHAGIC DISEASE OF THE NEWBORN

In NSW the practice of giving vitamin K to neonates to prevent haemorrhagic disease of the newborn (HDN) began in the 1950s. Initially it was given only to neonates considered to be at increased risk of intracranial haemorrhage (e.g. after difficult instrumental deliveries). In 1971 the NSW Maternal and Perinatal Committee recommended that all newborn infants receive vitamin K1 prophylaxis, and in subsequent years the intramuscular (IM) administration of 1mg of vitamin K1 (phytomenadione) at birth became the universal regimen.

Before the widespread use of vitamin K, HDN was an important cause of infant morbidity and mortality. The incidence is difficult to assess, but 13 deaths were attributed to HDN in NSW in 1969 (15.1 per 100,000 live births), and 14 deaths each year in 1970-71 (15.8 and 14.2 per 100,000 live births respectively). Mortality from HDN declined sharply during the 1970s (Figure 1), and a total of only four deaths was recorded in the 10 years 1980-89 (0.5 per 100,000 live births). The incidence has also declined. That the condition is virtually unknown in NSW today testifies to the effectiveness of IM vitamin K in prevention.

Three types of HDN are recognised:

- **Early**, in the first 48 hours of life, and almost always related to maternal drug therapy (especially phenytoin)
- **Classical**, in the second to seventh day of life
- **Late**, occurring between one week and six months of age.

All three types present with a spectrum of severity ranging from slight bleeding to severe haemorrhage, and with a variety of possible bleeding sites including the skin, umbilicus, gastrointestinal tract, circumcision site, or intracranial. Late HDN is the most likely to be severe and to present with intracranial haemorrhage.

VITAMIN K AND CHILDHOOD CANCER

In 1990 Golding et al published the results of a 10-year follow-up of a representative sample of 16,193 infants delivered in Great Britain in one week during 1970[1]. A case-control study of the 33 children identified as having cancer, with controls selected from the same cohort, suggested an association between cancer and prophylactic vitamin K given at birth to prevent HDN.

This unexpected finding led to a separate case-control study of children diagnosed with cancer between 1971 and 1991 and born in the two major Bristol maternity hospitals between 1965 and 1987. Exposure factors in this study were vitamin K administration at birth (oral or IM) and pethidine given to the mother in labour. The main findings, expressed as odds ratios and 95 per cent confidence intervals, were as follows[2]:

For all cancers:

Oral vs no vitamin K	1.15 (0.5-2.7)
IM vs oral or no vitamin K	1.97 (1.3-3.0)
Pethidine vs no pethidine	1.05 (0.7-1.5)

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For leukaemias:
IM vs oral or no vitamin K 2.65 (1.3-5.2)

Since the publication of these findings in August 1992[2] there has been much discussion of their implications and possible alternative vitamin K regimens. The debate has focused on:

- the validity and biological plausibility of the findings, and their consistency with observed childhood cancer incidence trends; and
- the nature and likely efficacy of oral vitamin K regimens, and the logistic difficulties of ensuring that all infants receive the repeated doses needed to prevent late HDN.

Validity
In their case-control study Golding et al had difficulty in:

- reconstructing historical (1965-87) data on vitamin K administration (they relied on known hospital policy rather than individual records in an unstated proportion of subjects);
- obtaining comprehensive historical data on confounders for all cases and controls;
- and completely ascertaining all cases of cancer in the hypothetical cohort which yielded the cases and controls (i.e. in the infants born in the two major Bristol maternity hospitals during 1965-1987).

It is beyond the scope of this article to provide a full critical appreciation of the reported case-control study. In a circular to all doctors in England and relevant nursing and public health personnel[3], the British Chief Medical Officer and Chief Nursing Officer weighed its contribution thus:

> *Although the data analysed were consistent with intramuscular vitamin K being associated with an increased risk of childhood cancer, the study fell far short of providing conclusive evidence.*

Biological plausibility
Golding et al cite three lines of evidence for this[2]. First, very high concentrations of vitamin K (such as the levels achieved in an infant's plasma 12-24 hours after an IM dose) have been shown to increase sister chromatid exchanges in human placental lymphocytes in vitro and sheep foetal lymphocytes in vivo. Second, vitamin K1 appears to play an adjuvant role in benzo(a)pyrene mutagenicity and carcinogenicity, and the injectable vitamin K preparation contains phenol as well as vitamin K1. Third, experimental vitamin K deficiency in rodents appears to reduce tumour growth.

Consistency with observed childhood cancer incidence trends
Based on some assumptions about the extent of IM vitamin K use in England and Wales, Golding et al asserted that the increase in leukaemia incidence in children born during 1962-74 was compatible with a vitamin K effect[2]. While in the UK sales of 1mg vitamin K ampoules increased steadily from 1958 to 1983, the cumulative incidence of childhood leukaemia increased in birth cohorts only until the early 1970s, and was fairly constant in subsequent birth cohorts. This pattern militates against an association with vitamin K[4]. Data from the US cities of Atlanta, Detroit and San Francisco-Oakland and the States of Connecticut and Iowa showed no increase in childhood leukaemia in 1969-84 compared with 1947-50, yet almost all newborns in the US received IM vitamin K after 1961[5]. In NSW cancer incidence data are available for the period 1972-90. A detailed analysis of these data will be published in a forthcoming issue of the NSW Public Health Bulletin. Initial analysis suggests the total cancer incidence in children under 14 years of age increased slightly, but the incidences of leukaemia and central nervous system cancers (the major solid tissue tumour in children) were fairly constant (Figure 2).

FIGURE 1

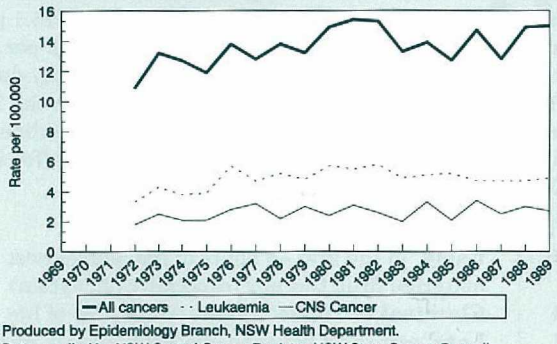
DEATHS FROM HAEMORRHAGIC DISEASE OF THE NEWBORN, NSW, 1969-88

Note: No deaths from this disease occurred after the first year of life.
Produced by Epidemiology Branch, NSW Health Department

FIGURE 2

INCIDENCE OF CANCER IN CHILDREN AGED 0-14 YEARS, NSW, 1972-89

Rates per 100,000 population directly standardised by age and sex to WHO world population



Produced by Epidemiology Branch, NSW Health Department.
Data supplied by NSW Central Cancer Registry, NSW State Cancer Council

Oral vitamin K regimens
In January 1993 the National Health and Medical Research Council (NHMRC), the Australian College of

Paediatrics (ACP) and the Royal Australian College of Obstetricians and Gynaecologists (RACOG), issued a joint statement on vitamin K prophylaxis[6]. While recognising that the epidemiological evidence for an association between IM vitamin K and childhood cancer was limited, the statement pointed out that the evidence could not be ignored, and that a non-invasive form of prophylaxis was preferable in any situation. The interim recommendation therefore was that vitamin K could be given orally to healthy full-term infants.

A single oral dose of vitamin K effectively protects against early and classical HDN, but may not protect against late HDN. Additional doses are needed for the latter. The interim NHMRC/ACP/RACOG recommendation was for three 1mg oral doses: the first at birth, the second at three-five days of age, and the last in the fourth week of life. This regimen could be adjusted for infants who were preterm, sick or unable to tolerate oral vitamin K; such infants could be given an 0.1mg IM vitamin K dose at birth, with subsequent doses to be either 1mg orally or 0.1mg IM, depending on the clinical condition.

The oral use of vitamin K is common in some countries, including Japan. However, there is little information on the pharmacodynamics of vitamin K, and the suggested oral regimens have been proposed by overseas and Australian expert panels extrapolating from the available data. It is unclear whether the lack of an association between oral vitamin K and childhood cancer reported by Golding et al was based on one dose of vitamin K at birth, repeated doses, or a variety of different regimens among the cases and controls.

As infant formulas contain vitamin K, it is unlikely that fully formula-fed infants require the third oral dose.

Logistic difficulties of oral vitamin K administration

The NHMRC/ACP/RACOG recommendations present two difficulties as regards implementation.

First, no approved preparation suitable for oral administration to infants is available in Australia. Vitamin K can be administered orally using the IM injectate solution taken from glass ampoules. Alternatively, hospital pharmacists can make up extemporaneous solutions of appropriate strength for oral administration. Neither of these preparations is approved by the Australian Drug Evaluation Committee for oral use, and there are only limited data on their pharmacodynamics following oral administration.

Second, even if a suitable preparation were to be approved, there would be a need to ensure infants received the full course, i.e. three doses. The first and second doses do not present a problem - the first can be given shortly after birth, and the second at the time of newborn screening (either in hospital or as part of an early discharge program). However, there is no scheduled regular encounter with a health professional during the fourth week of life, when the last dose is due.

The NSW Health Department has urged the Commonwealth to approve an oral preparation for infants as soon as possible. Pending this, the Department has had preliminary discussions with relevant professional organisations about service arrangements for administration of the repeated oral doses. If vitamin K is to be given orally, it is likely that maternity units will be responsible for informing parents of the importance of completing the course. An information sheet will be prepared. It is imperative that the date, dose and route of vitamin K administration be recorded in the Personal Health Record.

THE PUBLIC HEALTH DILEMMAS

The 1992 report[2] of the association between IM vitamin K and childhood cancer has created a situation which is unusual in public health. An important clinical policy change is being considered in Australia and elsewhere largely on the basis of a single study. The effectiveness of IM vitamin K in preventing HDN is established, and it is easy to administer as a single large dose that can be given routinely by the birth attendant. Following the 1992 report, the **certainty** of preventing HDN in the first six months of life must be balanced against the **possibility** of a doubling of the risk of cancer throughout childhood. If IM vitamin K caused cancer, the resulting number of childhood cancer deaths would be much greater than the number of HDN deaths prevented. This poses a major problem of risk communication to the public.

The NHMRC/ACP/RACOG joint statement also poses a dilemma for a State Health Department which would ordinarily take immediate steps to implement a national clinical policy recommendation. If the NSW Health Department were to implement the interim recommendations, the Department would have to advise health professionals to use a drug in a manner other than that for which it was approved. Individual medical practitioners can legally prescribe any registered drug by any route, whether approved or not. However, if the Department were to recommend the non-approved use of a drug, this would undermine the national drug evaluation process. On the other hand, if the Department were to avoid implementing the interim recommendations, it would implicitly endorse the continuation of a clinical practice which could possibly have adverse effects.

Until an effective vitamin K preparation approved for oral use is available, parents, in consultation with clinicians, will have to decide whether to:

- decline vitamin K (and take the attendant risk of HDN);
- agree to IM administration of vitamin K, acceptaing that there may be a small but real risk of cancer to the child, which must be balanced against the certain benefit of protection against HDN; or
- agree to oral administration of vitamin K, recognising that no approved preparation for oral administration to infants is available in Australia.

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Vitamin K prophylaxis

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The dilemma confronting the Department also faces clinicians and parents of newborn infants. There is no clear immediate solution. The NHMRC/ACP/RACOG statement acknowledges the need for more information. It recommends that epidemiological surveillance of HDN and childhood cancer be enhanced and that research be undertaken into the pharmacology and potential carcinogenicity of vitamin K preparations. The Epidemiology and Health Services Evaluation Branch has a major role in the former.

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1 Golding J, Paterson M, Kinlen LJ. Factors associated with childhood cancer in a national cohort study. *Br J of Cancer*, 1990; 62:304-8.
2 Golding J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *Br Med J*, 1992; 305:341-346.
3 Calman KC, Moores T. Circular: Prophylaxis against Vitamin K Deficiency Bleeding in Infants. Numbers FL/CMO(92)20 and FL/CNO(92)14. Department of Health, London, December 1992.
4 Draper GJ, Stiller CA. Letter: Intramuscular vitamin K and childhood cancer. *Br Med J*, 1992, 305:709.
5 Miller RW. Letter: Vitamin K and childhood cancer. *Br Med J*, 1992, 305:1016-7.
6 National Health and Medical Research Council, Australian College of Paediatrics and Royal Australian College of Obstetricians and Gynaecologists. Joint Statement and Interim Recommendations on Vitamin K Prophylaxis for Haemorrhagic Disease in Infancy. NH&MRC, Canberra, January 1993.

Organ donations

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The plan's priorities are to:

- develop and implement health professional education/information programs;
- increase public awareness and acceptance for organ donation; and
- provide national coordination and linkage to these activities.

ACCORD is developing a national Australian donor hospital information program involving organisations concerned with health professionals' educational processes.

Michael McBride, Executive Officer.

1. Hibberd AD et al. *Br Med J*, May 1992; 304:1339-43.
2. Transplant. Council of Europe. Vol 04, July 1992.

INFECTIOUS DISEASES

TIMELINESS AND COMPLETENESS OF REPORTING

The following table lists the number of weekly reports made to the Epidemiology and Health Services Evaluation Branch in the past month, i.e. from Epiweek 1 to Epiweek 3.

Several Public Health Units experienced network problems during January. Although this affected their ability to transfer notification data centrally, it did not affect response to each notification.

TABLE 5

NUMBER OF WEEKLY REPORTS MADE TO EPIDEMIOLOGY BRANCH, JANUARY 1993

Public Health Unit	Number	Status
Central/Southern Sydney	2	Complete
Eastern Sydney	2	Complete
South Western Sydney	1	Incomplete
Western Sector	2	Complete
Northern Sydney	2	Complete
Central Coast	0	Incomplete
Illawarra	0	Incomplete
Hunter	2	Complete
North Coast	1	Complete
New England	1	Incomplete
Orana and Far West	1	Incomplete
Central West	2	Complete
South-West	2	Complete
South-East	2	Complete

TYPHOID FEVER IN NORTH COAST REGION

A woman aged 30 was admitted to a North Coast hospital on January 14, 1993 with fever, diarrhoea and a history of vomiting for two days. No rash was observed. The woman had returned from a visit to India with her husband and three children. The youngest child, aged 10 months, had similar symptoms and was also admitted to hospital.

Stool cultures from the mother grew Salmonella typhi, and the case was notified to the Public Health Unit on January 18. Antibiotic therapy was initiated for both mother and child. Stool specimens were taken from all family members. The infant was notified to the PHU on January 20 when a positive stool specimen result became available.

It was thought unnecessary to contact the airline as the neither case was thought to be contagious until after their return home. Hospital infection control staff advised other concerned relatives in close contact with the family of the necessary precautions. Hospital staff were advised that isolation was not required.

It could not be confirmed whether typhoid immunisation had been received. The source of the infection was thought to be a contaminated water supply in India.

(Contributed by Tim Sladden, North Coast Public Health Unit)