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POSITION PAPER
Vitamin K Prophylaxis and Childhood Cancer

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There has been considerable controversy over the past few years regarding a putative association between childhood cancer and vitamin K prophylaxis in infants. In this position paper, we review both the benefit and the potential harm associated with administration of vitamin K to the newborn. We conclude that the confirmed benefits of vitamin K far outweigh the hypothetical association with childhood cancer. Moreover, this association remains unproved given the inconsistencies among the epidemiologic studies reported to date.

BENEFIT OF VITAMIN K

All newborns have low plasma concentrations of vitamin K and deficiency of vitamin K-dependent coagulation factors II, VII, IX, and X. These deficiencies can lead to hemorrhagic disease of the newborn (HDN) [1]. HDN can occur very early (<24 hr, usually associated with maternal use of drugs such as anticonvulsants), classical (first 7 days of life), or late (from 2 to 12 weeks of age; reviewed by Zipursky [2]). Late HDN occurs almost exclusively in breast-fed infants who did not receive vitamin K prophylaxis at birth.

Administration of intramuscular (IM) or oral vitamin K to all infants was standard practice in many countries until 1990, when reports of a potential association with childhood cancer appeared [3]. For any prophylactic intervention to be used at a population-wide level, the problem must cause significant morbidity and/or mortality, the intervention must be both safe and effective, and the benefits should outweigh the cost.

Does HDN Cause Significant Morbidity and Mortality?

Classical HDN is associated with rectal, oral, umbilical, or circumcision bleeding; catastrophic central nervous system bleeding is infrequent. In contrast, late HDN is associated with a 50% incidence of central nervous system hemorrhage, often after earlier small, warning bleeds at other sites; morbidity and mortality are considerable (20%) [4–6]. The risk of bleeding in normal (unselected) children who receive no prophylaxis is estimated to be on the order of 10/100,000 births [4]. Morbidity and mortality are clearly severe enough to warrant intervention.

Is Vitamin K Safe?

The major safety concern regarding vitamin K has been the reported link with childhood cancer, as discussed below. Based on this purported association, some authors have advised using oral vitamin K, which generates lower peak levels than IM vitamin K (reviewed by Sutor et al. [7]). Additional reasons for using the oral route are that IM injections are painful and can lead to such complications as hemorrhage or inadvertent intravenous injection. They also may seem unduly invasive to families interested in a 'natural' or 'holistic' approach to childbirth.

Is Vitamin K Effective?

Intramuscular vitamin K is generally effective in preventing bleeding and is more effective than a single oral dose [4,6,8]. Cornelissen et al. [9] studied different schedules of administration in Australia, Germany, The Netherlands, and Switzerland and concluded that three oral doses of vitamin K are less effective than IM prophylaxis. A continuing daily dose of 25 μg following an

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initial dose of 1 mg might be as effective, but studies have shown compliance with oral medication to be incomplete, which reduces efficacy [10–12].

Do the Benefits of Vitamin K Prophylaxis Outweigh the Cost?

In a cost/benefit analysis from New Zealand, Brown et al. [13] estimated the cost for each life saved by oral vitamin K at $4,500 and for each life saved by IM vitamin K at $11,000 (the difference reflecting increased cost of administration and of drug). The cost to the state of no prophylaxis was estimated at $6.40 per child (for care of children who develop HDN), $0.81 for an oral prophylaxis program and $2.01 for IM prophylaxis. However, this decision analysis assumed that oral and IM prophylaxis are equally effective, an assumption not generally accepted [2]. Nevertheless, these data do support the contention that prophylaxis, by either route, is more cost effective than no prophylaxis.

Taken together the available evidence indicates that vitamin K prophylaxis is effective and prevents significant morbidity and mortality. Moreover, data suggest that IM administration provides more reliable prophylaxis than oral medication.

VITAMIN K AND THE RISK OF CHILDHOOD CANCER

As noted above, the epidemiologic observation by Golding et al. [3] raised the concern that vitamin K administration might be associated with an increased risk of childhood cancer, particularly leukemia. Insofar as it would obviously be unethical to expose individuals to a putatively harmful agent in order to evaluate outcomes, causality in epidemiologic studies is typically evaluated by evidence that supports the following criteria: specificity of the association, temporal relationship, strength of the association, dose-response, biologic plausibility, and consistency of the association (reviewed by Hennekens and Buring [14]). Summarized below is the available evidence with respect to vitamin K and childhood cancer.

Specificity of the association (i.e., is the exposure unique to the disease?). In the case of vitamin K, it has been suggested that exposure is associated with several different childhood cancers (predominantly leukemia). Risk factors for childhood cancer are often disease-specific, but lack of specificity in this case does not provide evidence against causation.

Temporal relationship (i.e., does the exposure come before the disease?). This criterion can be considered satisfied; most analytic studies have established that vitamin K administration occurred prior to the diagnosis of childhood cancer.

Strength of the association [i.e., are the relative risks (RR) notable?]. The elevated RR or odds ratios (OR) associated with intramuscular vitamin K administration have been approximately 1.5–2.0. These RR are modest, but, because of the ubiquitous use of IM vitamin K prophylaxis, a substantial proportion of cases could be attributable to this exposure (if the association is valid). The public health value of monitoring the strength of the association is dependent on two factors: the magnitude of the risk observed and the frequency of the exposure in the population. For example, with an RR of 1.75, assuming that the proportion of the population 'exposed' to IM vitamin K is 90%, nearly 40% of childhood cancers could potentially be attributable to vitamin K IM injections (using population attributable risk formula of Hennekens and Buring [14]). In this instance, the population attributable risk would be substantial *were the association true*.

Biological plausibility (i.e., does it make biologic sense?). Biologic evidence concerning the carcinogenecity of naturally occurring vitamin K is limited and contradictory. Vitamin K is a quinone, and the related synthetic quinone menadione (also known as vitamin K3) has been shown to induce DNA single- and double-strand breaks and to cause oxidative stress by generation of free radicals [15–17]. However, similar studies of the naturally occurring vitamins K1 and K2 indicate that neither causes detectable DNA strand breaks [16] or acquired somatic mutations [18]. These data stand in contrast with an in vitro study of sister chromatid exchanges (SCEs) in human placental lymphocytes, which showed increased frequency of SCEs after exposure to vitamin K1 [19]. Although this study is frequently cited as evidence that vitamin K might be carcinogenic, a limited (six cases, six controls) in vivo study of infants given vitamin K showed no increase in sister chromatid exchanges [20]. Taken together, the biologic evidence that vitamin K is carcinogenic in infants has not been convincingly established.

Dose response (i.e., does more exposure cause more disease?). For vitamin K, the standard dosage is 1.0 mg. However, in vivo levels with IM injection remain higher for longer periods than those with oral administration [2]. A single dose by IM injection produces a mean plasma level 20,000 times higher than age-dependent normal levels found in breast-fed infants given no prophylaxis (reviewed by Sutor et al. [7]). Plasma levels are also higher at 3 months of age in infants who received an IM injection compared to infants who received an oral dose [21]. It would seem appropriate to assume that a dose-response relationship exists: IM injection (high) vs. oral dose (medium to low). Given that there is some epidemiologic evidence that a positive association is observed only with IM injection [22,23], there is modest support for this criterion.

Consistency of findings (i.e., are similar results seen in different studies and in different populations?). There are at least three epidemiologic study designs that can explore associations between vitamin K and childhood cancer: ecologic study, case-control study, and cohort study. The ecologic study typically provides summary measures of the frequency of exposure to a putative risk factor and the frequency of disease occurrence. In the case of vitamin K and leukemia, four ecologic studies have examined secular trends in the incidence of childhood leukemia [24–27]. None of these studies provided convincing evidence that introduction of IM vitamin K prophylaxis resulted in an increase in childhood leukemia incidence rates. Were a strong relationship to exist, a notable increase in disease might have been expected, given the introduction of such a ubiquitous exposure. It is important to note, however, that the lack of evidence for a relationship in an ecologic study cannot rule out the possibility that an association does exist, because ecologic studies provide no data on individual exposure.

In a case-control study, individuals with a disease of interest are identified and compared to a similar population of individuals who do not have the disease. The few case-control studies to examine the putative association between vitamin K prophylaxis and childhood cancer were limited because of 1) potential selection bias in choice of cases or controls [22] or 2) the use of imputed values for vitamin K administration [27]. Both these factors could influence the interpretation of study findings. Five recent investigations have attempted to address these deficiencies in study design; four found no association [28–31], whereas the fifth demonstrated a positive association with childhood leukemia [32].

Finally, two nested studies within cohort studies evaluated this potential association [33,34]). The study by Ekelund et al. [33] involved the identification of 235 cases of childhood cancer from a cohort of 1.3 million full-term infants (noninstrument assisted deliveries). No association with vitamin K administration was observed. However, the route of administration of vitamin K was imputed from standard hospital practices. In the United States, Klebanoff et al. [34] had access to medical record data regarding vitamin K administration; they found no association with either childhood cancer or leukemia.

SHOULD THERE BE CHANGES IN CLINICAL PRACTICE?

Millions of children have received IM vitamin K with no apparent side effects. Any relationship between vitamin K and childhood leukemia, were it to exist, must occur rarely. Parker et al. [32], reporting from the most recent case-control study, suggest that a definitive conclusion regarding the relationship between vitamin K and childhood leukemia cannot yet be reached. Additional epidemiologic studies exploring this association, however, will probably not answer the question. If vitamin K prophylaxis given intramuscularly is associated with an increased risk of childhood leukemia, it is likely that it manifests in only a very small subpopulation of children who are at high risk for some unidentified biologic reason (e.g., perhaps individuals with decreased capacity to repair DNA). The public health benefits of IM vitamin K far outweigh the potential for harm, based on the currently available evidence. We therefore do not believe that changes in pediatric practice are warranted.

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