AMERICAN ACADEMY OF PEDIATRICS

Controversies Concerning Vitamin K and the Newborn

Vitamin K Ad Hoc Task Force

Vitamin K deficiency may cause unexpected bleeding (0.25% to 1.7% incidence) during the first week of life in previously healthy-appearing neonates (classic hemorrhagic disease of the newborn [HDN]). The efficacy of neonatal vitamin K prophylaxis (either oral or parenteral) in the prevention of classic HDN is firmly established. It has been the standard of care since the recommendation by the Committee on Nutrition was adopted as policy by the American Academy of Pediatrics in 1961.[1]

Late HDN, a syndrome defined as unexpected bleeding due to severe vitamin K deficiency in infants aged 2 to 12 weeks, occurs primarily in exclusively breast-fed infants who have received no or inadequate neonatal vitamin K prophylaxis. In addition, infants who have intestinal malabsorption defects (cholestatic jaundice, cystic fibrosis, etc) may also present with late HDN. The rate of late HDN (often manifested by sudden central nervous system hemorrhage) ranges from 4.4 to 7.2 per 100 000 births based on reports from Europe and Asia. When a single dose of oral vitamin K has been used as neonatal prophylaxis, the rate has decreased to 1.4 to 6.4 per 100 000 births. Parenteral neonatal vitamin K prophylaxis prevents the development of late HDN, with the rare exception of infants with severe malabsorption syndromes. Oral regimens that have a similar efficacy as parenteral vitamin K in prevention of late HDN include the repeated administration of oral vitamin K_1 (Germany) or K_2 (Japan) at birth, 1 week, and 2 to 4 weeks.

In 1990 Golding et al[2] reported a study of a 1970 birth cohort in Britain in which they noted an unexpected association between childhood cancer and pethidine given in labor and the neonatal administration of vitamin K. Subsequently, Golding and others[3] conducted a case-control study designed to examine the risk of cancer associated with intramuscular vitamin K administration among infants born in two hospitals in Avon between 1965 and 1987 and diagnosed with cancer between 1971 and 1989. They reported a significant association between intramuscular vitamin K and cancer when compared to no vitamin K or oral vitamin K. They recommended exclusive use of oral vitamin K. Draper and Stiller[4] have questioned this study based on other data from Great Britain and have called for large cohort studies.

The task force has reviewed the report of Golding et al and other information regarding the US experience and offers the following comments:

1. Golding et al concluded that intramuscular vitamin K doubles the incidence of leukemia in children younger than 10 years of age. (The peak incidence occurs in children younger than 5 years of age.)

If intramuscular vitamin K doubles the incidence of childhood leukemia, a sharp increase should have been seen after 1961, when the American Academy of Pediatrics first recommended that all neonates be given vitamin K at birth. Since the 1940s the peak incidence of leukemia has been in children younger than 5 years of age. In this age-interval, as shown in the Figure, no marked increase in incidence occurred between 1947 and 1950 and 1983 and 1984 among whites in five geographic areas of the United States.[5] The apparent increase in acute lymphocytic leukemia (ALL) is spurious—due to the fact that in the mid-1970s reporting shifted from a category of acute leukemia NOS (not otherwise specified) to ALL. This occurred because of improved laboratory techniques for diagnosing ALL and its several subtypes.[6]

2. Golding et al concluded that other forms of childhood cancer have also increased in incidence, but the rise was not statistically significant.

Cancer is not a single disease. There are many different types of cancer and many different causes. While some environmental agents, such as ionizing radiation, can induce more than one form of cancer, most environmental agents are associated with only a single type of cancer. Of the various tumors Golding et al listed, no extraneous causes are known for childhood cancers of the sympathetic nervous system, kidney, eye, liver, or germ cells.[7] Lymphomas have been induced by immunosuppressant drugs for organ transplantation, and high doses of radiation have induced osteosarcoma, brain cancers, and soft tissue sarcomas.

3. To give biological plausibility to their hypothesis, Golding et al cited several reports that sister chromatid exchanges (SCEs) have been induced by exposing cultures of human placental lymphocytes or sheep lymphocytes to vitamin K. They noted that SCEs are related to mutagenesis, a step toward carcinogenesis. The authors acknowledge that one

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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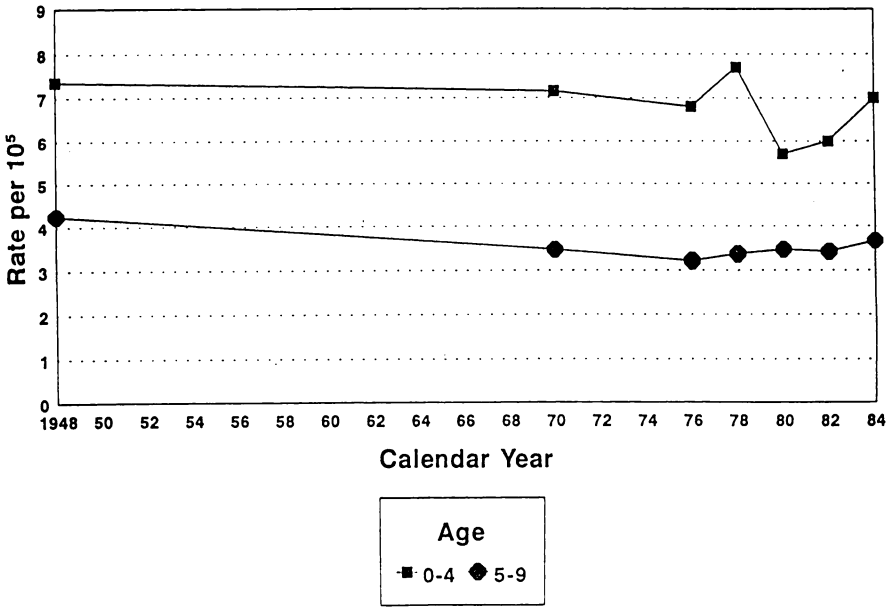

Fig 1. Leukemia: average annual incidence rate per 10^5 among whites in five geographic areas of the United States (from Devesa et al[5]).

study of six babies who had vitamin K administered intramuscularly showed no differences in SCEs when compared with six control infants who did not receive vitamin K. Golding et al implied that an effect may have gone undetected because of the small sample size.

Although a study of greater sample size would be helpful, the negative results are stronger than indicated by Golding et al. Of all genetic toxicological measures, structural chromosomal aberrations induced in cultures of rodent lymphocytes correlate most highly with human carcinogens. Shelby et al[8] have reported a concordance of approximately 95% between induction of in vivo chromosome aberrations and organic chemicals deemed to be human carcinogens. When a chemical tests negative in both this assay and the Ames assay (for mutagenesis in bacteria), the probability of the agent's being a human carcinogen is extremely small.[8] The finding of an increase in SCEs in some studies of vitamin K pales by comparison. Extensive review of reports of carcinogenicity testing shows no evidence that chemicals in the vehicle should be suspect.

There is no evidence of an increase in childhood leukemia since the period of 1947 to 1950, well before intramuscular vitamin K at birth was first recommended for US children. An increase in diverse forms of childhood cancer, claimed to be a result of vitamin K administration at birth, was not seen even among children of Hiroshima and Nagasaki exposed to the atomic bomb, and such diversity has not been seen in adults exposed to other human carcinogens. The biological mechanism of carcinogenesis (induction of SCEs) proposed by Golding et al does not accord with other information from the literature about in vivo effects of vitamin K or other tests of carcinogenicity.

RECOMMENDATIONS

Since parenteral vitamin K prevents a life-threatening disease of the newborn and the risks of cancer are unproven and unlikely, the American Academy of Pediatrics recommends:

1. Vitamin K_1 should be given to all newborns as a single, intramuscular dose of 0.5 to 1 mg.[9]
2. Further research on the efficacy, safety, and bioavailability of oral formulations of vitamin K is warranted.
3. An oral dosage form is not currently available in the United States but ought to be developed and licensed. If an appropriate oral form is developed and licensed in the United States, it should be given at birth (2.0 mg) and should be administered again at 1 to 2 weeks and at 4 weeks of age to breast-fed infants. If diarrhea occurs in an exclusively breast-fed infant, the dose should be repeated.
4. The conflicting data of Golding et al[2] and Draper and Stiller[4] and the data from the United States suggest that additional cohort studies are unlikely to be helpful.

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