Vitamin K and the management of patients with cystic fibrosis

Peter R. Durie, MD, FRCPC

Objective: To assess the advisability of routine vitamin K supplementation in patients with cystic fibrosis (CF).
Data sources: Studies identified through a MEDLINE search with the use of MeSH terms vitamin K, cystic fibrosis, PIVKA-II (protein induced by vitamin K absence-II), coagulation abnormality and cystic fibrosis, and hepatic disorder and cystic fibrosis.
Study selection: Six articles published between January 1981 and December 1992 were selected: one general review of vitamin K in infancy and five studies involving clinical trials of vitamin K supplementation or screening for fat-soluble vitamins, vitamin K or PIVKA-II in patients with CF. Review articles on nutrition in patients with CF, technical reports, letters, comments and case studies not bearing directly on these issues were excluded.
Data extraction: Findings in these articles were analysed and compared to determine whether routine supplementation in all patients with CF is indicated, whether specific subgroups of these patients are susceptible to vitamin K deficiency and areas in which future research is needed.
Results: There is no consensus on routine vitamin K supplementation in patients with CF. Studies have found a few cases of vitamin K deficiency among the population of people with CF. In addition, various factors — including pancreatic failure, liver disease, bowel resection and long-term use of antibiotics — can put some of these patients at risk of vitamin K deficiency.
Conclusions: Specific indications for routine vitamin K supplementation in all patients with CF have not yet been identified. Pending further studies, it would be prudent to consider routine supplementation in patients with CF and severe noncholestatic and cholestatic liver disease, major small-bowel resection, pancreatic insufficiency or lung disease necessitating frequent use of antibiotics. A stronger body of evidence is needed as a basis for clinical strategies.

Objectif : Évaluer s'il est souhaitable d'administrer de routine des suppléments de vitamine K à des patients atteints de fibrose kystique (FK).
Sources de données : Études repérées à la suite d'une recherche dans MEDLINE à l'aide des termes MeSH «vitamin K, cystic fibrosis, PIVKA-II, coagulation abnormality and cystic fibrosis» et «hepatic disorder and cystic fibrosis» (vitamine K, fibrose kystique, acarboxy-facteur II [protéine induite par l'absence de vitamine K-II], anomalie de la coagulation et fibrose kystique, et troubles hépatiques et fibrose kystique).
Sélection d'études : On a choisi six articles publiés entre janvier 1981 et décembre 1992 : une revue générale de la vitamine K chez le nouveau-né et cinq études comportant des essais clinique de l'administration de suppléments de vitamine K ou de dépistage de vitamines liposolubles, de vitamine K ou d'acarboxy-facteur II chez les patients atteints de FK. On a exclus

Dr. Durie is in the Department of Pediatrics, University of Toronto, and the Division of Gastroenterology, Hospital for Sick Children, Toronto, Ont.

Reprint requests to: Dr. Peter R. Durie, Department of Paediatrics, Rm. 1448, 555 University Ave., Hospital for Sick Children, Toronto, ON M5G 1X8

les articles de revue sur la nutrition chez les patients atteints de FK, les rapports techniques, les lettres, les commentaires et les études de cas ne portant pas directement sur ces questions.
Extraction de données : On a analysé et comparé les constatations établies dans ces articles pour déterminer si l'administration routinière de suppléments à tous les patients atteints de FK est indiquée, si des sous-groupes précis de ces patients sont vulnérables à une déficience en vitamine K et les domaines où des recherches futures s'imposent.
Résultats : Il n'y a pas de consensus sur l'administration routinière de suppléments de vitamine K à des patients atteints de FK. Des études ont révélé quelques cas de déficience en vitamine K dans la population des sujets atteints de FK. En outre, divers facteurs — y compris défaillance du pancréas, hépatite, résection intestinale et utilisation prolongée d'antibiotiques — peuvent exposer certains de ces patients à une déficience en vitamine K.
Conclusion : On n'a pas encore établi d'indications précises en faveur de l'administration routinière de suppléments de vitamine K à tous les patients atteints de FK. En attendant d'autres études, il serait prudent d'envisager d'administrer de routine des suppléments aux patients atteints de FK et d'hépatite grave avec ou sans cholestase, qui ont subi une résection majeure de l'intestin grêle, qui souffrent d'une insuffisance du pancréas ou de pneumopathie qui les oblige à prendre régulièrement des antibiotiques. Il faut plus de preuves plus solides sur lesquelles fonder des stratégies cliniques.

In theory, patients with cystic fibrosis (CF) are at risk of coagulation abnormalities as a result of vitamin K deficiency. There are four possible causes of this deficiency: (a) fat malabsorption due to pancreatic failure, with a deficiency of pancreatic lipase and colipase or intraluminal bile acids resulting from excessive bile-salt precipitation or both; (b) cholestatic or noncholestatic liver disease, with an intraluminal bile-salt deficiency; (c) reduced production of vitamin K by colonic flora due to the long-term use of antibiotics; and (d) resection of the small bowel for gastrointestinal complications such as meconium ileus, which could lead to malabsorption of vitamin K because of the reduced surface area of the intestine or malabsorption of bile acids or both.

On the basis of these concerns most Canadian CF clinics have, until recently, provided routine supplementation with a water-soluble form of vitamin K, Synkayvite (menadiol sodium diphosphate, Hoffmann-La Roche Ltd., Mississauga, Ont.). A synthetic derivative of vitamin K_3 (menadione), menadiol is recommended for routine use in patients with hepatobiliary or malabsorption syndromes because of its superior absorption in the absence of intraluminal bile salts. After absorption menadiol is converted to menadione, and its biologic potency is approximately half that of menadione. However, in 1992 the manufacturer discontinued production of the oral formulation of Synkayvite.

Other products contain vitamin K_1, a viscous liquid that is insoluble in water. Mephyton, a vitamin K_1 preparation, is available in tablet form in the United States and can be obtained in Canada from Merck Frosst (Pointe-Claire, Que.) through the Emergency Drug Release Program, Health Protection Branch, Health Canada. Alternatively, Scandipharm Canada (Markham, Ont.) is now marketing a multivitamin product called ADEK, which includes vitamin K_1. As yet, however, there is no suitable alternative to Synkayvite, and the discontinuation of this product has given increased prominence to questions associated with vitamin K supplementation.

Specifically, is there solid evidence supporting routine vitamin K supplementation in all patients with CF? Are there subgroups of patients with CF who are more susceptible to vitamin K deficiency? This review assesses the advisability of routine vitamin K supplementation in patients with CF.

Methods

A MEDLINE search was conducted with the use of MeSH terms vitamin K, cystic fibrosis, PIVKA-II (protein induced by vitamin K absence-II), coagulation abnormality and cystic fibrosis, and hepatic disorder and cystic fibrosis.

This review is based primarily on six articles[1-6] published between January 1981 and December 1992, one of which reviewed vitamin K in infancy, and five of which involved clinical trials of vitamin K supplementation or screening for fat-soluble vitamins, vitamin K, or PIVKA-II in patients with CF. Review articles on nutrition in patients with CF, technical reports, letters, comments and case studies that did not bear directly on these issues were not used.

The findings of these studies were analysed and compared in the context of well-established evidence on the dietary occurrence, biochemical aspects, biologic function and intestinal absorption of vitamin K[7-10] to determine whether routine supplementation should be a clinical norm in the treatment of all patients with CF, whether specific subgroups of patients with CF are particularly susceptible to vitamin K deficiency, and where future research is needed to reach definitive conclusions and formulate clinical guidelines.

Results

A review of the literature provides conflicting and incomplete answers. Lane and Hathaway,[1] in a general review of vitamin K in infancy, state that:

cystic fibrosis is a well-known cause of vitamin K deficiency at any age. In one survey, 58% of patients with cystic fibrosis had laboratory evidence of vitamin K deficiency. In infancy, vitamin K deficiency haemorrhage may be the first sign of cystic fibrosis, the initial manifestations may be bruising, hematemesis or intracranial haemorrhage. One child with cystic fibrosis was referred for evaluation of possible non-accidental trauma. In two well-documented cases, the correct diagnosis was discovered only at autopsy in infants who died of sudden intracranial haemorrhage.

Corrigan and associates[2] reported vitamin K deficiency in 14 of 24 patients with CF whom they studied. Only one of these patients had clinical evidence of multilobular cirrhosis. This patient and another had abnormal results of tests for liver function. On the basis of this observation, the authors recommended routine supplementation with vitamin K in patients with CF. Unfortunately, in this study the PIVKA-II determination was carried out by an indirect method and the sensitivity of the technique has been questioned.[3]

Sokol and collaborators[4] evaluated the vitamin status of infants with CF who had been identified through screening of newborns. Of 21 patients with CF identified before 6 weeks of age, none had a vitamin K deficiency. After supplementation with pancreatic enzymes and multiple vitamins not containing vitamin K, vitamin K status remained normal at 6 months and 12 months of age in the 16 patients who were monitored. On the basis of these findings, these authors did not recommend vitamin K supplementation in infants with CF unless antibiotics were administered. However, infants in whom the diagnosis is made on the basis of symptoms instead of through neonatal screening are likely to be older and to have experienced longer periods of malabsorption before being treated. Deficiencies of fat-soluble vitamins A, D and E are commonly found in such patients. Furthermore, most complications of vitamin K deficiency in infants have been reported before CF was diagnosed, although there are rare examples of such complications in older patients.[11]

Three studies have assessed vitamin K status in patients older than 1 year with CF. Choonara and colleagues[3] examined plasma concentrations of vitamin K_1 in 37 patients with CF (mean age 10.6 years, extremes 2 and 23 years) and 16 control subjects. The median plasma concentration of vitamin K_1 in the patients with CF and the control subjects did not differ. In contrast, the mean vitamin K_1 concentration was significantly lower in the patients with CF than in the control group. Some of the patients with CF had an abnormal prothrombin time, but there was no relation between this abnormality and the plasma concentration of vitamin K_1. The authors concluded that "routine vitamin K supplementation for patients with cystic fibrosis is not required." However, the article did not state whether any of the patients with CF were receiving vitamin K supplements or oral antibiotics at the time of the study. In addition, seven of the patients with CF involved in this study had undetectable levels of vitamin K_1, whereas only two of the control subjects had such levels.

In a recent study by Cornelissen and coworkers[5] the investigators measured simultaneously concentrations of vitamin K_1 and of PIVKA-II in 24 children with CF. Eight patients were receiving vitamin K_1 supplements (4 to 30 mg/d orally), and 16 were receiving no supplements. In the patients receiving supplements the plasma concentration of vitamin K_1 was extremely high. None of these patients had an abnormal level of PIVKA-II. One of 16 patients not receiving supplements had an abnormal vitamin K_1 determination and a detectable concentration of PIVKA-II. This patient had received antibiotic treatment for 4 weeks had an abnormal result of a liver-enzyme test. However, the authors of this study failed to establish control values for vitamin K_1 plasma concentrations.

In a study by de Montalembert and associates[6] vitamin K_1 and PIVKA-II concentrations were evaluated in 43 patients with CF. All but two of these patients were receiving vitamin K (5 to 10 mg/d orally), and four had liver damage. The serum concentrations in all the CF patients receiving supplements were within the normal range. However, 33% (14/43) of the patients, including the two not receiving vitamin K supplements, had abnormal serum concentrations of PIVKA-II. One patient not receiving supplements had a low serum level of vitamin K. There was a significant, positive correlation between the serum concentration of PIVKA-II and antibiotic use.

Conclusions

Results of recent studies suggest that vitamin K deficiency is probably unusual in patients with CF not receiving vitamin K supplements. However, most patients studied to date were receiving vitamin K supplements, and patients at risk of a vitamin K deficiency have not been evaluated adequately.

A stronger body of evidence on which to base clinical strategies must be developed. However, until investigators undertake further studies, particularly to identify risk factors more clearly, it seems prudent to continue to prescribe vitamin K for patients with CF and the following clinical abnormalities: (a) severe noncholestatic or cholestatic liver disease; (b) major small-bowel resection because of intestinal complications such as meconium ileus; (c) pulmonary disease that necessitates long-term use of antibiotics; and (d) pancreatic insufficiency.

In accordance with the Consensus Conference of the Cystic Fibrosis Foundation on Nutritional Assessment and Management in Cystic Fibrosis (held in April 1990),[12] the following dosages of vitamin K supplements are recommended. (Oral administration is the usual route; however, in the presence of prolonged prothrombin time or vitamin K deficiency due to severe cholesta-

tic or noncholestatic liver disease, parenteral administration of vitamin K may be required.)

- Age 0 to 12 months: 2 to 5 mg every week; 2 to 5 mg twice a week if the patient is receiving long-term antibiotic treatment.
- Age over 1 year: 5 mg twice a week if the patient is receiving long-term antibiotic treatment or has severe cholestatic or noncholestatic liver disease.

Research goals

The following research studies are recommended:

1. Studies of the requirements for vitamin K supplementation in infants in whom CF is newly diagnosed.

2. Prospective studies to evaluate the requirements for routine vitamin K supplementation in patients with CF who may be at risk of vitamin K deficiency, including patients with the following complications.

- Pancreatic insufficiency. These studies should include an evaluation of vitamin K_1 absorption in patients with pancreatic insufficiency who are receiving pancreatic enzyme supplements.
- Long-term cholestatic or noncholestatic liver disease. These studies should define the relation between severity of liver disease and the requirements for vitamin K.
- Intestinal resection.
- Pulmonary disease requiring long-term treatment with antibiotics. These studies should include an evaluation of the relation between concentrations of vitamin K and levels of PIVKA-II.

This study was supported by the Canadian Cystic Fibrosis Foundation. A previous version of this article was solicited and endorsed by the Clinic Subcommittee of the Medical/Scientific Advisory Committee of the foundation. We thank Dr. Rod Morrison for his assistance in preparing this manuscript.

References

1. Lane PA, Hathaway WE: Vitamin K in infancy. *J Pediatr* 1985; 106: 351–359
2. Corrigan JJ, Taussig LM, Beckerman R et al: Factor II (prothrombin) coagulant activity and immunoreactive protein: detection of vitamin K deficiency and liver disease in patients with cystic fibrosis. *J Pediatr* 1981; 99: 254–256
3. Choonara IA, Winn MJ, Park BK et al: Plasma vitamin K_1 concentrations in cystic fibrosis. *Arch Dis Child* 1989; 64: 732–734
4. Sokol RJ, Reardon MC, Accurso FJ et al: Fat-soluble-vitamin status during the first year of life in infants with cystic fibrosis identified by screening of newborns. *Am J Clin Nutr* 1989; 50: 1064–1071
5. Cornelissen EAM, van Lieburg AF, Motohara K et al: Vitamin K status in cystic fibrosis. *Acta Paediatr* 1992; 81: 658–661
6. De Montalembert M, Lenoir G, Saint-Raymond A et al: Increased PIVKA-II concentrations in patients with cystic fibrosis. *J Clin Pathol* 1992; 45: 180–181
7. Dam H, Schonleyder F: The antihemorrhagic vitamin of the chick. *Nature* 1935; 135: 652–653
8. Quick AJ, Stanley-Brown M, Bancrof FW: A study of the coagulation defect in hemophilia and in jaundice. *Am J Med Sci* 1935; 190: 501–511
9. Hawkins WB, Brinkhour KM: Prothrombin deficiency as the cause of bleeding in bile fistula dogs. *J Exp Med* 1936; 63: 795–801
10. Suttie JW: Vitamin K. In Diplock AT (ed): *The Fat Soluble Vitamins*, Heinemann, London, England, 1985: 225–311
11. Komp DM, Selden RF Jr: Coagulation abnormalities in cystic fibrosis. *Chest* 1970; 58: 501–503
12. Ramsey BW, Farrell PM, Pencharz P and the Consensus Committee: Nutritional support and management in cystic fibrosis. *Am J Clin Nutr* 1992; 55: 108–116