Chapter 1

Introduction

Bronchopulmonary dysplasia (BPD) remains one of the most significant costs of survival for the very low-birth weight (VLBW) infant. Many of the risk factors for the evolution of this multi-factorial disorder are well known. Although some of these risk factors can be modified after birth, others, such as lung immaturity and impaired lung repair process, are less well understood and, therefore, have been less susceptible to therapy. Research data suggest strongly that vitamin A deficiency and alterations in vitamin A kinetics increase the risk of BPD in VLBW infants. Further, it has been hypothesized that treatment of the BPD prone infant with doses of vitamin A designed to correct this deficiency can reduce the incidence of BPD.

Vitamin A is a general term for natural and synthetic compounds that exhibit the biologic properties of retinol, one of a small family of molecules termed retinoids. Retinoids consist of three chemically related but functionally distinct molecules (retinol, retinaldehyde, and retinoic acid) and their synthetic analogues. Carotenoids are a family of more than 600 naturally occurring molecules, but only a few of these (eg, beta carotene) are precursors of retinol. In this study, vitamin A applies to retinol and its esters (eg,

retinyl palmitate) that are commercially available for use in humans. Retinol is supplied as retinyl esters in diets of animal origin or is generated in the gut from beta carotene present in diets of vegetable origin.

Some physicians mistakenly think that vitamin A is synonymous with retinoic acid. Retinoic acid, the oxidative metabolite of retinol, is a drug used to treat acne and some malignancies and has been implicated as a teratogen if the fetus is exposed to high doses in the first trimester. Retinoic acid is produced enzymatically from retinol in vivo and is a potent signaling molecule, but the production, kinetics, and cellular pool sizes for retinoic acid are tightly regulated.

The classification of retinol as a vitamin also is a source of confusion. Traditionally, the term vitamin was applied to compounds that only could be obtained from dietary sources and that served as cofactors or catalysts in biochemical reactions. The functional consequences of an oversupply or under supply of these so-called micronutrients have been determined in animal experiments and experiments with human volunteers or described in anecdotal case reports. However, recent evidence suggests that the retinol metabolite retinoic acid is more than a simple cofactor; in fact, it is a signaling molecule more akin to cortisol or thyroxine. Thus, retinol metabolites exhibit potent and site-specific effects on gene expression and on lung growth and development.

Indeed, if a fetus is deprived of vitamin A, its metabolites, its receptors, or its binding proteins, normal lung development is impossible.

What is the Vitamin A Status of the VLBW Infant?

Compared with the term infant, the majority of infants born at less than 32 weeks' gestation have a generalized deficiency of vitamin A and a specific carrier protein called plasma retinol-binding protein (RBP). Premature infants have low plasma retinol and RBP levels in cord blood and low levels of vitamin A stored in liver and lung. Moreover, these deficiencies cannot be restored to normal levels by postnatal administration of conventional doses of vitamin A by the enteral route or by the use of commercially available parenteral vitamin preparations. In addition, vitamin A irreversibly oxidizes and loses its biologic activity when exposed to light, making administration via intravenous alimentation solutions unreliable.

Functional Consequences of Vitamin A Deficiency for the Developing Lung

The functional consequences of vitamin A deficiency in the lung have been identified using classic animal models of vitamin A deficiency and more recently, by producing defects in the pathways of vitamin storage, metabolism, or signaling capability. These studies indicate that lung development and response to injury are abnormal in the presence of either vitamin A deficiency or dysregulation. In addition, there is evidence that

vitamin A must be supplied continuously to the developing lung because the developing infant cannot recycle retinol and has a limited capacity for uptake of storage of retinol esters. In early fetal development, the change of the trachea from a simple tube to a branched structure with 22 divisions is critically dependent on vitamin A and its metabolites. Alveolar development also is impaired in the presence of vitamin A deficiency, leading to reduced surface area for gas exchange, reduced capillary formation, abnormal epithelial cell differentiation, and altered surfactant production. [1,2]

Even after the lung is formed, vitamin A deficiency can cause a loss of ciliated cells, Clara cells, and goblet cells. The loss of these cells results in impaired mucociliary clearance and the loss of the protective antioxidant-rich layer of mucoid secretions overlying the airway surface, rendering the airway surface susceptible to oxidant injury and to infection. Thus, vitamin A has a crucial role in lung growth, development, and function. The development of vitamin A therapy for the premature infant began with the observation that the histologic appearance of the lungs of vitamin A-deficient rodents resembled that of infants who had BPD. Subsequent studies demonstrated that these lung lesions could be reversed by supplying vitamin A to deficient animals and that plasma retinol levels could be increased by the administration of retinol. This latter study set the stage for the first clinical trial of vitamin A supplementation in premature infant. [2]

Because of poor nutritional intake from gastrointestinal tract and unreliable absorption of vitamin A from parenteral route[3-5], intramuscular vitamin A injection is prefer to obtain normal serum level.[6]

Objectives

1. To study vitamin A from blood samples of 40 VLBW premature infants weighed less than 1,500 g. and 80 healthy full-term newborn infants to define values in Thai neonates and compare to the levels of their mothers
2. To assess the effectiveness of vitamin A supplementation intramuscularly in prevention of bronchopulmonary dysplasia at postmenstrual age of 36 weeks' gestation in 80 VLBW premature infants who received mechanical ventilation or oxygen supplementation at 24 hours of age compared with control group
3. To study the effects of vitamin A supplementation to other diseases caused by oxygen free radicals eg. necrotizing entrecolitis, sepsis, retinopathy of prematurity

Scope of research

1. Blood samples from healthy full-term newborn infants delivered at Srinagarind Hospital, Khon Kaen University, were analyzed for vitamin A. The values obtained from this study will be used as reference values of Thai newborn infants.

2. Blood samples from VLBW premature infants who received mechanical ventilation or oxygen supplementation at 24 hours of age admitted at NICU or semi-intensive care unit Srinagarind Hospital, Khon Kaen University, were analyzed for vitamin A. The values obtained from this study will be used as reference values of Thai VLBW premature infants.

3. VLBW premature infants who received mechanical ventilation or oxygen supplementation at 24 hours of age admitted at NICU or semi-intensive care unit Srinagarind Hospital, Khon Kaen University, were enrolled to a double-blinded, randomized controlled trial to assess the effectiveness and safety of vitamin A supplementation as compared to control VLBW premature infants in prevention of BPD at postmenstrual age of 36 weeks' gestation