

Safety and Pharmacokinetics of Vitamin A Therapy for Infants with Respiratory Syncytial Virus Infections

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Infants with respiratory syncytial virus infection have low serum vitamin A levels. We treated 21 respiratory syncytial virus-infected children with 12,500 to 25,000 IU of oral vitamin A. Vitamin A levels were normalized at 6 h, and none of the children experienced vitamin A toxicity or exacerbation of respiratory illness. Vitamin A treatment of previously healthy respiratory syncytial virus-infected infants at these doses is safe and well tolerated.

The majority of children acutely ill with respiratory syncytial virus, a common cause of severe respiratory disease in young children worldwide, have low serum vitamin A levels that are associated with increased severity of illness (11, 12). This is similar to measles infection, in which disease severity correlates with low serum vitamin A levels (4). Vitamin A supplementation has diminished morbidity and death caused by measles and would be an attractive therapy for respiratory syncytial virus infection because of its low cost, wide availability, and ease of administration.

While vitamin A in large doses (200,000 IU) has been given safely to children 6 to 24 months of age with measles (1, 4, 6, 7), its safety is less certain in infants less than 6 months of age, the age group at highest risk for severe respiratory syncytial virus lower respiratory tract disease. Excess rates of acute vitamin A toxicity, specifically vomiting and bulging fontanelle, have been reported for infants treated with 50,000 to 100,000 IU of oil-based vitamin A preparations (5, 16). Serum vitamin A levels were not available in these studies. Water-soluble vitamin A preparations, the form most readily available in the United States, have more rapid absorption and reach higher peak levels in serum than oil-based preparations in children (9, 10). However, the effect of the improved absorption on manifestations of vitamin A toxicity is unclear. We conducted a prospective, open-label trial to assess the safety and pharmacokinetics of aqueous vitamin A therapy for respiratory syncytial virus-infected infants.

Previously healthy, full-term children less than 6 months of age, admitted to Vanderbilt University Hospital between December 1993 and March 1994 with mild respiratory syncytial virus infection as determined by respiratory score (14) and with lower respiratory tract symptoms for less than 4 days, were studied. The diagnosis of respiratory syncytial virus was made as previously described (11). Approval to use vitamin A in this study was obtained from the Food and Drug Administration (investigational new drug no. 43724). Informed consent was obtained from a parent or guardian with the approval of the Vanderbilt Institutional Review Board. Previously healthy children who had mild respiratory illness as determined by respi-

ratory score and qualified for the study, but for whom consent was not obtained, were used as the comparison group for length of hospital stay.

The study design was an open-label, nonrandomized dose escalation trial, starting at 12,500 IU of water-miscible vitamin A in oral, liquid form (Aquasol A; Astra Pharmaceutical Products, Inc., Westboro, Mass.). Children received a second equivalent dose of vitamin A 24 h after the first dose if they showed no clinical signs of toxicity, had a serum vitamin A level of <80 µg/dl, and were expected to remain in the hospital for an additional 24 h. Clinical and laboratory data were collected at baseline, 6 h after drug administration, daily while children were hospitalized, and 6 weeks after discharge. Levels of serum retinol and retinol-binding protein were measured as previously described (11, 15). A subset of children had additional sera available for measurement of retinol, retinyl palmitate, and vitamin E levels by high-pressure liquid chromatography (HPLC) (3) (Beckman 343 HPLC; Beckman, Fullerton, Calif.). Statistical analysis was performed by means of a Macintosh StatWorks program. All *P* values were determined by the Student *t* test or Spearman rank correlation coefficient.

Twenty-one children with mild respiratory syncytial virus infection as determined by respiratory score and a mean age of 2.3 months (range, 1 to 6 months) were enrolled in the study. Fourteen children received 12,500 IU of oral retinyl palmitate within 24 h of presentation, and eight of these children received a second dose 24 h later. Seven subjects received 25,000 IU, and three of these infants received a second equivalent dose. None of the children experienced acute vitamin A toxicity. There was no exacerbation of respiratory illness as determined by differences in respiratory rate, oxygen saturation, or auscultatory examination of the lung. Children treated with vitamin A did not have prolonged hospital stays in comparison with children with similar severity of illness who qualified for the study but for whom consent was not obtained (hospital stay of 1.6 ± 0.5 days in study group versus 2.2 ± 1.0 days in comparison group).

Mean baseline serum vitamin A levels were low, compared with previously published levels in healthy controls of similar age (11), and increased significantly 6 h after treatment with vitamin A (27.3 ± 1.4 µg/dl versus 42.3 ± 3.1 µg/dl, respectively; *P* = 0.0004, Student's paired *t* test). At baseline, serum vitamin A was predominantly in the form of retinol, and retinyl palmitate levels were uniformly low (mean, 2.8 ± 0.73 µg/dl;

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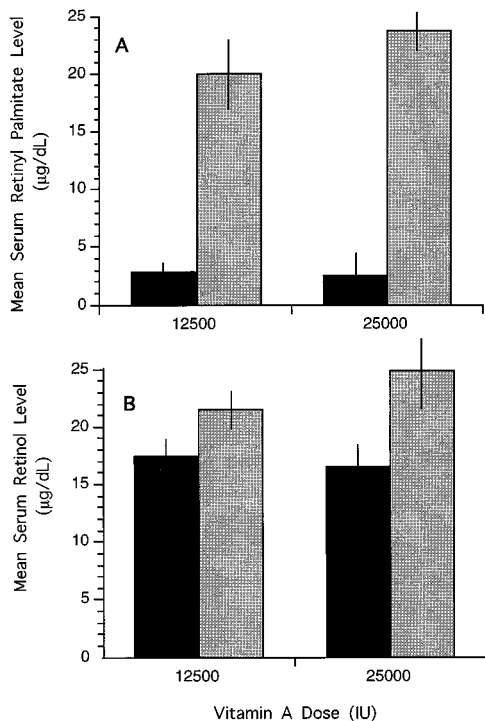


FIG. 1. Bars depict mean \pm standard error of the mean of serum retinyl palmitate (A) and retinol (B) levels before (solid bars) and after (stippled bars) administration of vitamin A in 17 children (11 children in 12,500-IU group and 6 children in 25,000-IU group). Retinyl palmitate levels increased significantly at 6 h in both dosage groups (2.9 ± 0.73 $\mu\text{g/dl}$ versus 20.0 ± 3.0 $\mu\text{g/dl}$ for 12,500 IU [$P = 0.003$] and 2.5 ± 1.3 $\mu\text{g/dl}$ versus 23.7 ± 1.6 $\mu\text{g/dl}$ for 25,000 IU [$P = 0.0004$, Student's paired t test]). Retinol levels also increased at 6 h in both groups, and this increase was significant in the 25,000-IU group (16.5 ± 1.8 $\mu\text{g/dl}$ versus 24.8 ± 3.0 $\mu\text{g/dl}$; $P = 0.004$, Student's paired t test).

range, 0 to 8 $\mu\text{g/dl}$). Retinyl palmitate levels increased significantly 6 h after treatment with vitamin A in both treatment groups (Fig. 1). Retinol levels also increased at 6 h, and this increase was significant for the total group (17.1 ± 1.5 versus 22.6 ± 1.6 $\mu\text{g/dl}$; $P = 0.0004$, Student's paired t test) and the subset receiving 25,000 IU of vitamin A (16.5 ± 1.8 versus 24.8 ± 3.0 $\mu\text{g/dl}$; $P = 0.004$, Student's paired t test). Levels of retinol-binding protein, the carrier protein for serum retinol, were low at presentation and increased 6 h after the first vitamin A dose (1.5 ± 0.1 mg/100 ml versus 1.9 ± 0.1 mg/100 ml; $P = 0.001$, Student's paired t test). Seventeen children had sera obtained at the 6-week follow-up visit. Mean vitamin A levels were higher at day 3 and week 6 compared with baseline in groups receiving at least 25,000 IU of total vitamin A (Fig. 2). There were no differences in mean serum vitamin E levels at baseline, at 6 h after administration of vitamin A, at day 3, or at 6 weeks.

Individual trials on the effects of vitamin A treatment for acute respiratory disease in children have differed markedly in regard to dose, vitamin A preparation, study population, and outcome. While it is clear that high-dose supplementation benefits children with measles (1, 6, 7), a recent placebo-controlled trial failed to demonstrate a beneficial effect of vitamin A therapy for nonspecific childhood respiratory disease (8). The benefits of vitamin A may be disease specific, and there may be characteristics of measles pneumonia, such as its extensive epithelial damage, that make rapid availability of vitamin A particularly important. Diseases caused by other pathogens that share these characteristics, such as respiratory syncytial

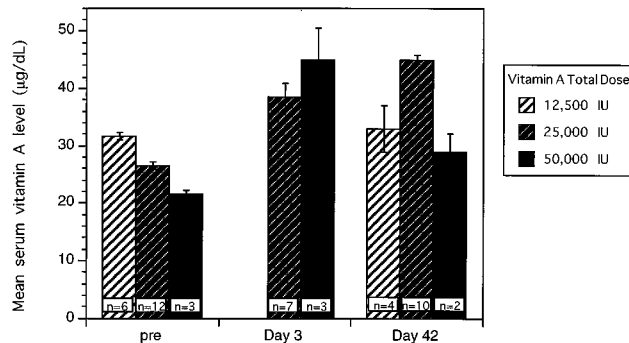


FIG. 2. Bars depict mean \pm standard error of the mean of serum vitamin A levels at baseline and days 3 and 42 after treatment and grouped according to total vitamin A dose. Children in the 12,500-IU group represent those who were discharged prior to receiving a second dose and therefore do not have day 3 levels available. Vitamin A levels increased significantly compared with baseline at days 3 and 42 ($P = 0.005$, day 3 levels versus preadministration levels; $P = 0.0001$, day 42 levels versus preadministration levels).

virus, may also benefit from supplementation. Another factor that may affect outcome is absorption; levels of vitamin A in serum after administration of vitamin A supplements were not reported in any of the efficacy trials. If safe, aqueous vitamin A may be the preferred preparation for treatment of children with respiratory disease on the basis of its high levels in serum in healthy children and its proven efficacy in measles. This study was designed to obtain safety and pharmacokinetic data for aqueous vitamin A in a well-defined population of children with a specific respiratory disease, as a preliminary step in better characterizing the role of vitamin A in the treatment of childhood respiratory infections.

In our small cohort of patients with mild respiratory syncytial virus lower respiratory tract disease, baseline vitamin A levels were low, consistent with previous data from children with acute respiratory syncytial virus infection (11). Aqueous vitamin A treatment in doses of 12,500 and 25,000 IU normalized vitamin A levels in most children at 6 h postadministration, with increases in both exogenous (retinyl palmitate) and endogenous (retinol) sources of vitamin A. The increased retinol-binding protein levels in this cohort suggest that there was also a release of preexisting liver stores of vitamin A. The retinol increase at 6 h was statistically significant in the 25,000-IU treatment group but not in the 12,500-IU treatment group, supporting the concept that large doses of vitamin A may be required to stimulate retinol-binding protein, and thus retinol, release from the liver (13).

The possibility of acute vitamin A toxicity has limited the use of very high doses of vitamin A in children less than 6 months of age. The same pharmacokinetics that make water-soluble vitamin A more appealing as a treatment also make it potentially more toxic, as toxicity is attributed to high levels of retinyl palmitate or free retinol unbound to retinol-binding protein (2). The side effects of high-dose vitamin A supplementation include nausea, vomiting, diarrhea, and increased intracranial volume as manifested by bulging fontanelle. The incidence of side effects increases with higher dosing regimen, younger age at administration, and malnutrition (5, 16). Despite the very young age of the children in our study, none experienced acute vitamin A toxicity. In addition, the vitamin A-treated children had hospital stays that were shorter than those of children with a similar severity of illness at presentation who were not entered into the study.

In summary, we have shown that oral, aqueous vitamin A in total doses of up to 50,000 IU is safe and well tolerated in previously healthy infants hospitalized with mild respiratory syncytial virus infection. Further safety and placebo-controlled efficacy trials in children with moderate to severe illness need to be performed.

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