Adverse Effects of High-dose Vitamin A Supplements in Children Hospitalized With Pneumonia

Charles B. Stephensen, PhD‡; Luis Miguel Franchi, MD‡; Helminio Hernandez, MD‡; Miguel Campos, MD, PhD§; Robert H. Gilman, MD, DTMH¶#; and Jose O. Alvarez, PhD*<

ABSTRACT. Objective. To test the hypothesis that high-dose vitamin A supplements will enhance recovery of children hospitalized for the treatment of community-acquired pneumonia.

Design. We conducted a randomized, double-blind, placebo-controlled clinical trial of high-dose vitamin A supplements among children 3 months to 10 years of age (N = 95) admitted to hospital with community-acquired pneumonia in Lima, Peru. Children <=1 year of age received 100 000 IU of water-miscible vitamin A on admission to the hospital and an additional 50 000 IU the next day. Children >1 year of age received 200 000 IU on admission and 100 000 IU the next day.

Results. Children receiving vitamin A (n = 48) had lower blood oxygen saturation (the mean difference on day 3 in hospital was 1.1%), higher prevalence rates of retractions (37% in the vitamin A group vs 15% in the placebo group on day 3), auscultatory evidence of consolidation (28% in the vitamin A group vs 17% in the placebo group on day 3), and were more likely to require supplemental oxygen (21% in the vitamin A group vs 8% in the placebo group on day 3) than children in the placebo group (n = 47). Adjustment for baseline severity of disease and nutritional status did not alter the association of vitamin A with increased clinical severity, although the difference in blood oxygen saturation was no longer statistically significant. No differences were seen in duration of hospitalization or in chest x-ray changes 14 days after admission. No deaths occurred, and toxicity of vitamin A was not seen.

Conclusions. This study indicates that high-dose vitamin A supplements cause modest adverse effects in children recovering from pneumonia and should not be used therapeutically in such patients unless there is clinical evidence of vitamin A deficiency or concurrent measles infection. PEDIATRICS 1998;101(5). URL: http://www.pediatrics.org/cgi/content/full/101/5/e3; vitamin A, pneumonia, children, Peru, respiratory, lung, retinol.

ABBREVIATIONS. UPCH, Universidad Peruana Cayetano Heredia; PPD, purified protein derivative; ANOVA, analysis of variance; SD, standard deviation; RSV, respiratory syncytial virus.
immediately and read by the attending physician. Children were then admitted to the pediatrics ward, and those with pulmonary infiltrate or consolidation confirmed by x-ray were eligible for recruitment into the study. A purified protein derivative (PPD) skin test was applied at the time of admission to the pediatrics ward and was read 48 hours later. Criteria for exclusion from the study included a previously diagnosed immunodeficiency of any origin, regular use of vitamin A supplements, a weight-for-height below the 70th percentile of the National Center for Health Statistics reference standards, a history of bronchial asthma or repeated bronchospasm, suspicion of clinically active tuberculosis (including a positive PPD skin test with a diameter of >10 mm), and the presence of underlying chronic disease. Informed, written consent was obtained at the time of admission to the ward by one of the study nurses from a parent or guardian of the potential subject after admission criteria (except PPD test reading) had been verified by the nurse. All admission criteria were reviewed and confirmed by the study coordinator, typically within 24 hours.

Forty-seven subjects were admitted to the vitamin A group and 49 to the placebo group. Three subjects in the placebo group subsequently decreased their PPD skin test of >10 mm and were immediately withdrawn from the study. These subjects were included in analysis of the admission history and physical examination data, but were excluded from all other analysis. One subject who should have been excluded from the study (because of Downs syndrome) was inadvertently admitted to the placebo group but was subsequently excluded from all data analysis. Thus, admission history and physical examination data from four subjects were not included in the analysis. Data from these subjects were included in all analyses until the time of withdrawal. This research protocol was reviewed and approved by the human subjects committees both at the University of Alabama at Birmingham and at UPCH.

Vitamin A and Placebo

At the time of admission to the study, subjects were randomized to the treatment or placebo group using a list of sequential numbers in which treatment or control had been randomly assigned within blocks of four numbers. Bottles containing the vitamin A and placebo preparations were assigned from the same list. The study was double-blind in that neither the investigators nor the subjects had knowledge of which numbers corresponded to treatment or control. Vitamin A and placebo preparations were administered orally. Aquasol A (Astra USA, Westborough, MA), a water-miscible preparation of retinol containing 50 000 IU/mL, was used as the treatment, and an identical preparation was used as the placebo. One subject was withdrawn from the placebo group during the first hospital day because of medical complications unrelated to his infection or the study protocol. Data from these subjects were included in all analyses until the time of withdrawal. This research protocol was reviewed and approved by the human subjects committees both at the University of Alabama at Birmingham and at UPCH.

Statistical Analysis

Statistical analysis was performed using SPSS software version 4.01 (SPSS Inc, Chicago, IL). Kruskal–Wallis one-way analysis of variance (ANOVA) was used for comparing continuous data between two groups. Pearson’s χ² was used to compare categorical data, except when the expected number of observations in any particular cell was less than 5, in which case Fisher’s exact test was used. Comparisons of continuous variables (eg, blood oxygen saturation) between groups over time were made by analysis of covariance. Comparisons of discrete variables (eg, presence of

Severity Score

We developed a numerical severity score based on the principal outcome variables to monitor clinical recovery. The calculation of this score is outlined in Table 1.

Antibiotic Treatment Regimens

Antibiotic treatment regimens are standardized within the pediatrics unit at UPCH. Decisions regarding selection of antibiotics and dosage were not controlled by study personnel and were made by attending physicians.

Bacterial and Viral Diagnostics

A blood sample was collected aseptically into sterile blood culture bottles (Fisher Scientific, Atlanta, GA) at the time of admission for culturing and identifying Haemophilus influenza and Strepococcus pneumonia using standard techniques. Within 24 hours of admission, a nasopharyngeal lavage specimen was collected. Cells were washed, spun onto a glass slide, and examined for the influenza A; influenza B; parainfluenza types 1, 3, and 4; adenovirus; and measles by immunofluorescent antibody analysis using commercial reagents (Chemicon International, Inc, Temecula, CA).

Statistical Analysis

Statistical analysis was performed using SPSS software version 4.01 (SPSS Inc, Chicago, IL). Kruskal–Wallis one-way analysis of variance (ANOVA) was used for comparing continuous data between two groups. Pearson’s χ² was used to compare categorical data, except when the expected number of observations in any particular cell was less than 5, in which case Fisher’s exact test was used. Comparisons of continuous variables (eg, blood oxygen saturation) between groups over time were made by analysis of covariance. Comparisons of discrete variables (eg, presence of
retractions) between groups over time were made by logistic regression. In both cases, time since admission and group \( \times \) time interaction terms were always included in the model. Significant differences indicated in the text for these analyses refer to \( P < .05 \) for either the group or group \( \times \) time variables; if one of these variables is not identified, it was not significant. When other factors (eg, baseline weight for height) were included in the analysis, they are indicated in the text. Duration of hospitalization was evaluated using the Lee–Desu statistic to compare survival experience.

**RESULTS**

Comparability of the Groups at Baseline

Physical examination and medical history data collected at the time of hospital admission were compared between the placebo and control groups to assess the success of randomization in producing comparable groups with regard to demographic variables, nutritional status, and indicators of disease severity. Nineteen of these variables are shown in Table 1. No significant differences were found. At the beginning of the clinical observation period in hospital, before the administration of vitamin A or placebo, there were no significant differences between the groups in the mean values or prevalence rates for the individual clinical indicators of disease severity (Table 4). The prevalence rates of central cyanosis and the mean values for respiratory rate and the aggregate clinical severity score (calculated as shown in Table 1) all were marginally higher (0.05 \( \leq P < .10 \)) in the vitamin A group than in the placebo group, suggesting that the children in this group tended to have more severe disease at admission.

Antibiotic Treatment of Pneumonia

Antibiotics were prescribed according to standard practices on this unit and were not proscribed by the study protocol. The percentage of children receiving antibiotics did not differ between the vitamin A (39/47, 83%) and placebo groups (38/45, 84%; \( P = 1.00 \)). Nor did the types of antibiotic given (\( P = .64 \)) or duration of use (\( P = .68 \)) differ between the groups. Penicillin was the most common antibiotic used (vitamin A, 34% placebo, 36%), followed by ampicillin or amoxicillin (vitamin A, 26%; placebo, 29%) and chloramphenicol (vitamin A, 13%; placebo, 16%).

Comparison of Clinical Outcomes During Recovery

We monitored changes in 12 clinical indicators of disease severity during hospitalization. Because treatment effects could change over time, our initial analysis took into account study group (the group term), time in hospital (the time term) and a group \( \times \) time interaction term. The 12 variables analyzed in this manner included the clinical severity score, its eight individual components (see Table 1), the need

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**TABLE 1.** Calculation of Clinical Severity Score

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Points Given for Each Level of Severity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Heart rate by age (per min)</td>
<td></td>
</tr>
<tr>
<td>3–11</td>
<td>&lt;140</td>
</tr>
<tr>
<td>12–35</td>
<td>&lt;120</td>
</tr>
<tr>
<td>36–59</td>
<td>&lt;100</td>
</tr>
<tr>
<td>≥60</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Respiratory rate by age (per min)</td>
<td></td>
</tr>
<tr>
<td>3–11</td>
<td>&lt;50</td>
</tr>
<tr>
<td>12–35</td>
<td>&lt;40</td>
</tr>
<tr>
<td>36–59</td>
<td>&lt;30</td>
</tr>
<tr>
<td>≥60</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>&lt;37.5</td>
</tr>
<tr>
<td>Presence of retractions</td>
<td>No</td>
</tr>
<tr>
<td>Presence of central cyanosis</td>
<td>No</td>
</tr>
<tr>
<td>Appetite (% of meal consumed)</td>
<td>100</td>
</tr>
<tr>
<td>Appetite (impression of mother)</td>
<td>Normal</td>
</tr>
<tr>
<td>Blood oxygen saturation (%)</td>
<td>&gt;96</td>
</tr>
</tbody>
</table>

*The aggregate score is the sum of the value given to each of these eight variables and thus ranges from 0 (least severe) to 24 (most severe). The score was three times per day, using the most recent data for each variable.
Some x-rays could not be evaluated on all criteria and were not included in this table.

**TABLE 3. Chest X-ray Data at Admission and Follow-up (14 Days After Admission)**

<table>
<thead>
<tr>
<th>Interpretation of Chest X-ray</th>
<th>Vitamin A</th>
<th>Placebo</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects†</td>
<td>47</td>
<td>41</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>16 (34%)</td>
<td>12 (29%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Perihilar infiltrate</td>
<td>10 (21%)</td>
<td>9 (22%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Interstitial infiltrate</td>
<td>10 (21%)</td>
<td>8 (20%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Consolidation</td>
<td>39 (83%)</td>
<td>29 (71%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>13 (28%)</td>
<td>6 (15%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Effusions</td>
<td>9 (19%)</td>
<td>6 (15%)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

* By Kruskal–Wallis one-way ANOVA for continuous data, Pearson’s χ² for categorical data and Fisher’s exact test for categorical data with cell sizes <5.
† Some x-rays could not be evaluated on all criteria and were not included in this Table.
also seen with the aggregate severity score ($P = .021$ for the group term) (data not shown). The clinical importance of the resulting difference between the two groups also was seen in the resulting need for supplemental oxygen. The percent of subjects receiving oxygen initially was the same in the two groups, but the rate increased rapidly in the vitamin A group, with the result that significantly more children in the vitamin A group than in the placebo group eventually required supplemental oxygen ($P < .0005$ for the group $\times$ time term), as seen in Fig 1. In addition, the prevalence of auscultatory evidence of consolidation initially was the same in the two groups (Fig 2), but the prevalence decreased steadily in the placebo group while staying nearly constant in the vitamin A group, resulting in a significant difference between the groups ($P = .0014$ for the group $\times$ time term).

Although the clinical measures of disease severity showed that vitamin A had adverse effects on recovery, other indicators of disease severity were unaffected by vitamin A treatment. The mean duration of hospitalization did not differ between the vitamin A (5.9 ± 3.5 d) and placebo groups (6.0 ± 4.9; $P = .74$), nor were differences seen between the groups in degree of inflammation in chest x-rays taken at follow-up (Table 3). Finally, there were no deaths in either group and only two cases (one in each group) of pneumonia did not resolve adequately by the end of the study.

### Adjusting Analysis for Baseline Severity of Disease, Age, and Diagnosis

The vitamin A group had a marginally higher clinical severity score at baseline ($P = .05$), lower...
weight-for-height z score on admission ($P < .05$), and different distribution of days with respiratory symptoms before admission ($P < .05$) than did the placebo group. Thus, we included these continuous variables as covariates in our analysis to adjust for these imbalances. These adjustments did not fundamentally alter the findings described above, although addition of these three variables caused the association between treatment and blood oxygen saturation, and between treatment and heart rate, to lose statistical significance ($P > .05$ for both group and group $\times$ time terms). However, the association of vitamin A treatment with a higher prevalence of refections ($P < .0005$ for the group $\times$ time term) and greater need for supplemental oxygen ($P < .005$ for the group term) remained highly significant after adjustment, as did the difference in prevalence of auscultatory evidence of consolidation ($P = .0014$ for the group term and $P = .0001$ for the group $\times$ time term), indicating that treatment group, rather than baseline disease severity, had the stronger association with these and the other significant outcome variables. Thus, the vitamin A treatment itself, rather than a chance imbalance between the treatment groups in the baseline severity of disease, is the most probable cause of the greater clinical severity of disease seen in these subjects. In addition, inclusion of the subject’s age or diagnosis of viral versus bacterial pneumonia as covariates, either alone or with the baseline severity of disease indicators, did not significantly alter these findings described above.

**DISCUSSION**

The results of this clinical trial show that high-dose vitamin A supplements are not beneficial in improving recovery from pneumonia in hospitalized children. Furthermore, the study provides clear and consistent evidence that this supplementation regimen produces adverse effects that are of clinical importance. These adverse effects included longer duration of clinical signs and a greater need for supplemental oxygen, which requires more nursing time and higher patient care costs. These adverse effects were not so severe as to require longer hospitalization or produce untoward clinical outcomes or to cause significant differences in chest x-ray findings at the follow-up examination. Although the randomization protocol produced clearly comparable groups at baseline for most variables, there were imbalances between the groups in weight for height, duration of disease before admission, and the baseline clinical severity score. Adjustment for these imbalances did not fundamentally alter the outcome of our analysis and thus does not detract from our conclusions.

Our findings differ from those of other clinical trials of vitamin A in children with pneumonia, which have found no consistent benefit to such supplements but, in contrast to our study, have not found evidence of harm. The first such study published was conducted among 263 Guatemalan children 3 months to 5 years of age hospitalized with community-acquired pneumonia (90% of subjects) or bronchiolitis. A single oil-based retinyl palmitate supplement (100 000 IU to those <1 year and 200 000 IU to older children) was given at admission. Similar exclusion criteria and endpoints were used, but no significant differences were seen between the vitamin A and placebo groups in any of these variables or in duration of hospitalization. Two additional placebo-controlled studies using higher doses of oil-based vitamin A (400 000 IU over 2 days in children >1 year of age and half this dose in younger subjects) have been completed recently in Brazil and Vietnam. In Brazil, 472 inpatients and outpatients 6 months to 5 years of age with a clinical diagnosis of pneumonia were studied. Fever, respiratory rate, and blood oxygen saturation were monitored daily in inpatients and on days 3 and 11 in outpatients. Duration of pneumonia was not affected by vitamin A, but the prevalence of fever was lower at day 3 in the vitamin A group than in the placebo group (16% vs 26%; $P = .008$). The clinical failure rate for the first-line antibiotic was 29% higher in the placebo group than in the vitamin A group, although the statistical significance of this finding was marginal ($P = .054$). In Vietnam, 592 inpatients 1 to 59 months of age with a clinical diagnosis of pneumonia were studied. No differences in duration of hospitalization or time to normalization of fever and respiratory rate were seen in the group as a whole or in subgroup analysis based on sex, age, or severity of disease at admission. However, in children with moderate malnutrition duration of hospitalization was shorter in the vitamin A group (6.8 days) than in the placebo group (8.6 days; $P = .04$). The real significance of this finding is unclear given its borderline statistical significance, particularly in light of the multiple comparisons made in that study. A principal methodology difference between our study and these other pneumonia studies is the type of vitamin A supplement used. We used water-miscible retinol (rather than oil-based retinyl palmitate) both because water-miscible preparations are absorbed more efficiently than oil-based preparations, thus giving higher peak serum concentrations as vitamin A is transported to the liver, and because water-miscible supplements were used in the trial of Hussey and Klein, which showed the clinical efficacy of such supplements.

Three recent clinical trials of vitamin A in subjects with respiratory syncytial virus (RSV) infection also have given mixed results. These studies involved substantially different patient populations than did the pneumonia trials. In general, the pneumonia subjects were older, had fewer underlying chronic health problems, and had pneumonia of multiple etiologies (eg, only 6% of our subjects had confirmed RSV infection). In comparison, the majority of RSV patients admitted to hospital are <6 months of age, may have been born prematurely, and are more likely to have underlying health problems, including chronic heart or lung disease. A small trial ($n = 33$) among children hospitalized in the United States found neither benefit nor detriment to the use of vitamin A, although those receiving vitamin A tended to have longer durations of hospitalization than did the placebo recipients (6.6 days vs 3.5 days; $P = .08$). Bresee et al studied 239 subjects 1 month to 6 years of age in a multicenter
trial in the United States. Subjects received a single dose of retinyl palmitate in oil (50,000 IU for those <6 months, 100,000 IU for those 6 to 11 months, and 200,000 IU for those ≥12 months of age). No differences between the treatment and placebo groups were found for most clinical outcomes but, as in the previous study, subjects receiving vitamin A did have a longer duration of hospitalization than did subjects in the placebo group (5.0 days vs 4.4 days; $P = .01$). The same investigators conducted a parallel trial among 180 RSV-infected subjects in Santiago, Chile, using essentially the same study protocol and supplementation regimen. This study found "no significant benefit from vitamin A treatment for the overall group in duration of hospitalization, need for supplemental oxygen or time to resolve hypoxemia." However, these authors did find a more rapid recovery from tachypnea ($P = .01$) in the subgroup of children in the vitamin A group admitted with blood oxygen saturations <90% (15% and 26% of the placebo and vitamin A groups, respectively). Thus, the principal finding of these RSV trials was that vitamin A supplementation did not hasten recovery from infection. However, in the two trials in the United States, an increase in duration of hospitalization was seen.

Why do high-dose vitamin A supplements not promote recovery from community-acquired pneumonia (or RSV infection) when they are of benefit in measles? One possible explanation is that the subjects in the measles trial of Hussey and Klein may have been more severely vitamin A-deficient than were the subjects in our study (or other pneumonia studies) and thus may have benefitted more from the administration of vitamin A supplements. Although subjects with clinical evidence of vitamin A deficiency were excluded from all of these clinical trials, it is difficult to evaluate vitamin A status biochemically during acute infections, because serum retinol concentrations are depressed by the acute phase response. However, the mean admission serum retinol concentration in the measles subjects was 0.4 mol/L, slightly higher than that seen in our subjects, although somewhat lower than that seen in other studies. Thus, it seems unlikely that a substantial difference in vitamin A status accounts for the different results of these studies. A second possible explanation for the benefit seen in measles that has not been reproduced in pneumonia is simply that measles is different from pneumonia and that subjects recovering from measles benefit from vitamin A supplements whereas those recovering from other infections do not. For example, vitamin A supplements could enhance some aspect of the immune response (eg, antiviral natural killer cell activity), which would be of particular benefit in recovery from measles but of lesser importance in pneumonia and RSV infections.

Our study raises one additional question: How could high-dose vitamin A supplements increase the severity of pneumonia? Two explanations seem plausible. First, high-dose vitamin A may enhance some aspect of the immune response, which would increase inflammation in the lungs, thereby increasing the severity of disease. High-dose retinoids can enhance some aspects of immunity mediated by Th2 cells and IL-4 in mice. Because eosinophil- and IgE-mediated responses are promoted by IL-4 and Th2 cells, a boost to pathogen-specific responses involving these effector mechanisms may have transiently increased the severity of lung inflammation in our subjects who received vitamin A. Such a phenomenon also might account for the longer duration of hospitalization seen in subjects with RSV infection who received vitamin A supplements. A second possibility is that our vitamin A regimen produced toxic side effects. Signs of acute vitamin A toxicity are produced, at least in part, by the damaging effects of retinol on biological membranes. If our treatment regimen with oral water-miscible retinol produced particularly high serum retinol levels, this may have damaged endothelial cells in alveolar capillaries, particularly at sites of inflammation where increased permeability already would be present because of the inflammation associated with pneumonia. Such damage could result in increased effusion of fluids into alveoli, thus impairing oxygen diffusion into the blood and possibly increasing the prevalence of retractions and the need for supplemental oxygen, as seen in our subjects receiving vitamin A. Such signs of acute toxicity may not have been evident in the previous clinical trials of water-miscible vitamin A, which was given to subjects with measles, because different clinical variables were monitored and because underlying lung inflammation is less severe in measles than it is in pneumonia.

In conclusion, this study demonstrates that high-dose vitamin A supplements cause modest adverse effects in children recovering from community-acquired pneumonia. Therefore, we recommend that vitamin A supplements not be used therapeutically in such patients to hasten recovery from pneumonia, unless there is clinical evidence of vitamin A deficiency (ie, xerophthalmia) or concurrent measles virus infection. Administration of high-dose vitamin A supplements after recovery from infection to prevent or treat vitamin A deficiency is not contraindicated by this study.

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