Vitamin A Supplementation of Vitamin A Deficient Measles Patients Lowers the Risk of Measles-Related Pneumonia in Zambian Children

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ABSTRACT This is an a posteriori analysis of previously published data to assess whether improving vitamin A (VA) status resolves measles-related pneumonia (MP). Nonhospitalized acute measles patients (2 d of rash onset) had their VA status determined based on the molar ratio of retinol-binding protein to transthyretin (RBP/TTR). Using a cutoff value of ≤0.36, indicative of marginal VA deficiency, 82 children were diagnosed as marginally VA deficient and 114 were diagnosed as VA sufficient. At baseline, marginally VA-deficient patients had significantly lower serum retinol and higher serum C-reactive protein concentrations than VA-sufficient children. At the 2-wk follow-up visit, serum retinol and the RBP/TTR ratio were significantly greater in marginally VA-deficient measles patients receiving VA supplements than in those receiving placebo; whereas in VA-sufficient measles patients, retinol increased in those receiving VA supplements or placebo. Concomitantly the odds ratio of unresolved pneumonia in marginally VA-deficient measles patients receiving VA supplements compared with those receiving placebo was 0.20 (95% confidence interval, 0.05–0.71). In conclusion, VA supplements compared with those receiving placebo was 0.20 (95% confidence interval, 0.05–0.71). In conclusion, VA supplements were followed for 1 mo (13). Blood samples (5 ml) were drawn at baseline and at the 2-wk evaluation for biochemical determinations and measles antibodies (12,13). The samples were protected from light and placed inside a cool box at 8°C and allowed to coagulate. Within hours, serum was separated and stored at −20°C. Serum retinol levels were determined by HPLC at the Tropical Diseases Research Centre, Ndola, Zambia (12). Serum RBP, TTR

The reduction in measles morbidity and mortality with vitamin A (VA) supplements has been well documented (1), but there is less acceptance of the mechanism by which VA improves the survival of these patients. Recently Taylor and Higgs (2) argued that this lack of knowledge might impede the general acceptance of VA supplements as standard treatment for measles patients in developing and developed countries.

The correction of low circulating retinol concentrations during measles infection with VA supplements has not been suggested as a possible mechanism of the impact of VA. Hospital-based studies in developing and developed countries have demonstrated that measles severity is closely related to low serum retinol concentrations (3,4). Hussey and Klein (5) suggested that measles infection impaired the distribution of VA to peripheral tissues through the reduction of serum retinol concentrations, and Coutsoudis et al. (6) confirmed that supplementation increased serum retinol levels 8 d after two doses of 210 µmol of retinol. However, serum retinol also increased in children receiving placebo, raising the question of whether correcting serum retinol was necessary to reduce measles morbidity.

Others have suggested that it is the VA status before infection that determines the risk of morbidity and mortality during measles infection. A review of four community-based prophylaxis trials of VA supplements showed that measles-specific mortality rate was reduced by 50% (7). However a community-based prophylaxis trial of VA supplements that directly examined acute measles case fatality in relation to premorbid VA supplementation found no effect (8). A problem with these studies is that they used serum or plasma retinol as an indicator of VA status, which may not be indicative of VA status but rather of the effect of the acute phase response of inflammation (9). Recently it was shown that the molar ratio of retinol-binding protein to transthyretin (RBP/TTR) can selectively detect those with marginal VA deficiency regardless of whether inflammation is present (10,11). In this a posteriori analysis, VA status was determined on the basis of the RBP/TTR ratio before and after VA supplementation or placebo administration, and the relationship between improved VA status and measles morbidity was examined.

SUBJECTS AND METHODS

This a posteriori analysis was conducted on data previously published (12,13). Briefly, a total of 200 acute measles patients, aged 5 mo to 17 y, not requiring hospitalization were enrolled in a randomized double-blind placebo-controlled trial from March through September 1991 (13). The study was conducted at urban health centers in Ndola, Zambia; children received by random assignment a single oral dose of 210 µmol retinol as retinyl esters or a placebo and were followed for 1 mo (13). Blood samples (5 ml) were drawn at baseline and at the 2-wk evaluation for biochemical determinations of serum retinol, RBP, TTR, C-reactive protein (CRP) concentrations and measles antibodies (12,13). The samples were protected from light and placed inside a cool box at 8°C and allowed to coagulate. Within hours, serum was separated and stored at −20°C. Serum retinol levels were determined by HPLC at the Tropical Diseases Research Centre, Ndola, Zambia (12). Serum RBP, TTR

1 To whom correspondence should be addressed. E-mail: fjr5@psu.edu.
2 Abbreviations used: CI, confidence interval; CRP, C-reactive protein; MP, measles-related pneumonia; OR, odds ratio; RBP, retinol-binding protein; TTR, transthyretin; VA, vitamin A.

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Whitney test, a P of 0.36 is indicative of marginal vitamin A deficiency. We assessed the relationship between VA status and MP. MP was diagnosed on the basis of the presence of cough and a respiratory rate above an assessment criterion at baseline and the 2-wk evaluation to allow for biochemical determinations at baseline and the 2-wk evaluation. A cutoff value of the ratio of retinol-binding protein to transthyretin (RBP/TTR) (10). A ratio of 0.36 is indicative of marginal vitamin A deficiency (11). Table 1 shows the proportion of acute measles patients with MP observed probability. Differences were considered significant at P < 0.05.

RESULTS

Forty-two percent of children with acute measles [n = 196 (four patients of the original 200 were missing either RBP or TTR determinations)] had RBP/TTR ratios of ≤0.36, representing marginal VA deficiency. Half were allocated to receive VA supplements. At baseline, marginally VA-deficient measles patients had significantly lower serum retinol concentrations and RBP/TTR ratios and significantly higher serum CRP concentrations than VA-sufficient children. However, the VA and placebo treatment groups did not differ (Table 1). Vitamin A supplements increased serum retinol concentrations after controlling for baseline VA status (Fig. 1). At the 2-wk evaluation, marginally VA-deficient measles patients receiving VA supplements had significantly higher serum retinol concentrations than those receiving placebo (Fig. 1A). In VA-sufficient children, the treatment groups did not differ (Fig. 1A) but serum retinol concentrations increased from baseline to 2-wk evaluation. Serum CRP concentrations decreased by >50% from the baseline to the 2-wk evaluation; however, the distribution of CRP at 2-wk did not differ due to treatment or baseline VA status (Fig. 1B). The distribution of RBP/TTR values among the groups paralleled those of serum retinol concentrations (Fig. 1C).

There were proportionally fewer cases of MP in marginally VA-deficient patients receiving VA supplements than in those receiving placebo (Fig. 2). In VA-sufficient measles patients, the proportion of patients with MP was significantly lower in those receiving placebo compared with those receiving VA supplements. A longitudinal analysis showed that the probability of unresolved MP in marginally VA-deficient children

TABLE 1

Demographic, clinical and biochemical characteristics of acute measles patients by vitamin A status and treatment allocation at baseline

<table>
<thead>
<tr>
<th>Vitamin A status</th>
<th>Vitamin A deficient</th>
<th>Placebo</th>
<th>Vitamin A sufficient</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>39</td>
<td>43</td>
<td>49</td>
<td>65</td>
</tr>
<tr>
<td>Children, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;12 mo</td>
<td>38.5</td>
<td>30.2</td>
<td>34.7</td>
<td>30.8</td>
</tr>
<tr>
<td>12-60 mo</td>
<td>46.2</td>
<td>44.2</td>
<td>30.6</td>
<td>40.0</td>
</tr>
<tr>
<td>&gt;60 mo</td>
<td>15.4</td>
<td>25.6</td>
<td>34.7</td>
<td>29.2</td>
</tr>
<tr>
<td>Gender, male, %</td>
<td>46.2</td>
<td>34.9</td>
<td>44.9</td>
<td>50.8</td>
</tr>
<tr>
<td>Chronic undernutrition, weight/age &lt; −2 Z-score, %</td>
<td>41.0</td>
<td>34.9</td>
<td>30.6</td>
<td>33.8</td>
</tr>
<tr>
<td>Measles rash, %</td>
<td>78.5</td>
<td>90.7</td>
<td>79.6</td>
<td>87.7</td>
</tr>
<tr>
<td>Rectal temperature, °C</td>
<td>38.7 (37.8–40.0)</td>
<td>38.7 (37.8–39.4)</td>
<td>38.9 (38.3–39.4)</td>
<td>38.7 (38.3–40.0)</td>
</tr>
<tr>
<td>Serum retinol, μmol/L</td>
<td>0.36 (0.24–0.62)a</td>
<td>0.31 (0.24–0.51)a</td>
<td>0.48 (0.34–0.64)b</td>
<td>0.45 (0.29–0.66)b</td>
</tr>
<tr>
<td>Molar ratio of RBP/TTR</td>
<td>0.24 (0.21–0.30)a</td>
<td>0.25 (0.21–0.28)a</td>
<td>0.54 (0.43–0.65)b</td>
<td>0.50 (0.44–0.68)b</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>30 (7–56)b</td>
<td>27 (8–66)b</td>
<td>11 (2–27)a</td>
<td>11 (4–48)a</td>
</tr>
</tbody>
</table>

1 For continuous variables, values represent the median and, in parentheses, the 25th and 75th percentiles.
2 Vitamin A status of acute measles patients was determined using the molar ratio of retinol-binding protein to transthyretin (RBP/TTR) (10). A ratio of 0.36 is indicative of marginal vitamin A deficiency (11).
3 Comparisons were between marginally VA-deficient and -sufficient children. Different superscripts indicate significant differences (Mann-Whitney test, P ≤ 0.01). For categorical variables, groups were compared by χ² statistics.
The case-fatality rate is still high at 2%, even though there is high morbidity and mortality among children in Zambia. Measles infection is one of the major causes of death in the Western Hemisphere. In the United States, there were only 86 confirmed measles cases reported in 2000. The reported incidence of measles has declined to <1 case per 1 million population for the past several years (18). In other areas of the world, however, an estimated 30 million cases and 875,000 deaths are attributed to measles infection yearly, representing 10% of all deaths in children under the age of 5 y (18). In Zambia, measles infection is one of the five major causes of morbidity and mortality among children <5 y, and the measles case-fatality rate is still high at 2%, even though there is high rate of vaccination (72–93%) (19). In March 2001, the World Health Organization (WHO)/United Nations Children’s Fund Global Strategy Plan established specific goals for reducing global measles deaths that included improving measles case management. This is important because prophylactic efficacy of antibiotics to reduce mortality has not yet been determined (20), whereas the efficacy of VA supplements was demonstrated more than a decade ago (5), although its mechanism of action is not yet known.

A recent review suggested that both VA deficiency and measles virus reduce synergistically the host’s immune system and thus might enhance the risk of secondary infection (21). The author cautioned that no definitive conclusion could yet be reached because the inflammatory response of measles infection makes it difficult to confirm the effects of VA supplements on serum retinol. Therefore it is not possible to confirm the VA status of infected children (21).

In an earlier analysis of these data, no effect of VA supplements was found based on the concentration of serum retinol (13). More important, cross-sectional and longitudinal analyses showed no efficacy of VA supplements in reducing MP by the 2-wk evaluation (13). In the present analysis, only marginally VA-deficient children receiving placebo did not have increased serum retinol concentrations at the 2-wk evaluation. In the remaining groups, an increase in serum retinol was not attributed to a reduction of inflammation alone because serum CRP concentrations did not differ among the four groups (Fig. 1B). Therefore these results indicate that VA supplements increased serum retinol concentrations of marginally VA-deficient measles patients, whereas in VA-sufficient measles patients, an increase in serum retinol was most likely because of amelioration of inflammation. The response of circulating retinol to VA from supplements or diet has been demonstrated to depend on hepatic VA stores (22). In VA deficiency, serum retinol is stored in the liver (22). A recent review suggested that both VA deficiency and measles virus reduce synergistically the host’s immune system and thus might enhance the risk of secondary infection (21).

Cross-sectional and longitudinal analyses indicated that marginal VA deficiency increased the likelihood of unresolved MP from baseline to the 2-wk evaluation. Among children receiving placebo, the OR between marginally VA-deficient and -sufficient children was 2.5 (95% CI, 1.1–5.7), and VA supplementation of deficient children reduced it. In VA-sufficient measles patients, however, VA supplements increased the likelihood of unresolved MP compared with those receiving VA supplements was 30% (n = 20), and for those receiving placebo, 68% (n = 19) with an OR of 0.20 [95% confidence interval (CI), 0.05–0.71]. On the other hand, the probability of unresolved pneumonia in VA-sufficient children receiving VA supplements was 58% (n = 19), and in those receiving placebo, 32% (n = 19), with an OR of 3.0 (95% CI, 0.80–11.2).

**DISCUSSION**

Measles infection has almost been eradicated in the Western Hemisphere. In the United States, there were only 86 confirmed measles cases reported in 2000. The reported incidence of measles has declined to <1 case per 1 million population for the past several years (18). In other areas of the world, however, an estimated 30 million cases and 875,000 deaths are attributed to measles infection yearly, representing 10% of all deaths in children under the age of 5 y (18). In Zambia, measles infection is one of the five major causes of morbidity and mortality among children <5 y, and the measles case-fatality rate is still high at 2%, even though there is high rate of vaccination (72–93%) (19). In March 2001, the World Health Organization (WHO)/United Nations Children’s Fund Global Strategy Plan established specific goals for reducing global measles deaths that included improving measles case management. This is important because prophylactic efficacy of antibiotics to reduce mortality has not yet been determined (20), whereas the efficacy of VA supplements was demonstrated more than a decade ago (5), although its mechanism of action is not yet known.

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