Absorption of high-dose enteral vitamin A in low-birth-weight neonates

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A randomised, double-blind placebo-controlled trial was designed to determine whether high-dose (25 000 IU) enteral vitamin A, to correct deficiency, would be absorbed and well tolerated in low-birth-weight (LBW) neonates.

Thirty-five LBW infants (950 - 1 700 g; gestational age 27 - 36 weeks) were allocated to receive either placebo or vitamin A (25 000 IU) via nasogastric tube on the first day of the study (between 36 and 60 hours after delivery). The dose was repeated on study days 4 and 8. Serum retinol concentrations were determined pre- and post-supplementation. Toxic effects of vitamin A were monitored by noting vomiting, drowsiness and irritability, and palpatlng for a bulging fontanelle.

The mean serum retinol concentration was significantly higher following supplementation in the vitamin A-treated group than in the placebo group (45.77 ± 17.07 µg/dl v. 12.88 ± 6.48 µg/dl; P = 0.0001). Toxic effects were not detected in any of the infants.

In conclusion, high-dose enteral vitamin A is well absorbed in LBW neonates and three doses of 25 000 IU given over a period of 8 days are not associated with any detectable toxic effects.


Developing countries have a high incidence of low-birth-weight (LBW) deliveries; low birth weight is a major cause of perinatal mortality, and these infants are at increased risk of respiratory infections. It has been well established that infants born prematurely have low liver stores of vitamin A as well as low serum retinol concentrations. As retinol is essential for epithelial cell differentiation, it is hypothesised that vitamin A deficiency in these infants could result in pathological changes in the respiratory epithelium with consequent respiratory problems. Three studies have investigated the role of vitamin A therapy in bronchopulmonary dysplasia (BPD); however, in developing countries, the major problem for LBW infants is not BPD but rather pneumonia and other respiratory infections, both in the immediate neonatal period and during the first year of life. We therefore undertook a randomised, double-blind, placebo-controlled trial to investigate the effect of vitamin A supplementation on the incidence and severity of respiratory infections in LBW infants during their first year of life.

Although there is consensus on the dose of vitamin A to be administered to children both in measles and in community studies, there are no clear guidelines on what dosage of vitamin A to use in LBW infants. We hypothesised that high doses of vitamin A should be used as soon as possible, preferably within the first week, the most vulnerable period for the LBW infant, during which measures to promote the integrity of the respiratory epithelium and strengthen the immune response are likely to produce maximum benefits. As a dose of 50 000 IU has been shown to be safe in full-term neonates we chose to use half this dose, viz. 25 000 IU, and to administer it on study days 1, 4 and 8.

Another consideration in vitamin A therapy for LBW infants is the route of administration. It has generally been assumed that the absorption and bio-availability of enteral vitamin A is reduced relative to that of intramuscular vitamin A, although no study has systematically studied the kinetics of vitamin A metabolism after absorption in LBW infants.

The previous supplementation trials in LBW neonates used intramuscular vitamin A on alternate days or three times a week for 28 days. The use of repeated intramuscular injections in such tiny infants has many disadvantages, including the risk of muscle trauma and infection. We therefore decided to use oral vitamin A in this intervention study.

In this paper we describe the first part of the study, viz. the investigation, in the first 35 infants enrolled in the large intervention trial, of whether orally administered vitamin A would be well absorbed and whether 25 000 IU doses would be safe. Acute toxicity from vitamin A is reported generally to occur within 48 hours and the symptoms include bulging of the fontanelle due to increased intracranial pressure, anorexia, drowsiness, irritability, vomiting and liver damage. We undertook to monitor side-effects that did not require invasive methods, viz. bulging of the fontanelle, vomiting and neurological signs (drowsiness and irritability).

Subjects and methods

Subjects and treatment. The first 35 infants who were enrolled in a vitamin A intervention trial to test the effect of vitamin A supplementation on respiratory morbidity were included in this interim study. This represented a 25% subsample of the intervention trial sample. The infants delivered at King Edward VIII Hospital, Durban, between June and November 1993 were enrolled in the study. This hospital mainly serves a black disadvantaged community where childhood infections and pregnancy complications are common. The infants (of gestational age < 36 weeks and birth weight 950 - 1 700 g) were enrolled into this double-blind study with parental consent. Relevant details about each baby including sex, birth weight, gestational age and
Results

The characteristics of the infants are shown in Table I. Mothers' age, infants' gestational age, weight and sex distribution were comparable in the two groups at delivery.

Table I. Placebo and vitamin A group baseline characteristics and response to vitamin A supplementation (mean ± SD)

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Vitamin A</th>
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<tbody>
<tr>
<td>No.</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Male/female</td>
<td>7:11</td>
<td>7:10</td>
</tr>
<tr>
<td>Mother's age (yrs)</td>
<td>24.36 ± 6.73</td>
<td>24.23 ± 6.36</td>
</tr>
<tr>
<td>Gestational age (wks)</td>
<td>31.17 ± 2.23</td>
<td>31.81 ± 2.83</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1 290 ± 150</td>
<td>1 290 ± 270</td>
</tr>
<tr>
<td>Vitamin A (μg/dl)</td>
<td>9.83 ± 5.45</td>
<td>10.36 ± 6.50</td>
</tr>
<tr>
<td>(before supplement)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A (μg/dl)</td>
<td>12.88 ± 6.48</td>
<td>45.77 ± 17.07*</td>
</tr>
<tr>
<td>(after supplement)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A (μg/dl)</td>
<td>3.04 ± 4.89</td>
<td>35.41 ± 15.72*</td>
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<tr>
<td>(individual response to supplement)</td>
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* Differences between placebo and vitamin A groups statistically significant (P = 0.0001).

The mean serum retinol concentration before administration of the supplement was similar in the two groups. However, thereafter the vitamin A-supplemented group had higher mean serum retinol concentrations than the placebo group (45.77 ± 17.07 μg/dl v. 12.88 ± 6.48 μg/dl; P = 0.0001). This difference between the groups was also present when the mean increase in serum retinol for each individual was determined (35.41 ± 15.72 μg/dl v. 3.04 ± 4.89 μg/dl; P = 0.0001).

No infant in either the placebo or the vitamin A group was found to have feeding difficulties (failure to feed or vomiting); a bulging fontanelle; or neurological signs either before or after administration of vitamin A.
Discussion

The premature infants, in the group as a whole, had low initial concentrations of serum retinol. These findings confirm both our and others' observations that preterm infants have lower serum retinol concentrations than full-term infants. Only 1 infant in each group had a serum retinol concentration above the cut-off point for adequacy, viz. 20 μg/dL.

This study has shown that enteral vitamin A was well absorbed in LBW babies who were fed by nasogastric tube and that the serum retinol levels reached normal values. This finding supports the use of enteral vitamin A in interventions to test its putative beneficial effects in these infants. The advantage of using enteral vitamin A instead of intramuscular vitamin A in a placebo-controlled clinical trial is that it prevents the unnecessary use of injections in the placebo group. Landman et al.10 have shown that vitamin A deficiency in preterm infants can be corrected by supplementing feeds with 5 000 IU per day for 28 days. They compared this enteral route with 2 000 IU of intramuscular vitamin A on alternate days for 28 days and found it to be as effective as the latter, which was used by Shenai et al.13 A recent study by Rush et al.16 showed, however, that intramuscular vitamin A was more effective than enteral vitamin A in increasing vitamin A levels in very LBW neonates. The differences between the two studies could be accounted for by the differences in the sample population; the infants in Rush et al.'s study all required mechanical ventilation, and had higher mean initial serum retinol levels and a lower mean birth weight than those in Landman et al.'s study. Our study population was very similar to that of Landman et al. and it would seem from our results and the above studies that in healthy LBW infants vitamin A is well absorbed when given by the enteral route.

In this study, none of the side-effects commonly associated with the vitamin A doses used occurred. The study of toxic effects was, however, limited by small numbers and lack of information on biochemical changes in liver function tests.

In conclusion, this study confirms that 75 000 IU of vitamin A administered enterally over 8 days in three separate doses of 25 000 IU are well absorbed by LBW infants and no acute side-effects are associated with these doses. Using three large doses, rather than small daily doses or doses on alternate days, is obviously advantageous as it leads to cost-efficiency in terms of personnel and other provisions and chances of missing doses are minimised. We would therefore suggest that future attempts to reverse vitamin A deficiency in LBW infants could use 25 000 IU vitamin A as soon as nasogastric/oral feeding is established, followed by two repeat doses at intervals of 3-4 days.

We thank Thembile Ngubane for her assistance in dispensing the medications and monitoring patients; the doctors and nursing staff of the prem nursery for co-operation; Eleanor Gouws of the MRC Department of Biostatistics for assistance in data analysis; Inge Elson of the Analytical Unit, Department of Physiology, University of Natal, for vitamin A analysis and Dr Mike Brown, Roche Products, South Africa for the generous donation of Arovit drops and placebo.

The study was supported by grants from Gerber-Purity, the Medical Research Council and the Faculty of Medicine, University of Natal.

REFERENCES


Accepted 17 May 1996.