Vitamins for Very Low Birthweight Infants

Marcello Orzalesi and Renato Lucchini

Instituto di Puericultura, Università "La Sapienza," 58 Via dei Sardi, 00185 Rome, Italy

During the past few years much attention has been paid to vitamin requirements for very low birthweight (VLBW) infants and numerous original papers and review articles, as well as guidelines and recommendations from official bodies, have appeared in the literature (1-9). This brief review will focus specifically on the following questions:

1. What is the evidence that "normal," enterally fed, VLBW infants have different vitamin requirements from those of normal full-term infants?
2. Is there any disease state specific to the VLBW infant related to vitamin insufficiency and/or where supplementation or even pharmacological treatment with vitamins is indicated?
3. Do babies receiving total parenteral nutrition (TPN) present special problems related to vitamin requirements and/or administration?

VITAMIN REQUIREMENTS OF VLBW INFANTS

The major factors determining the requirements of vitamins and the need for supplementation in VLBW infants are (a) gestational age, which is in turn related to placental transfer and body stores of vitamins at birth; (b) the vitamin content of the feeds (human milk or formula) used in these infants; and (c) the volume and the macronutrient composition of the feeds (6,7).

The length of gestation and the nutritional status of the mother will affect the infant's vitamin stores at birth (10). This is particularly true for lipid-soluble vitamins, which cross the placenta by simple and/or facilitated diffusion and accumulate in fetal tissues throughout pregnancy (6,7,11-13). The levels of these vitamins in cord blood are lower than in maternal blood and their body stores at birth are reduced in preterm infants and in infants of poorly nourished mothers (6,7,12-14). On the other hand, water-soluble vitamins cross the placenta by active transport and their levels in fetal blood are generally higher than in maternal blood, with the exception of vitamin B₆, which crosses the placenta with some difficulty early in gestation (6,7,
TABLE 1. Vitamin content of human milk and infant formulas compared to minimum recommended levels and advisable intakes for healthy infants from birth to 6 months of age

<table>
<thead>
<tr>
<th>Vitamins</th>
<th>Pooled human milk per dl&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Infant formulas per dl&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Minimum recommended levels per dl&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Advisable intakes per day&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A, μg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60</td>
<td>50–120</td>
<td>40</td>
<td>140</td>
</tr>
<tr>
<td>Vitamin D&lt;sub&gt;3&lt;/sub&gt;, μg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.1–0.2</td>
<td>1–2</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Vitamin E, mg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.35</td>
<td>0.25–1.25</td>
<td>0.3</td>
<td>0.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitamin K&lt;sub&gt;1&lt;/sub&gt;, μg</td>
<td>1.5</td>
<td>3.0–10.0</td>
<td>1.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Thiamine (B&lt;sub&gt;1&lt;/sub&gt;), μg</td>
<td>16</td>
<td>30–160</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Riboflavin (B&lt;sub&gt;2&lt;/sub&gt;), μg</td>
<td>31</td>
<td>60–260</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Niacin, μg</td>
<td>230</td>
<td>450–900</td>
<td>230</td>
<td>175</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt;, μg</td>
<td>5.9</td>
<td>35–160</td>
<td>5</td>
<td>25&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;, μg</td>
<td>0.01</td>
<td>0.09–1.75</td>
<td>0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>Folic acid, μg</td>
<td>5.2</td>
<td>0.7–10.0</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Pantothenic acid, μg</td>
<td>260</td>
<td>200–350</td>
<td>200</td>
<td>210</td>
</tr>
<tr>
<td>Biotin, μg</td>
<td>0.76</td>
<td>1.0–2.1</td>
<td>0.5</td>
<td>1.05</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>3.8</td>
<td>5–10</td>
<td>3.0</td>
<td>5.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data for pooled human milk, see ref. 19.
<sup>b</sup> Data for infant formulas from manufacturer's information.
<sup>c</sup> Values in first column see ref. 20; second column see ref. 18.
<sup>d</sup> From ref. 21.
<sup>e</sup> Expressed as retinol: 1 μg retinol = 3.33 IU vitamin A.
<sup>f</sup> Expressed as cholecalciferol: 1 μg cholecalciferol = 40 IU vitamin D<sub>3</sub>.
<sup>g</sup> Expressed as α-tocopherol: 0.7 mg α-tocopherol = IU vitamin E.
<sup>h</sup> At least 0.5 mg/g of PUFA and not less than 0.5 mg/100 kcal.
<sup>i</sup> Niacin can be synthesized from tryptophan; 60 mg of tryptophan yield 1 mg of niacin. Therefore, requirements and levels can also be expressed as niacin equivalents = niacin (mg) + tryptophan (mg) × 0.017.
<sup>j</sup> Not less than 15 μg/g of proteins.

11,14,15). Nevertheless, preterm infants and infants of undernourished mothers also have reduced levels of water-soluble vitamins at birth (6,7,14–16).

The vitamin and macronutrient concentrations in feeds as well as the total volume of feeding are obvious important factors to be considered. As shown in Table 1, the average vitamin content of both human milk and artificial formulas may be quite variable; since most commercially available formulas are supplemented, their levels are in general equal to or higher than those found in human milk (6,7,17–20). The recommendations of the various bodies may differ, and therefore the minimum recommended levels of vitamins in infant formulas may also vary depending on the reference standards (17,18,20). The discrepancies are more obvious for the water-soluble vitamins, as indicated in Table 1, which reports the recommendations of the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) and those of the British Department of Health (18,20).

If we compare the composition of human milk and formulas with these recommendations we find that the vitamin content of most infant formulas is equal to or higher than the minimum recommended levels. This is not true for human milk, which has lower levels of vitamins D and K. The levels of vitamins B<sub>1</sub>, B<sub>2</sub>, and B<sub>6</sub> are also on the low side when compared to the minimum recommendations.
The composition of feeds is important as well. Higher intakes of vitamin C may be necessary to prevent a transient hypertyrosinemia in VLBW infants (6,7). Protein intake will modify the requirements of vitamin B<sub>6</sub> (minimum 15 μg of vitamin B<sub>6</sub> per g protein), while the amount of linoleic acid or generally that of polyunsaturated fatty acids (PUFA) in the diet will determine the minimum requirement for vitamin E (at least 0.9 mg of α-tocopherol per gram PUFA (6,7). Niacin can be synthesized from tryptophan in the presence of vitamin B<sub>6</sub>, therefore the requirements of this vitamin will depend on the amounts of tryptophan in the diet (6,7).

The total intake of vitamins with the diet, even when the vitamin content of feeding is above the minimum recommended levels, will depend upon the volume of feeding given. The recommended daily allowance (RDA) of vitamins for healthy infants up to 6 months of age are shown in Table 1 (21). In order to achieve these intakes the total volume of human milk or formula should range between 500 and 1000 ml/d, depending on the vitamin. The RDAs are substantially higher than the true minimum intakes necessary to prevent deficiency and are calculated for infants ranging in weight from 3 to 8 Kg in the first 6 months of life (21). In fact, a full-term infant with a volume intake of 450 to 750 ml/d will receive sufficient amounts of all vitamins except D and K when fed either human milk or a supplemented formula (6,7). However, if the total volume of feeding falls below 400 ml/d the vitamin intake may become marginal or insufficient. This is the situation in VLBW infants during their first weeks of life or until they reach a body weight of about 2000 g (6,7). Under these circumstances multivitamin supplementation appears reasonable, as suggested by the ESPGAN Committee for the Nutrition and Feeding of Preterm Infants (see Table 2) (5-7).

Late anemia of prematurity due to vitamin E deficiency does not develop when the tocopherol/PUFA ratio in the diet is equal to or higher than the recommended levels (0.9 mg/g) (6,7).

Vitamin K deficiency can be prevented by the intramuscular or oral administration of 0.2 to 1 mg of vitamin K at birth, although recent evidence suggests that biochemical and clinical signs of deficiency may develop later on, during the first 6 months of life, when intake is insufficient, as may happen in some exclusively breastfed infants or in infants treated with antibiotics (6,7,22). Under these circumstances repeated administration of vitamin K is indicated (5-7).

Exclusively breastfed infants rarely develop rickets; nevertheless a daily supplement of vitamin D is usually recommended in both breastfed and formula-fed term infants up to a total intake of 400 IU/d (10 μg/d) (6,7). This dosage has been shown to be harmless and capable of preventing vitamin D deficiency in situations where sun exposure in either mother or infant is low or where maternal vitamin D intake is insufficient (6,7,23,24). The evidence presently available does not support the need for higher intakes of vitamin D in VLBW infants, as suggested in the past (24,25). Indeed, absorption, hydroxylation, and utilization of enterally administered vitamin D seems to be normal in preterm infants even at low gestational ages (24,25). Intakes of vitamin D over 400 IU/d (up to 800 to 1200 IU) may only be necessary under particular circumstances (low maternal sun exposure and/or low vitamin D intakes, delivery during the winter
TABLE 2. Guidelines for vitamin supplementation in very low birthweight infants

<table>
<thead>
<tr>
<th>Vitamins</th>
<th>Suggested allowance</th>
<th>Need for supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (retinol)</td>
<td>200–800 μg/d</td>
<td>Supplementation needed with human milk or in formula</td>
</tr>
<tr>
<td>D (chole- or</td>
<td>10–20 μg/d (400–800 IU)</td>
<td>Supplementation needed with both human milk and formula</td>
</tr>
<tr>
<td>ergocalciferol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (tocopherol)</td>
<td>0.9 mg of α-tocopherol/g of PUFA in diet</td>
<td>Supplementation not needed if α-tocopherol/PUFA ratio ≥0.9 mg/g</td>
</tr>
<tr>
<td>K (phyloquinone)</td>
<td>0.2–1 mg at birth (i.m. or p.o.)</td>
<td>Repeat initial dose i.m. in infants receiving human milk or antibiotics</td>
</tr>
<tr>
<td>B&lt;sub&gt;1&lt;/sub&gt; (thiamine)</td>
<td>2–3 μg/kg/d p.o.</td>
<td>Supplementation needed when feeding heat-treated human milk</td>
</tr>
<tr>
<td>B&lt;sub&gt;2&lt;/sub&gt; (riboflavin)</td>
<td>25 μg/kg/d</td>
<td>Supplementation may be needed in infants fed human milk or treated with phototherapy</td>
</tr>
<tr>
<td>B&lt;sub&gt;6&lt;/sub&gt; (pyridoxine)</td>
<td>60 μg/kg (≥15 μg/g of protein)</td>
<td>Supplementation may be needed in infants fed human milk</td>
</tr>
<tr>
<td>Folic acid</td>
<td>65 μg/d</td>
<td>Supplementation needed with human milk and with formulas with low folic acid content</td>
</tr>
<tr>
<td>C (ascorbic acid)</td>
<td>20 mg/d</td>
<td>Supplementation needed with human milk and with formulas with low content of vitamin C</td>
</tr>
</tbody>
</table>

A multivitamin preparation should provide a daily intake of the following vitamins: A, 500 μg; D, 15 μg; E, 5 mg; K, 5 μg; B<sub>1</sub>, 50 μg; B<sub>2</sub>, 200 μg; B<sub>6</sub>, 100 μg; C, 20 mg; folic acid (separate or added), 60 mg; niacin, biotin, vitamin B<sub>12</sub>, and pantothenic acid can be omitted.

months, extremely low gestational age), but cannot be recommended on a routine basis (10,24,25).

Since thiamine is heat-labile, VLBW infants fed heat-treated human milk should be supplemented up to a daily intake of 25 μg/kg.d (6,7).

Recent reports have indicated that LBW infants undergoing phototherapy and infants fed human milk may show transient biochemical signs of riboflavin deficiency (6,7,15,26). Therefore it seems reasonable to give a vitamin B<sub>2</sub> supplement to VLBW infants fed human milk (up to 80 μg/kg.d), particularly if they are treated with phototherapy (6,7,10,15).

It has been recommended that at least 15 μg of pyridoxine should be provided per gram protein in the diet (6,7). This, however, may not be sufficient for VLBW infants, who show low blood levels (and possibly body stores) at birth and who may require higher intakes due to their rapid rate of postnatal growth (15). Therefore, a daily allowance of up to 60 μg/kg has been suggested in these infants (6,7). Since most commercial formulas contain greater amounts of vitamins B<sub>1</sub>, B<sub>2</sub>, and B<sub>6</sub> than human milk, artificially fed infants do not need to be supplemented with these vitamins (5–7).

The present information on the vitamin A status in VLBW infants is incomplete (6,7,27). Plasma concentration of both retinol and retinol-binding protein (RBP), as
VITAMINS

well as liver reserves, have been shown to be lower in preterm than in term infants (6,7,9). Although a true deficiency state has not been recognized clinically, VLBW infants with severe respiratory insufficiency and/or bronchopulmonary dysplasia (BPD) may have very low plasma concentrations of retinol, suggesting subclinical deficiency and/or increased utilization on the vitamin (6,7,9,27). Because of the low body stores at birth, the rapidly growing VLBW infant may need greater amounts than term infants to ensure adequate tissue stores (6,7,14,27). Therefore the current practice of supplementing these infants with vitamin A can be supported (5–7).

The folic acid content of human milk is sufficient for the normal breastfed term infant. This is not true for the preterm infant, however, due to the low body stores at birth and the rapid postnatal growth (6,7,10,28). Subclinical deficiency states have been reported in preterm infants; these signs were reversed or prevented by the daily administration of 60 to 65 µg of folic acid (6,7,28). Since folic acid is non-toxic and readily eliminated by the kidneys it seems advisable to provide this intake in VLBW infants (5–7,28).

Some controversy still exists concerning the recommended allowance of vitamin C. The vitamin C content of human milk and formulas may be quite variable depending on maternal nutrition and/or heat treatment of the feed (6,7). Therefore a supplement of 20 mg/day of vitamin C has been suggested in VLBW infants fed human milk or formulas with a low vitamin C content (5–7,10).

On the basis of the above considerations, it appears that vitamin supplementation in VLBW infants is indicated for vitamins A, D, C, and folic acid, while for vitamins E, K, B₁, B₂, and B₆ the daily intake may become marginal under special circumstances or with human milk feeds (Table 2), so supplements may be required.

Many neonatal units routinely give multivitamin preparations to VLBW infants and this procedure has not been associated with harmful side effects. Since water-soluble vitamins are non-toxic and are readily eliminated when given in slight excess, there is no reason to discontinue this practice, provided that the daily intakes are maintained within the ranges suggested by the ESPGAN Committee on Nutrition of the Preterm Infant (5–7). Unfortunately the commercially available oral multivitamin preparations do not contain the various vitamins in the appropriate proportions to meet the needs of VLBW infants. As indicated in Table 2 a reasonable multivitamin preparation for VLBW infants could provide in a single dose a daily intake of the following vitamins: vitamin A, 500 µg; vitamin D, 15 µg; vitamin E, 5 mg; vitamin K, 5 µg; vitamin B₁, 50 µg; vitamin B₂, 200 µg; vitamin B₆, 100 µg; vitamin C, 20 mg; and folic acid (separate or added) 60 µg. Vitamin B₁₂, niacin, biotin, and pantothenic acid can be omitted from the preparation. Particular attention should be given to the osmolarity of the solution.

PREMATURITY, DISEASE, AND VITAMINS

Recently the attention of many investigators has focused on the possible role of vitamins in the prevention and/or treatment of some disease states that are typical
of extreme prematurity. These include osteopenia and rickets, early hypocalcemia, hemorrhagic disorders, anemia, hyperbilirubinemia, peri-intraventricular hemorrhage (PIVH), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and infections. The respective vitamins involved are vitamin D and its metabolites, vitamin K, folic acid, vitamin E, and vitamin A. Some possible adverse effects of vitamins have also been reported, such as an increased incidence of necrotizing enterocolitis (NEC) and sepsis, or even a higher neonatal mortality, associated with high doses of vitamin E.

We shall try to summarize briefly for each vitamin the evidence presently available in favor of or against such claims. In doing so we shall use an approach to evaluation similar to that adopted by Sinclair and Bracken (29). Whenever possible the efficacy of vitamin therapy or prophylaxis will be based on the results of randomized or non-randomized controlled trials. The effects of vitamin treatment on the ultimate outcome (event) will be expressed by the “event rate ratio” (ERR) between treated and control subjects. Where the effect is beneficial the ERR is less than 1, and its 95% confidence intervals (CI) should also both fall below 1. Where the effect is adverse, the ERR and 95% CI will be higher than unity.

As already mentioned the metabolism and action of vitamin D in VLBW infants is adequate and, as illustrated by Salle elsewhere in this volume, the origin of osteopenia and rickets is related to insufficient phosphorus and calcium intakes (9,30). Therefore administration of vitamin D or its metabolites in amounts above the recommended allowances does not prevent osteopenia of prematurity (9,30,31). Various attempts to prevent early hypocalcemia by treating preterm infants with 1,25-dihydroxyvitamin D have also been unsuccessful (9).

Three randomized controlled trials have shown that folic acid supplementation has a beneficial effect on hemoglobin levels at 6 months of age in preterm infants (9). This effect, though statistically significant, is of minor clinical importance since the average increase in hemoglobin concentration is only about 1 g/dl (9).

A possible beneficial effect of vitamin K prophylaxis at birth in lowering the incidence of classic hemorrhagic disease of the newborn is suggested by two randomized controlled trials on a large number of subjects (32). It should be noted, however, that both trials were performed in term infants and included any type of bleeding as their clinical end point. Therefore, the real efficacy of prophylactic vitamin K administration on the incidence of true classic hemorrhagic disease of the newborn is still to be proven (32). The efficacy of a second dose of vitamin K at 2 weeks of age has been investigated by one trial in exclusively breastfed term infants. Vitamin K-dependent coagulation tests were significantly improved in treated infants, suggesting a lower risk of late hemorrhagic disease (32). These results are probably applicable to preterm infants as well.

The most pertinent and interesting effect of vitamin K is a reduction in the incidence and severity of PIVH when the vitamin is given antenatally to the mothers of preterm infants (33). The three randomized controlled trials supporting this finding are concordant and statistically significant, but are also affected by some methodological errors and possible bias. Therefore they need to be confirmed before this kind of vitamin K prophylaxis can be recommended on a routine basis (33).
### A. Clinical evidence of possible beneficial effects of vitamin A (retinol) (from refs. 35–40)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study Details</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy of prematurity (ROP)</td>
<td>RCT: 20T vs 20C</td>
<td>0.42</td>
<td>0.15, 0.83</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (BPD)</td>
<td>2 RCT: 44T vs 46C</td>
<td>0.69</td>
<td>0.50, 0.95</td>
</tr>
<tr>
<td>Airway infection</td>
<td>1 RCT: 19T vs 20C</td>
<td>0.38</td>
<td>0.15, 1.00</td>
</tr>
</tbody>
</table>

### B. Clinical evidence of possible beneficial effects of vitamin E (α-tocopherol) (from refs. 32,33,35,36,41)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study Details</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperbilirubinemia (μmol/liter)</td>
<td>4 RCT: 75T vs 69C</td>
<td>-12.4</td>
<td>-20.4, 4.4</td>
</tr>
<tr>
<td>Anemia (g/liter)</td>
<td>7 RCT: 232T vs 265C</td>
<td>5.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (BPD)</td>
<td>8 RCT: 706T vs 733C</td>
<td>0.92</td>
<td>0.73, 1.16</td>
</tr>
<tr>
<td>Peri-intraventricular hemorrhage (PIVH)</td>
<td>2 RCT: 136T vs 136C</td>
<td>-12.4</td>
<td>-20.4, 4.4</td>
</tr>
<tr>
<td>Patent ductus arteriosus (PDA)</td>
<td>2 RCT: 34T vs 30C</td>
<td>0.9</td>
<td>1.62</td>
</tr>
<tr>
<td>Retinopathy of prematurity (ROP)</td>
<td>8 RCT</td>
<td>0.91</td>
<td>0.78, 1.07</td>
</tr>
<tr>
<td>Necrotizing enterocolitis (NEC)</td>
<td>7 RCT: 73ST vs 769C</td>
<td>1.37</td>
<td>0.97, 1.93</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 RCT: 410T vs 422C</td>
<td>1.54</td>
<td>1.02, 2.32</td>
</tr>
<tr>
<td>Death</td>
<td>7 RCT: 737T vs 763C</td>
<td>1.14</td>
<td>0.92, 1.41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Index Event</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC? ?</td>
<td>ERR 1.37 CI</td>
<td>0.97</td>
<td>1.93</td>
</tr>
<tr>
<td>Sepsis ?</td>
<td>ERR 1.54 CI</td>
<td>1.02</td>
<td>2.32</td>
</tr>
<tr>
<td>Mortality?</td>
<td>ERR 1.14 CI</td>
<td>0.92</td>
<td>1.41</td>
</tr>
</tbody>
</table>

E-Ferol i.v. | Severe toxicity and death

RCT, randomized controlled trial; NRCT, non-randomized controlled trial; T, treated; C, control; ERR, event rate ratio; CI, 95% confidence interval.

Perhaps the most exciting studies are those related to the natural antioxidant and epithelial-endothelial cell protective properties of vitamins A and E (27,34).

Several studies have been performed with vitamin A for the prevention of two severe complications of extreme prematurity and oxygen therapy, namely retinopathy of prematurity and bronchopulmonary dysplasia (Table 3) (35–40). The results of these studies are contradictory. After the original observation of Shenai and co-workers (37) (one randomized controlled trial) on the beneficial effects of early retinol
supplementation on the incidence of both these conditions, only one study has con-

firmed the results, and only for bronchopulmonary dysplasia (36). Two more recent

randomized controlled trials have failed to show any effect of retinol supplementation

on either retinopathy of prematurity (35) or bronchopulmonary dysplasia (38,39).

These discrepancies might be explained on the basis of a much better vitamin A

status at birth in the infants studied in the later trials and/or by the fact that recent

approaches to the prevention and treatment of the respiratory distress syndrome,

including prenatal steroids and postnatal surfactant administration, may have reduced

the importance of the role played by vitamin A.

Shenai et al. also reported a lower incidence of respiratory infections in infants

treated with retinol (37,40); this might have been related to the lower incidence of

bronchopulmonary dysplasia in their study, since they did not find any effect of

vitamin A on the incidence of sepsis. Therefore the possible beneficial effects of

vitamin A remain to be proven (35,36,40).

Vitamin E has been studied more extensively than vitamin A (Table 3). Its possible

protective effects against oxidative damage to red blood cells have been investigated

in studies on the prevention of hyperbilirubinemia and anemia of prematurity (32).

In relation to hyperbilirubinemia, randomized controlled trials have given concordant

and statistically significant results; however, any clinical benefit has been marginal

since the average decrease in peak serum bilirubin level was less than 1 mg/dl (32).

In relation to anemia of prematurity, only the first six studies showed a significant,

though marginal, benefit on hemoglobin levels at 6 to 10 weeks of age (less than 1

g/dl) (32). One more recent study and four non-randomized controlled trials have

shown no effect (32). This may be due to the fact that over the years the composition

of formulas for LBW infants has been improved, leading to a more physiological ratio

of α-tocopherol/PUFA (above 0.9 mg/g) (6,7,32). Evidence from three randomized

controlled trials that vitamin E reduces the incidence and severity of peri-intraventric-

ular hemorrhage, is very suggestive, though somewhat equivocal in that the effect

is not consistent and is often limited to only part of the population of infants studied

(33). Furthermore six other (non-randomized) controlled trials have also given con-

flicting results (33).

No effect of vitamin E has been shown on the incidence of bronchopulmonary

dysplasia or patent ductus arteriosus (36,41). The most controversial studies with

vitamin E are those relating to the prevention of retinopathy of prematurity. Meta-

analysis of the results of the numerous controlled trials performed so far shows no

conclusive beneficial effect of vitamin E on the incidence and severity of retinopathy

(35,42).

Several studies have suggested that there may be severe adverse effects of large

doses of vitamin E in VLBW infants (Table 3) (35,40,43,44). Two randomized con-

trolled trials have shown a significant increase in the incidence of sepsis (40); the

results of two other studies, on NEC (43) and overall mortality (35), while not signifi-

cant, do point in a worrying direction. We should not forget the disastrous conse-

quences of the utilization in LBW infants of an intravenous preparation of vitamin E

(E-Ferol), which had been conceived for adult use (44).

In summary, with the evidence presently available we can provisionally conclude

that there is no clear evidence that vitamin administration to VLBW infants in
amounts exceeding those sufficient to prevent deficiency is of benefit for the prevention and/or treatment of some common complications of extreme prematurity, such as retinopathy of prematurity, bronchopulmonary dysplasia, peri-intraventricular hemorrhage, or patent ductus arteriosus; more extensive and convincing studies are necessary before any routine of this kind can be recommended. One should also be aware of the dangers involved in performing such studies, because of the possible severe side effects of excessive amounts of some vitamins.

TOTAL PARENTERAL NUTRITION AND INTRAVENOUS VITAMINS

There are two major differences between the enteral and parenteral administration of vitamins: (a) with the intravenous route the infusion is continuous, and (b) the liver is initially bypassed. This on the one hand can increase the renal losses of some vitamins while increasing the risk of toxicity; on the other hand it can modify the capacity of the liver for storage and biotransformation of vitamins (45,46).

Other problems are related to the insolubility in water of lipid-soluble vitamins and to the fact that some solubilizing agents that are used for adult preparations, such as polysorbate and acetate, may be toxic in VLBW infants (44,47). Finally, some vitamins, and particularly vitamin A, can adhere to the plastic intravenous delivery system, with a substantial reduction in the calculated intake (45,46,48). Other types of biotransformation in the solution, such as photodegradation (vitamin A, riboflavin, folic acid), with possible free radical generation are also problems to be considered (45,46,49). All these problems are complicated by the fact that some of the methods used for evaluating the adequacy of vitamin intakes are indirect and more suitable for detecting a deficiency state than a toxic level (45,50–53).

For all these reasons the recommended intakes of vitamins given intravenously may differ substantially from those accepted for enterally fed infants (45,46,54,55). The most recent suggested intravenous intakes for preterm infants, proposed by the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition (45), are different from those previously suggested (54,55) in that the amount of vitamin A is higher (to account for the losses in the delivery system) and the intakes of vitamins C, B₁, B₂, and B₆ are lower. These guidelines are yet to be validated clinically and will be difficult to meet since the presently available commercial preparations are inadequate for that purpose (45,46).

Two intravenous preparations are available on the market. One of these (No. 1) is used in the USA as a single preparation at a suggested dosage of 2 ml/kg/d. In the other preparation, which is available in Europe (No. 2), the water-soluble vitamins (in a dose of 0.15 ml/kg/d) are separate from the fat-soluble vitamins, which are solubilized in a lipid emulsion (at a dosage of 4 ml/kg/d). Neither product is available in Italy, where we must use a mixture of intravenous preparations, given daily, and intramuscular preparations, given weekly (preparation No. 3). The vitamin intakes provided by these three preparations are compared with the suggested intravenous requirements in Table 4. Preparations 1 and 2 both provide adequate amounts of
TABLE 4. Estimated intravenous vitamin requirements (per kg/d) and intravenous vitamin intakes (per kg/d) with three commercially available preparations in VLBW infants on TPN

<table>
<thead>
<tr>
<th>Vitamins</th>
<th>Requirements (per kg/d)</th>
<th>Prep. 1</th>
<th>Prep. 2</th>
<th>Prep. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A µg</td>
<td>500 µg retinol equivalents</td>
<td>280</td>
<td>276</td>
<td>747</td>
</tr>
<tr>
<td>Vitamin D µg</td>
<td>4 µg (160 IU) ergocholecalciferol</td>
<td>4</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Vitamin E mg</td>
<td>2.8 mg α-tocopherol</td>
<td>2.8</td>
<td>2.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Vitamin K µg</td>
<td>80 µg phyloquinone</td>
<td>80</td>
<td>80</td>
<td>143</td>
</tr>
<tr>
<td>Vitamin C mg</td>
<td>25 mg ascorbic acid</td>
<td>32</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>Folic acid µg</td>
<td>56 µg</td>
<td>56</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>Vitamin B₁ µg</td>
<td>350 µg thiamine</td>
<td>480</td>
<td>450</td>
<td>980</td>
</tr>
<tr>
<td>Vitamin B₂ µg</td>
<td>150 µg riboflavin</td>
<td>560</td>
<td>540</td>
<td>680</td>
</tr>
<tr>
<td>Vitamin B₆ µg</td>
<td>180 µg pyridoxine</td>
<td>400</td>
<td>600</td>
<td>440</td>
</tr>
<tr>
<td>Vitamin B₁₂ µg</td>
<td>0.3 µg</td>
<td>0.4</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Niacin mg</td>
<td>6.8 mg</td>
<td>6.8</td>
<td>6.0</td>
<td>6.8</td>
</tr>
<tr>
<td>Biotin µg</td>
<td>6 µg</td>
<td>8</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>Pantothenic acid mg</td>
<td>2 mg</td>
<td>2.0</td>
<td>2.2</td>
<td>0.78</td>
</tr>
</tbody>
</table>

From Greene et al. (45) and manufacturer's information.

Prep. 1: US preparation. Prep. 2: European preparation. Prep. 3: Various i.v. and i.m. preparations available in Italy.

lipid-soluble vitamins, with the exception of vitamin A, which is too low. Preparation No. 3 provides excessive amounts of all lipid-soluble vitamins. All three preparations tend to provide excessive amounts of most water-soluble vitamins, particularly B₁, B₂, and B₆.

CONCLUSIONS

In conclusion, if we return to the three questions listed in the introduction we cannot be satisfied with the answers and with the published evidence presently available.

Concerning the first question, it appears that vitamin requirements of VLBW infants may possibly be higher than those of full-term infants only for vitamins A, B₂, C, and folic acid. The increased needs are related to the low body stores at birth, to the immaturity of some enzyme systems, and to the rapid postnatal growth of these infants. It is also likely that VLBW infants will tolerate vitamin deprivation in early life less well than term infants since their body reserves are rapidly depleted. Adequate intakes of all vitamins should therefore be guaranteed immediately after birth.

The answer to the second question is still in doubt, since the numerous studies performed so far are inconclusive. There are, however, some situations where vitamin therapy looks promising, such as the possible prevention of peri-intraventricular hemorrhage by the prenatal administration of vitamin K to the mother and the decreased risk or severity of bronchopulmonary dysplasia following early supplementation with vitamin A.
Finally, there is no question that the administration of vitamins by the intravenous route poses special problems in VLBW infants on total parenteral nutrition. The presently suggested recommendations need to be validated and better multivitamin preparations for intravenous use should be made available on the market.

The factors involved in determining the vitamin requirements and the need for supplementation in VLBW infants are numerous, complex, heterogeneous, and ever changing, besides being partially unknown. In this area, as in many other areas of infant nutrition, there is room for further studies and improvement in care.

ACKNOWLEDGMENT

Work supported in part by a grant from the Italian Ministry of Health.

REFERENCES


VITAMINS 165


DISCUSSION

Dr. Delvin: What is the stability of multivitamin preparations used in parenteral nutrition? What losses can be expected, particularly of vitamins such as A, E, and K that are easily oxidized and tend to be adsorbed onto plastic?

Dr. Orzalesi: Losses can be very high. For example for vitamin A they can be as much as 50% to 60% of the administered dose. This will of course depend on the length of time that the preparation remains in the giving set and on the amount of light that it is exposed to. Most units are quite intensely illuminated and for vitamins such as B₁, B₂, and folic acid degradation could be quite substantial; therefore we always cover the IV administration bags to protect them from light. If you put the lipid-soluble vitamins in lipid solution the stability is much better. Folic acid is not stable in multivitamin solutions and should be added at the last minute or given separately.

Dr. Delvin: These are important matters. When clinical studies are done in which effects of vitamins are reported there is likely to be a lack of consistency in the results.

Dr. Orzalesi: You are right. This is one of the weak points about the studies reported so far. One solution would be to sample at the very end of the IV tube so that you know what is really going into the baby. The situation is analogous to the problem of calcium. You can add calcium to the formula but you may not know how much of it has been precipitated when you do your balances.

Dr. Simmer: We have measured fat-soluble vitamins at the end of the tubing just before the solution enters the baby. We found that delivery of vitamin A was only 10% of what was added to the bag. Delivery of vitamin E was 90% to 100%. About half the infants had biochemical evidence of vitamin A deficiency.

Dr. Lucas: Protection against photodegradation is also important for enteral feeds and this is often ignored. Some years ago we showed that with a 3-hour light exposure you can expect to lose something like 70% of vitamin A and 50% of riboflavin from an enteral feed preparation. Such exposure would be common in clinical practice. Modern preterm formulas are designed
to meet the vitamin requirements of preterm infants without the addition of multivitamin supplements, yet they are often given by continuous infusion under phototherapy lights. Do you have any recommendations about this?

Dr. Orzalesi: The recommendations are obvious from your comments. I can add to the confusion by pointing out that heat treatment, as is often applied to pasteurize human milk in neonatal units, causes a further decrease in the vitamins you mentioned. In our unit we prefer to give feeds by small boluses rather than by continuous infusion. This lessens the light exposure time.

Dr. Salle: I don’t agree with what Dr. Lucas says in relation to the vitamin adequacy of preterm formulas. It is certainly not true with respect to vitamin D. Do low birthweight formulas fulfill the requirement for vitamin A?

Dr. Lucas: I am saying that increasingly attempts are being made by formula manufacturers to meet the vitamin requirements of preterm infants in formulas. I agree that vitamin D is an exception. So far as vitamin A, and in particular riboflavin, is concerned—where real attempts to meet requirements are being made—there is a risk that people might not give any supplementary vitamins under conditions in which much of the vitamin content of the formula is being degraded before it enters the baby.

Dr. Bracci: Although I partly agree with Dr. Orzalesi’s doubts about the benefit of vitamin E in various conditions, we have to keep in mind that oxygen toxicity in the preterm infant is a very complicated story and is unlikely to respond only to vitamin E. There is nevertheless an important requirement for vitamin E and there is evidence that the requirement may change depending not only on the ratio with fatty acids but also because of changes in the consumption of vitamin E by membranes. We know that the content of vitamin E in membranes in premature infants is very low. The requirement for vitamin E should probably be revised.

Dr. Simmer: Could you comment on the association between intramuscular vitamin K injections and increased risk of cancer?

Dr. Orzalesi: I am aware of the epidemiological association but I have no personal knowledge of this matter.

Dr. Von Kries: Following a chance finding of this association in a cohort from the 1970s, Professor Jean Golding has carried out a case-control investigation in 1992 involving 195 cases and 558 controls (1). There was a twofold increase in cancer risk; odds ratio = 1.37 with 95% confidence interval of 1.3 to 3.0.

Dr. Orzalesi: What cancer?

Dr. Von Kries: This is the problem. The increased risk was for all cancers and no one is anxious to believe that one drug given to a baby could cause all types of cancer. However, nobody in the epidemiological world has found any evident mistake in Professor Golding’s study. If the study is true we should see many more cases of cancer than prevented cases of hemorrhagic disease! The conclusion that we now draw from this in Germany is that we should withhold intramuscular prophylaxis from healthy infants and reduce the dose given to premature and sick babies to the minimal effective dose, which is 200 µg with the preparations now available, and to repeat these doses at 1 week and 6 weeks of age. This is the current German recommendation, though I know that in the USA everyone still gets intramuscular vitamin K. For normal babies we give oral vitamin K. There is reasonable evidence that repeated oral doses will give as good protection as a single intramuscular dose.

Dr. Verellen: Low birthweight infants are often on intravenous infusions so this is a convenient route to give the vitamin K. If the baby is not receiving an infusion but is of low or
borderline birthweight, he can usually be given the vitamin orally or intragastrically. Is there really any place for intramuscular vitamin K any more?

Dr. Orzalesi: In the ESPGAN recommendations for preterm infant feeding, repeated administration of vitamin K is not considered necessary unless the infant is exclusively fed on breast milk or if antibiotics that may change the intestinal flora are being given. Otherwise it is considered that the amount of vitamin K provided in artificial formulas is sufficient.

Dr. Fukagawa: How do you monitor adequacy of vitamin nutrition?

Dr. Orzalesi: Most of the methods we use are indirect. Either you replenish what is missing to make an enzymatic reaction proceed or you look for biochemical evidence of deficiency. Blood levels of vitamins, which can now be measured by HPLC, are not necessarily a good index of deficiency. It is not the level in the plasma that matters so much as the level in membranes. None of the methods in use is of any value for identifying potential toxicity.

Dr. Salle: I have read many times that the concentration of retinol in plasma does not reflect the vitamin A pool and that it is better to measure the vitamin in the liver or to measure the retinol-binding protein concentration. If you have a low vitamin A concentration in the plasma it does not necessarily mean that the vitamin A pool is depleted. Do you agree with this?

Dr. Delvin: You have to look at both retinol and retinol-binding protein (RBP). It is known that there is a feedback mechanism at the level of the liver that relates retinol-binding protein synthesis to vitamin A intake.

Dr. Orzalesi: It may be that you should measure total lipids as well. It should also be remembered that malnutrition will affect RBP synthesis and it may be very difficult to distinguish the effects of protein-energy deficiency from those of single vitamin malnutrition. The full picture is never given only by the blood level of a vitamin.

Dr. Simmer: It seems probable that cells should be used rather than plasma. Cellular markers are likely to be better than plasma markers.

REFERENCE